PERIODIC BENEFIT-RISK EVALUATION REPORT
PERIODIC SAFETY UPDATE REPORT

Eylea®

BAY No. 86-5321
(Aflibercept)

No. 9.0

01 DEC 2018 to 30 NOV 2019

INTERNATIONAL BIRTH DATE
18 NOV 2011 (United States of America)

Date of Report:
16 JAN 2020

Approved by: 16 Jan 2020
Date

[redacted]

Approved by: 16. Jan 2020
Date

Confidential

According to the Guideline on Good Pharmacovigilance Practices (GVP), Module VII signature authority has been designated to the respective PV Therapeutic Area Head.

Executive Summary

Introduction

This is the 9th PBRER/PSUR for Eylea (aflibercept). It covers the reporting interval from 01 DEC 2018 to 30 NOV 2019.

Aflibercept is a recombinant protein consisting of human VEGF receptor extracellular domains fused to the Fc portion of human immunoglobulin (Ig) G1. It contains portions of the extracellular domains of two different VEGF receptors. Aflibercept is formulated for intravitreal (IVT) administration.

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and placental growth factor (PlGF) with higher affinity than their natural receptors, and thereby can inhibit the binding and activation of these cognate VEGF receptors.

Aflibercept has been investigated and is approved for the treatment of wet age-related macular degeneration (AMD), macular edema secondary to central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO), diabetic macular edema (DME), diabetic retinopathy, and myopic choroidal neovascularization (mCNV).

Estimated cumulative exposure

Approximately 4,635 patients have been enrolled in larger company-sponsored interventional clinical trials with Eylea until data lock point of this PBRER/PSUR.

The number of vials sold during this reporting period represents an estimated exposure of 1,101,678 patient years. The cumulative post-marketing exposure since 2011 is estimated at 4,540,798 patient years.

Marketing approval

Eylea® is currently authorized to be marketed in 110 countries and is marketed in 94 countries.

Summary of the overall benefit-risk analysis evaluation

No information has become available during the period of this PBRER/PSUR which would have an impact on the benefit-risk profile of aflibercept. The benefit-risk profile of aflibercept in the indications AMD, CRVO, BRVO, DME, DR and mCNV remains favorable.

Neovascular (Wet) Age-Related Macular Degeneration

Wet AMD is a progressive disease that can cause profound and irreversible vision loss. In two pivotal studies (VIEW 1 and VIEW 2), primary efficacy analyses showed that aflibercept was consistently non-inferior to ranibizumab. During the clinical trial experience, the aflibercept safety profile mainly consisted of adverse reactions related to the IVT injection procedure. Serious injection-related events were rarely reported (less than 1:1000 injections). The long-term VIEW 1 extension study and the SIGHT study confirmed the efficacy results as demonstrated in the pivotal phase III wet AMD studies and showed maintenance of the visual

acuity as measured by BCVA with repeated (long-term) treatment. No new safety relevant data in studies with AMD became available during the reporting period.

Retinal Venous Occlusion

Retinal vein occlusion (RVO) is an important cause of vision loss, particularly in patients with associated chronic macular edema (1). The two major forms of the disease are central vein and branch vein occlusions. Aflibercept has been shown to be a beneficial treatment option in the management of CRVO and BRVO. The results of the individual CRVO studies have confirmed the superiority of aflibercept for improving visual acuity over sham treatment in subjects with macular edema secondary to CRVO. Visual improvement in macular edema secondary to BRVO with aflibercept was rapid, being seen as from Week 4, maintained through Week 24 with monthly injections until Week 52, with an extension of the treatment interval to bi-monthly starting at Week 24. Patients also showed improvements in morphology as assessed by optical coherence tomography (OCT). The safety profile in the clinical development program was consistent with that seen in the wet AMD phase III studies. Adverse reactions were mainly associated with the IVT injection procedure. No new safety relevant data in studies with RVO became available during the reporting period.

Diabetic Macular Edema

The primary and secondary efficacy results in VIVID and VISTA DME phase III studies confirm robust benefits of aflibercept over 52 weeks (primary endpoint). These were also confirmed by results through week 148 and remained consistent across all visual and anatomic outcomes, thus confirming superior improvement in BCVA with both aflibercept dosing regimens (2Q4 and 2Q8) when compared to laser photocoagulation. The safety profile was consistent with that seen across indications. Adverse reactions were mainly associated with the IVT injection procedure. No new safety relevant data in studies with DME became available during the reporting period.

Myopic Choroidal Neovascularization

Myopic choroidal neovascularization (mCNV) is a complication of pathologic myopia, and a frequent cause of vision loss in adults younger than 75 years of age. During the clinical development program, aflibercept has shown to be a beneficial treatment option in the management of myopic CNV. The primary and secondary efficacy analyses confirmed the statistical superiority of aflibercept over sham treatment. The safety profile was consistent with that seen in the wet AMD phase III studies. Adverse reactions were mainly associated with the IVT injection procedure. No new relevant data in studies with mCNV became available during the reporting period.

Neovascular Glaucoma

Neovascular glaucoma (NVG) is a secondary glaucoma triggered by the formation of new blood vessels (neovascularization) on the iris and the anterior chamber angle. Neovascular glaucoma is a serious condition that may lead to permanent loss of vision, a persistently painful eye and, especially in the advanced stages, is unlikely to respond to treatment. Bayer

investigated Eylea treatment in NVG in a randomized, double-masked, sham-controlled phase III study in Japanese patients with NVG (VEGA Study, 17584). A total of 63 subjects were screened and 54 subjects were randomized into the aflibercept group (N=27) and the sham group (N =27). The primary endpoint (difference in least square mean change of IOP from baseline to week1) was not met (-4.9 mmHg, CI -10.2 to 0.3 mmHg, p= 0.0644).However, the change in IOP in the aflibercept group was −9.9 mmHg (LS mean change), which was comparable to the expected clinically meaningful reduction used to design the study (assumption for the determination of sample size: mean ± SD of −10 ± 12 mmHg for the aflibercept group). Also, aflibercept remarkably regressed the iris neovacularization and angle neovascularization in both arms of the study. An additional single-arm open-label study in patients with NVG (VENERA, Study 19652) was completed during this reporting period. The VENERA study was a multicenter, single-arm, non-randomized, and open-label phase 3 trial to evaluate the primary efficacy variable "change in IOP from baseline to Week 1" of IVT administration of aflibercept in NVG patients. The study met its primary endpoint. The change in IOP from baseline to Week 1 (LOCF), was -8.3 ± 7.3 mmHg, with a 95% CI of -12.2 to -4.4 mmHg with an upper limit of the CI less than zero (pre-defined threshold) (p = 0.0004) for the PPS. The results of the secondary efficacy variable, the proportion of subjects with improvement in NVI grade at Week 1, and those of the exploratory efficacy variables on IOP, NVI and NVA also showed the clinically significant improvement after aflibercept injection. The results in IOP, NVI, and NVA consistently suggest that aflibercept could provide clinical meaningful improvements in efficacy in patients with NV. The phase III study program of Eylea in patients with neovascular glaucoma (VEGA/VENERA study) did not yield any new safety findings. In these studies, Eylea showed a similar safety profile compared to the safety profile in patients in the pivotal studies the in the indications wet AMD, BRVO, CRVO, DME and myopic CNV.

Diabetic Retinopathy (approved in USA)

In the Regeneron sponsored PANORAMA study, patients with moderately severe to severe NPDR were randomized 1:1:1 to receive aflibercept every 8 weeks following 5 initially monthly doses (2q8), aflibercept every 16 weeks following 3 initial monthly doses and 1 q8 interval, and sham injections. The primary outcome measure of the study is the proportion of patients who have improved by ≥2 steps from baseline on the DRSS in the combined 2Q8 and 2Q16 groups at week 24, and in each group separately at week 52. At week 24, a significant proportion of patients in the combined aflibercept dosing groups had a ≥2 step improvement from baseline on the DRSS compared to patients receiving sham injections (58% vs 6%). At week 52, 80% and 65% of patients in the 2Q8 and 2Q16 dosing groups, respectively, had a ≥2 step improvement, compared to patients receiving sham injections (15%). At week 100, the results seen at week 52 results were largely maintained with 50% and 62% of patients in the 2Q8→PRN and 2Q16 dosing groups, respectively having a ≥2 step improvement, compared to 12.8% patients receiving sham injections. No new safety signals were identified in this study. Aflibercept was shown to have a significant benefit for the treatment of diabetic retinopathy. The final clinical study report (CSR) is currently being finalized.

During the PBRER reporting period the MAH evaluated 9 safety topics cumulatively:

1. Arteriothromboembolic events (ATEs) (see **Appendix 12**)
2. Ischemic colitis (see **Appendix 12**)
3. Venous thromboembolic events (VTEs) (see **Appendix 12**)
4. Non-ocular hemorrhages (see **Appendix 12**)
5. Hypertension (see **Appendix 12**)
6. Artery dissection/aneurysm (see **Appendix 10**)
7. Macular Hole (MH) (see **Appendix 8**).
8. Macular atrophy (MA)/geographic atrophy (GA) (see **Appendix 6**)
9. Retinal Hemorrhages (RH) (see **Appendix 7**)

Bases on the cumulative reviews no causal association to aflibercept therapy could be confirmed.

Conclusions

No new information has arisen during the reporting interval that would change the overall evaluation of benefit-risk for aflibercept when used in wet AMD, macular edema following CRVO or secondary to BRVO, DME, DR and mCNV.

Based on the evaluation of the cumulative safety data and the benefit-risk analysis, no changes to the CCDS are considered necessary.

There is currently no need for other additional risk minimization activities.

The benefit-risk balance for aflibercept is considered favorable.

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List of Abbreviations

0.5Q4	0.5 mg treatment given every 4 weeks
2Q4	2 mg treatment given every 4 weeks
2Q8	2 mg treatment given every 4 weeks for the first 5 months, thereafter every 8 weeks
ADR	Adverse Drug Reaction
AE	Adverse Event
AMD	Age-related Macular Degeneration
AP-ROP	aggressive posterior retinopathy of prematurity
APTC	Antiplatelet Trialists' Collaboration
ASNV	anterior segment neovascularization
ATE	Arterial Thromboembolic Event
AVG	average cell size
BCVA	Best Corrected Visual Acuity
BIOSIS	BioSciences Information Service of Biological Abstracts
BMI	Body Mass Index
BRVO	Branch Retinal Vein Occlusion
CCDS	Company Core Data Sheet
CCT	central corneal thickness
CFH	complement factor H
CFT	Central Foveal Thickness
CHO	Chinese Hamster Ovary
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CI-DME	center-involved diabetic macular edema
CMT	Central Macular Thickness
CN	corneal nerves
CNV	Choroidal Neovascularization
COPD	Chronic Obstructive Pulmonary Disease

CoV	coefficient of variation of cell size
CRT	Central Retinal Thickness
CRVO	Central Retinal Vein Occlusion
CSMT	central subfield mean thickness
CST	central subfield thickness
CVD	Cardiovascular Disease / choroidal vascular diameter
CVH	Choroidal Vascular Hyperpermeability
CT	Choroidal Thickness
CNVM	Choroidal neovascular membrane
CVOS	Central Vein Occlusion Study
DLP	Data Lock Point
DH	deep hemorrhages
DHCPL	Choroidal neovascular membrane
DME	Diabetic Macular Edema
DMPK	Drug Metabolism & Pharmacokinetics
DR	Diabetic Retinopathy
DRCR.net	Diabetic Retinopathy Clinical Research Network
DRSS	Diabetic Retinopathy Severity Scale
DSUR	Development Safety Update Report
eCRF	electronic case report form
ECD	endothelial cell density
EDV	end-diastolic velocity
EMA	European Medicines Agency
EMBASE	Excerpta Medica DataBASE
ETDRS	Early Treatment Diabetic Retinopathy Study
FA/FAG	fluorescein angiography
FAS	Full Analysis Set
FPFV	First Patient First Visit
FT	fibrovascular tissue
GA	Geographic atrophy

GVP	Guideline on Good Pharmacovigilance Practices
HCP	HealthCare Professional
HUS	hemolytic-uremic syndrome
IAI	intravitreal aflibercept injection
IAC	intraarterial chemotherapy
IB	Investigator's Brochure
IC	information component
ICH	International Conference on Harmonization
ICSR	Individual Case Safety Reports
ICGA	Indocyanine Green Angiography
Ig	Human Immunoglobulin
IgG1	Immunoglobulin G subclass 1
IMH	Idiopathic Macular Hole
IMPACT	International Management Package for the Administration of Clinical Trials
INR	International Normalized Ratio
IOP	Intraocular Pressure
IOI	intraocular inflammations
IRF	individual fluid regions
IRMA	intraretinal microvascular abnormalities
ISI	Ischemic index
ISS	Investigator Sponsored Study
IVA (IVA-AFL)	intravitreal aflibercept
IVB	intravitreal bevacizumab
IV/IVT	Intravitreal
J-PMS	Japanese post-marketing study
KDR	VEGFR2
KIDS-KD	Korean Institute of Drug Safety & Risk Management-Korea Adverse Event Reporting System Database
LLOQ	Lower Limit of Quantitation

LPLV	Last Patient Last Visit
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
LSFG	laser speckle flowgraphy
MA	Macular atrophy
MAH	Marketing Authorization Holder
MAX	maximum of cell size
MBR	mean blur rate
MC	Medically Confirmed
MedDRA	Medical Dictionary for Regulatory Activities
MEDLINE	Medical Literature Analysis and Retrieval System Online
MH	Macular Hole
MI	Myocardial Infarction
mCNV	Myopic Choroidal Neovascularization
MNP	macular non-perfusion
MRI	Medical Literature Analysis and Retrieval System Online
nc	not calculable
NEI VFQ	National Eye Institute Visual Function Questionnaire
NMC	Non-Medically Confirmed
NPDR	non-proliferative diabetic retinopathy
ns	non serious
NSAIDs	non-steroidal anti-inflammatory drug
NV	neovascularization
NVA	neovascularization of the angle
NVD	neovascularization of the optic disc
NVE	neovascularization elsewhere
NVG	Neovascular Glaucoma
NVI	Neovascularization of the iris
OCT	Optical Coherence Tomography
ONH	optic nerve head

OR	Odds Ratio
OSDI	ocular surface disease index
OU	Oculus Uterque (each eye/both eyes).
PASS	Post-Authorization Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PBS	Pharmaceutical Benefits Scheme
PFS	prefilled syringe
PCV	Polypoidal Choroidal Vasculopathy
PDR	proliferative diabetic retinopathy
PDT	Photodynamic Therapy
PED	Pigment Epithelial Detachment
PlGF	Placental Growth Factor
PPCNV	Peripapillary choroidal neovascularization
PPS	Per Protocol Set
PRAC	Pharmacovigilance Risk Assessment Committee
PRN	*pro re nata* (as needed)
PRP	panrentinal photocoagulation
PRR	Proportional Reporting Ratio
PSP	Patient Support Program
PSUR	Periodic Safety Update Report
PT	MedDRA Preferred Term
PTC	Product Technical Complaint
PS	propensity score
PSUR	Periodic Safety Update Report
PSV	peak-systolic velocity
PV	Pharmacovigilance Department
QPPV	Qualified Person for Pharmacovigilance
QoL	Quality of Life
QSI	Quantitative Safety Indicators
RAO	retinal artery occlusion

RAP	retinal angiomatous proliferation
REP	Rochester Epidemiology Project
RH	Retinal hemorrhage
RI	resistive index
RMP	Risk Management Plan
RNP	retinal non-perfusion
ROP	retinopathy of prematurity
ROR	reporting odds ratio
RPE	Retinal Pigment Epithelium
RSI	Reference Safety Information
RVO	Retinal Venous Occlusion
s	serious
SAE	Serious Adverse Event
SAF	Safety Analysis Flag
SD	Standard Deviation
SRF	subretinal fluid
STs	Summary Tabulations
SMQ	Standardized MedDRA Query
SOC	System Organ Class (MedDRA)
SUSAR	Serious Unexpected Adverse Drug Reaction
T&E	Treat and Extend
tCRAO	transitory central artery occlusion
TEAE	Treatment Emergent Adverse Event
TGA	Australian Health Authority
TIA	Transient Ischemic Attack
TMA	Thrombotic microangiopathies
TS	Translational Sciences
TTP	thrombotic thrombocytopenic purpura
TTO	time to onset
USA	United States of America

VA	Visual Acuity
VAS	visual analog scale
VB	venous beading
VEGF	Vascular Endothelial Growth Factor
VEGF-A	Vascular Endothelial Growth Factor A
VEGFR	VEGF Receptor may be of type 1 or type 2 (i.e. VEGFR1 or VEGFR2)
VMT	Vitreomacular Traction
vPDT	Verteporfin for Photodynamic Therapy
VTC	vision-threatening complication
VTE	Venous Thromboembolic Event or, for clinical trial sections, VEGF-Trap eye (Eylea)
WHO	World Health Organization

1. Introduction

This is the 9th Periodic Benefit-Risk Evaluation Report (PBRER) / Periodic Safety Update Report (PSUR) for aflibercept. The International Birth Date is 18 NOV 2011, United States of America (USA). The report covers the period from 01 DEC 2018 to 30 NOV 2019. It is prepared for regulatory authorities according to the Guideline on Good Pharmacovigilance Practices (GVP), Module VII (R1), consistent with ICH guideline E2C (R2).

Aflibercept is a co-development by Bayer AG and Regeneron Pharmaceuticals, Inc.

Regeneron Pharmaceuticals, Inc. is the marketing authorization holder (MAH) for aflibercept in the USA, whilst Bayer AG is the MAH outside of the USA.

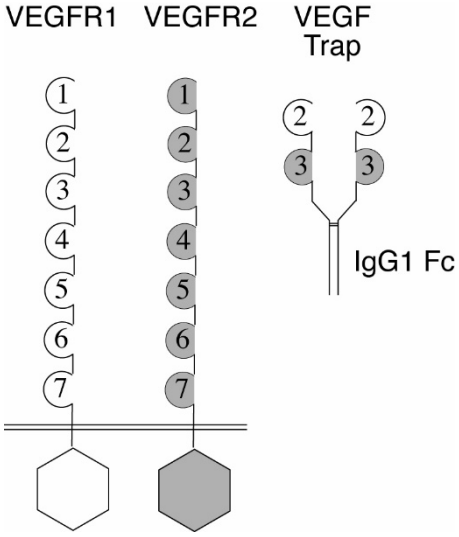
Formulations included in the report:

Eylea is a clear, colorless to pale yellow, iso-osmotic solution for injection (pH 6.2). One milliliter solution for injection contains 40 mg aflibercept.

Each single-dose, pre-filled syringe provides a usable amount to deliver a single dose of 50 µL containing 2 mg aflibercept.

Each vial provides a usable amount to deliver a single dose of 50 µL containing 2 mg aflibercept.

The active ingredient of Eylea is aflibercept. Aflibercept is a recombinant fusion protein consisting of human VEGF receptor (VEGFR) extracellular domains fused to the Fc portion of IgG1. It contains portions of the extracellular domains of 2 different VEGFRs (Figure 1-1).



IgG1: Immunoglobulin G subclass 1; VEGF: Vascular Endothelial Growth Factor; VEGFR1 or 2: VEGF Receptor of Type 1 or Type 2

Figure 1-1: Structure of Aflibercept

VEGFR1 (also known as Flt1) binds VEGF with high affinity (picomolar range), while VEGFR2 (also known as KDR or Flk1) binds VEGF much less tightly. The recombinant protein is expressed in Chinese Hamster Ovary (also known as CHO) K1 cells. Recovery and purification of the protein is accomplished via a combination of filtration and chromatographic techniques. Aflibercept is formulated for IVT administration.

Therapeutical class, mechanism of action:

Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR1 and VEGFR2, present on the surface of endothelial cells. PlGF binds only to VEGFR1, which is also present on the surface of leucocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularization and excessive vascular permeability. Further, PlGF can synergize with VEGF-A in these processes, and is also known to promote leucocyte infiltration and vascular inflammation (2). A variety of ocular diseases, including AMD, CRVO, DME, and mCNV, are associated with pathologic neovascularization and vascular leakage, and can result in thickening and edema of the retina, which is thought to contribute to vision loss.

These diseases are among the leading causes of acquired blindness in developed countries (3, 4).

Indications, populations being treated or studied:

The current reference safety information lists the following indications for Eylea:

- neovascular (wet) age-related macular degeneration (wet AMD)
- macular edema following central retinal vein occlusion (CRVO)
- macular edema secondary to branch retinal vein occlusion (BRVO)
- diabetic macular edema (DME)
- diabetic retinopathy (indication approved in USA)
- myopic choroidal neovascularization (myopic CNV)

Age-related macular degeneration is the most common degenerative disease of the macula and is the most common cause of legal blindness in the developed world. AMD is a disease of the elderly, and evidence suggests that 10% of individuals aged 65 to 74 years, and 30% of those aged 75 to 85 years, show signs of AMD (5). There are two forms of AMD, the dry and the wet form. The dry form is more benign and accounts for 90% of all AMD cases, but only for 10% of cases of blindness. Wet AMD affects 10% of the AMD patients and is the more aggressive form, which, if untreated, leads to rapid severe visual impairment and legal blindness. Anti-VEGF therapy has been shown to be effective in the treatment of neovascular AMD (6, 7).

Retinal venous occlusive disease is an important cause of vision loss particularly in patients with associated chronic macular edema (1). The two major forms of the disease are central vein and branch vein occlusions. Retinal vein occlusion commonly affects men and women equally and occurs predominantly in persons over the age of 65 years. In RVO, retinal ischemia occurs (more dramatically in CRVO, but also in BRVO to an extent depending on the importance of the occluded retinal branch) which signals the release of VEGF (8). Vascular endothelial growth factor (VEGF) has been reported to destabilize endothelial tight junctions and promote endothelial cell proliferation. Up-regulation of VEGF is associated with the breakdown of the blood/retina barrier, increased vascular permeability resulting in retinal edema, stimulation of endothelial cell growth, and neovascularization. Anti-VEGF therapy has been shown to be effective in the treatment of CRVO/BRVO.

Diabetic macular edema is a manifestation of diabetic retinopathy that may produce a loss of central vision. VEGF, which stimulates both angiogenesis and increases vascular permeability, is a major pathogenic factor in DME and plays a key role in the pathophysiology of DME (9). VEGF is increased in the vitreous and retina of patients with diabetes. Anti-VEGF therapy, therefore, represents a useful alternative therapeutic modality which targets the underlying pathogenesis of DME.

Diabetic Retinopathy (approved in USA)

In the Regeneron sponsored PANORAMA study, patients with moderately severe to severe NPDR were randomized 1:1:1 to receive aflibercept every 8 weeks following 5 initially monthly doses (2q8), aflibercept every 16 weeks following 3 initial monthly doses and 1 q8 interval, and sham injections. The primary outcome measure of the study is the proportion of patients who have improved by ≥2 steps from baseline on the DRSS in the combined 2Q8 and 2Q16 groups at week 24, and in each group separately at week 52. At week 24, a significant proportion of patients in the combined aflibercept dosing groups had a ≥2 step improvement from baseline on the DRSS compared to patients receiving sham injections (58% vs 6%). At week 52, 80% and 65% of patients in the 2Q8 and 2Q16 dosing groups, respectively, had a ≥2 step improvement, compared to patients receiving sham injections (15%). At week 100, the results seen at week 52 results were largely maintained with 50% and 62% of patients in the 2Q8→PRN and 2Q16 dosing groups, respectively having a ≥2 step improvement, compared to 12.8% patients receiving sham injections. No new safety signals were identified in this study. Aflibercept was shown to have a significant benefit for the treatment of diabetic retinopathy. The final clinical study report (CSR) is currently being finalized.

Myopic choroidal neovascularization is a frequent cause of vision loss in adults younger than 75 years of age (10). Pathologic myopia, the most severe form of myopia, may lead to myopic CNV as a complication. Eyes with pathologic myopia are elongated, often excessively, and have pathologic tissue alterations such as retinal pigment epithelial thinning and defects and lacquer cracks. These may lead to Bruch's membrane ruptures, choroidal neovascularization, sub-retinal hemorrhage, and choroidal atrophy, which ultimately lead to central macular degeneration and macular scarring (11). As a consequence of ruptures of Bruch's membrane, mCNV develops as a wound healing mechanism, and at the same time

represents the most vision-threatening complication of pathologic myopia. Substantial evidence has accumulated that VEGF plays an important role in the pathogenesis of ocular neovascularization including mCNV. There is evidence for the efficacy of anti-VEGF therapy in mCNV.

In addition, Eylea was investigated for the treatment of **neovascular glaucoma**. Neovascular glaucoma is a secondary glaucoma triggered by the formation of new blood vessels (neovascularization) on the iris and the anterior chamber angle. Neovascularization restricts aqueous outflow and consequently elevates intraocular pressure (IOP). Neovascular glaucoma is a serious condition that may lead to permanent loss of vision, a persistently painful eye and, especially in the advanced stages, is unlikely to respond to treatment. The management of NVG includes different strategies to lower the IOP. In addition to topical medication, cyclodestructive techniques and drainage procedures are used. Additionally, panretinal photocoagulation (PRP) and peripheral cryotherapy are applied in order to reduce the neovascular stimulus. As VEGF is a key modulator in the angiogenic cascade, its additional inhibition has been recently proposed as a therapeutic option in the treatment of NVG. Bayer did investigate Eylea treatment in NVG in a randomized, double-masked, sham-controlled phase 3 study in Japanese patients with NVG (VEGA Study, 17584). As VEGA showed clinically meaningful improvement of NVG but did formally not reach statistical significance of the primary endpoint, Bayer currently conducted an additional study in 16 patients to increase the pivotal trial experience for NVG (VENERA study). This additional single-arm open-label study in patients with NVG (VENERA, Study 19652) was completed during this reporting period. The VENERA study was a multicenter, single-arm, non-randomized, and open-label phase 3 trial to evaluate the primary efficacy variable “change in IOP from baseline to Week 1” of IVT administration of aflibercept in NVG patients. The study met its primary endpoint. The change in IOP from baseline to Week 1 (LOCF), was -8.3 ± 7.3 mmHg, with a 95% CI of -12.2 to -4.4 mmHg with an upper limit of the CI less than zero (pre-defined threshold) (p = 0.0004) for the PPS. The results of the secondary efficacy variable, the proportion of subjects with improvement in NVI grade at Week 1, and those of the exploratory efficacy variables on IOP, NVI (neovascularization of the iris) and NVA (neovascularization of the angle) also showed the clinically significant improvement after aflibercept injection. The results in IOP, NVI, and NVA consistently suggest that aflibercept could provide clinical meaningful improvements in efficacy in patients with NV. The phase III study program of Eylea in patients with neovascular glaucoma (VEGA/VENERA study) did not yield any new safety findings. In these studies, Eylea showed a similar safety profile compared to the safety profile in patients in the pivotal studies the in the indications wet AMD, BRVO, CRVO, DME and myopic CNV.

Retinopathy of prematurity is a complex disease process initiated in part by the lack of complete or normal retinal vascularization in premature infants. It typically involves abnormal development of the vascularization of the peripheral retina in premature infants only. ROP is only found in preterm infants (gestational age [GA] at birth <37 weeks). The disease may affect vision related and retinal anatomic outcomes, including causing retinal detachments in the more severe stages. The efficacy and safety of anti-VEGF agents for the treatment of ROP

have been evaluated in several case series and one large randomized controlled trial. The totality of the clinical evidence available indicates favorable results in regression of disease activity and prevention of unfavorable outcomes with anti-VEGF agents. Based on the pediatric written request from the FDA to evaluate the role of intravitreal aflibercept in the management of Retinopathy of Prematurity, Regeneron is conducting a Phase 3 randomized, controlled, multi-center study (BUTTERFLEYE) to assess the efficacy, safety, and tolerability of intravitreal aflibercept compared to laser photocoagulation in patients with retinopathy of prematurity. Bayer AG is the sponsor of the FIREFLEYE study, which is an ongoing phase 3, multicenter, randomized, 2-arm, open-label clinical study to assess the efficacy, safety and tolerability of 0.4 mg IVT aflibercept per treatment-requiring eye versus laser photocoagulation in subjects with treatment-naive ROP. A phase 3b extension study (study "FIREFLEYE NEXT") is planned to assess the long-term outcomes of patients who received study intervention in the ongoing FIREFLEYE phase 3 study, following them up until they are 5 years of age, to assess ocular effects, clinical and neurodevelopmental outcomes. All treated patients from the ongoing FIREFLEYE study must be offered participation in this follow-up. No study treatment will be administered in the extension study.

2. Worldwide Marketing Approval Status

The first marketing authorization for aflibercept (2 mg) in the indication neovascular (wet) AMD marketed by Regeneron Pharmaceuticals was granted in USA on 18 NOV 2011 and the first launch in USA was on 21 NOV 2011. The first marketing authorization for aflibercept outside USA marketed by Bayer Pharma was granted in Australia on 07 MAR 2012 and the first launch outside the USA was in OCT 2012 in Colombia.

Eylea® is currently authorized to be marketed in 110 countries and is marketed in 94 countries.

Authorized indications for Eylea® are:

- neovascular (wet) age-related macular degeneration (wet AMD)
- macular edema following central retinal vein occlusion (CRVO)
- macular edema secondary to branch retinal vein occlusion (BRVO)
- diabetic macular edema (DME)
- diabetic retinopathy (DR; indication approved in USA)
- myopic choroidal neovascularization (myopic CNV)

A tabular overview of the worldwide marketing authorization status and the invented trade names for VEGF Trap-Eye is provided in **Appendix 1**.

3. Actions Taken in the Reporting Interval for Safety Reasons

During the period of this report, no significant actions related to safety were taken by the marketing authorization holder, sponsors of clinical trial(s), data monitoring committees, ethics committees or competent authorities that could have a significant influence on the risk-benefit balance of the authorized medicinal product; and/or an impact on the conduct of a specific clinical trial(s) or on the overall clinical development program.

In JUL 2019 in Australia four adverse event reports of culture positive endophthalmitis (3 x Staph epidermidis, 1 Staph aureus) were reported to Bayer in association with a specific batch of Eylea. The review of the product complaints and adverse events databases did not identify a potential batch related issue. The cases were proactively communicated to HCPs to hold vials from that batch until quality investigation completed. Further, proactive communication to Australian HA (TGA) and wholesalers was done. TGA issued a Quarantine Notification. No quality defect was identified by Bayer for this batch and the Quarantine was closed out in AUG 2019.

December 2019: Physicians in Israel were concerned with intraocular inflammations following the injection of Eylea with 3 particular batches (KT03900, KT033KP, KT037VV). The Ministry of Health in Israel distributed a local DHCPL asking HCPs to avoid using these 3 batches until all quality investigations are completed (see also late-breaking information received after DLP). Not more than 5 cases of intraocular inflammation were received per batch, cases were spread across the months, some cultures returned negative and some were positive for different microorganisms (Staph. epidermidis, unspecified Streptococcus, Streptococcus viridans, Granulitacella adiacens). No further intraocular inflammation case from any other country worldwide was received from other batches coming from the same drug product batch. To date, no quality deficit of any of the 3 batches could be confirmed by Bayer or its filling facility. In the meantime, the Israeli Ministry of Health concluded their sterility investigations without any findings and communicated that the batches can continue to be used (January 2020).

Overall, to date no product related safety concern could be identified that would have led to the development of intraocular inflammations. The global reporting rate of intraocular inflammation rate remained stable, no increase was observed. These findings are considered local occurrences and do not change the positive benefit risk assessment of Eylea

For safety-related changes made to the Reference Safety Information during the report interval, see next section.

4. Changes to Reference Safety Information

The Company Core Data Sheets (CCDS) 12, dated 02 FEB 2018 (provided with the last PBRER/PSUR) and 13, dated 12 FEB 2019 (**Appendix 2)** for Aflibercept were used as the Reference Safety Information (RSI) for the reporting period 01 DEC 2018 to 30 NOV 2019 and were considered for this PBRER/PSUR.

In CCDS No 13, the Instructions for use/handling were updated related to description and illustrations for the new pre-filled syringe. This label update will be submitted to the authorities for implementation with the change to the new pre-filled syringe.

During the reporting period, changes were made to the CCDS and provided as part of the respective PBRER/PSUR.

New CCDS text is shown below in ***bold Italics***, deletions are ~~crossed out~~, unchanged text is shown in standard font. The updated illustrations are not included:

CCDS version 13, dated 12 FEB 2019

6.6 Instructions for use / handling

…

Pre-filled syringe:

…

3. To remove the syringe cap, hold the syringe in one hand while using your other hand to grasp the syringe cap with the thumb and fore finger. Please note: ~~Snap off (do not turn or twist),~~ ***Twist off (do not snap off) the syringe cap.***

New illustration

…

5. Using aseptic technique, firmly twist the injection needle onto the Luer-lock syringe tip.

New illustration

6. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top

New illustration

7. To eliminate all bubbles and to expel excess drug, slowly depress the plunger ***rod*** to align the cylindrical base of the ~~dome~~ plunger ***dome edge*** with the black dosing line on the syringe (equivalent to 50 microliters)

New illustrations

…

Vials:

…

9. Eliminate all bubbles and expel excess drug by slowly depressing the plunger so that the plunger tip aligns with the line that marks 0.05 mL on the syringe.

Corrected illustration

…

5. Estimated Exposure and Use Patterns

5.1 Cumulative Subject Exposure in Clinical Trals

A total of 4,635 patients have received at least one dose of Eylea in the Eylea clinical trial program including all wet AMD, CRVO, BRVO, myopic CNV, and DME studies (see Table 5-1). Please note that in this table only the number of exposed patients that is available in the Integrated Database has been considered (reference EU RMP 26.1).

Additional exposed patients in the ongoing or completed clinical trials during this reporting period are displayed in section 7.

Table 5-1: No. of subjects who were exposed to Eylea in the wet AMD, CRVO, BRVO, myopic CNV and DME studies (all enrolled subjects)

Study identifier	N enrolled	N not randomized	N randomized	Treatment group [a]	No. in SAF
Total	8455	2996	5459	**VTE total**	**4,635**
				VTE ≤1 mg	738
				VTE 2 mg	3,999
				VTE 4 mg	93
			Wet AMD		
VGFT-OD-0508 (SN 14394) *->VGFT-OD-0702*	299	140	159	**VTE total**	**157**
				VTE ≤1 mg	64
				VTE 2 mg	117
				VTE 4 mg	31
VGFT-OD-0502[b] (SN 14395) *->VGFT-OD-0702*	91	40	51	**VTE total**	**49**
				VTE ≤1 mg	29
				VTE 2 mg	22
				VTE 4 mg	37
VGFT-OD-0603 (SN 14396) *->VGFT-OD-0702*	30	10	20	**VTE total**	**20**
				VTE 2 mg	14
				VTE 4 mg	20
311523 (VIEW 2)	2031	791	1240	**VTE total**	**913**
				VTE ≤1 mg	297
				VTE 2 mg	616
311561 (VIEW 1) (VGFT-OD-0605) -> SN 14832 (extension study VGFT-OD-0910)	2073	856	1217	**VTE total**	**980**
				VTE ≤1 mg	304
				VTE 2 mg	763

Table 5-1: No. of subjects who were exposed to Eylea in the wet AMD, CRVO, BRVO, myopic CNV and DME studies (all enrolled subjects)

Study identifier	N enrolled	N not randomized	N randomized	Treatment group [a]	No. in SAF
SIGHT	451	147	304	**VTE total**	**299**
(SN 13406)				VTE 2 mg	299
ALTAIR (1 year)	288	41	247	**VTE total**	**254**
(SN 17668)				VTE 2 mg	254
				VTE total[c]	***2,672***
			CRVO		
14130	240	63	177	**VTE total**	**146**
(GALILEO)				VTE 2 mg	146
14232	273	85	188	**VTE total**	**171**
(COPERNICUS)				VTE 2 mg	171
				CRVO VTE total[c]	***317***
			BRVO		
15432 (VGFTe-RVO-1027)	281	98	183	**VTE total**	**158**
(VIBRANT)				VTE 2 mg	158
				BRVO VTE total[c]	**158**
			myopic CNV		
15170	173	51	122	**VTE total**	**116**
(MYRROR)				VTE 2 mg	116
				myopic CNV VTE total[c]	**116**
			DME		
VGFT-OD-0512	11	6	5	**VTE total**	**5**
(Phase I)				VTE 4 mg	5
VGFT-OD-0706	284	64	220	**VTE total**	**175**
(SN 13336)				VTE ≤1 mg	44
(DA VINCI)				VTE 2 mg	131
91745	604	198	404	**VTE total**	**380**
(VIVID-DME)				VTE 2 mg	380
VGFT-OD-1009	687	221	466	**VTE total**	**441**
(VISTA-DME)				VTE 2 mg	441
15657 [d]	100	27	73	**VTE total**	**72**
(VIVID-JAPAN)				VTE 2 mg	72
15161	539	158	381	**VTE total**	**299**
(VIVID-EAST)				VTE 2 mg	299
				DME VTE total[c]	***1,372***

VTE = VEGF-Trap Eye (Eylea)
a: Subjects may have received more than one dose. These subjects are considered for each dose, but once for VTE total.
b: SN 14395 (VGFT-OD-502): Part B is excluded from analysis.
c: VTE total per indication added by author.
d: Please note that one randomized and treated patient was excluded from the SAF because of his/her withdrawal of informed consent.
Source: Integrated Analysis - Pool 3 RMP exposure / AMD (up to year 3), CRVO (w76/100), BRVO (1y), DME (3y), mCNV (1y); Table 1.2/1

5.2 Cumulative and Interval Patient Exposure from Marketing Experience

5.2.1 Post-Authorization (Non-Clinical Trial) Exposure

Patient exposure and cumulative number of vials sold, during this reporting period, are based on two different cut-off-dates due to publicly availability, i.e. for Regeneron Pharmaceuticals Inc. 30 SEP 2019 (USA), and for Bayer HealthCare 30 NOV 2019 (rest of the world).

Post-authorization (Non-clinical Trial) Exposure, Calculation for Indication

The above estimations are used to determine the proportion of patients in the approved indications. This will be combined with the estimated number of vials used per patient per year.

The following assumptions are made based on posology and clinical trial experience.

Age-related Macular Degeneration: Based on the epidemiological analyses of the prevalence, it is estimated that 52% of patients using aflibercept are AMD patients. It is assumed that (in the first year) 7 injections are administered per patient (7 vials per year) based on the posology of 3 loading doses then every 8 weeks dosing to Week 52. The first year's regimen is used for calculating patient exposure as the injection frequency in the following months is dependent on the individual patient's visual outcome and cannot be standardized.

Central Retinal Vein Occlusion: Based on the epidemiological analyses of the prevalence, it is estimated that 6% of patients using aflibercept are CRVO patients. To determine the number of injections used per patient treated for macular edema secondary to CRVO, the most proper assessment was considered to be based on the 2 aflibercept randomized clinical control trials (Copernicus and Galileo) which resulted in a mean of 11.5 injections over 2 years with 8 in the first and 4 in the second year. This leads to an assumption of 6 vials per CRVO patient per year.

Branch Retinal Vein Occlusion: Based on the epidemiological analyses of the prevalence, it is estimated that 13% of patients using aflibercept are BRVO patients. In the VIBRANT study (1 year study duration) the mean number of injections over a one year period was 9 injections. Similar numbers of Eylea injections as in CRVO patients are to be expected over a longer treatment duration in BRVO patients, thus, similar to CRVO 6 vials per year on average are estimated per BRVO patient.

Diabetic Macular Edema: Based on the epidemiological analyses of the prevalence, it is estimated that 26% of patients using aflibercept are DME patients. It is assumed that (in the first year) 8 injections are administered per patient (8 vials per year) based on the posology of 5 loading doses then every 8 weeks dosing to Week 52. The first year's regimen is used for calculating patient exposure as the injection frequency in the following months is dependent on the individual patient's visual outcome and cannot be standardized.

Myopic Choroidal Neovascularization: Based on the epidemiological analyses of the prevalence, it is estimated that 3% of patients using aflibercept are mCNV patients. The recommended dose is 1 vial aflibercept per patient.

Taken together, this summarizes as follows:

- 52% of the patients have AMD (one patient needs 7 vials/year)
- 6% of the patients have CRVO (one patient needs 6 vials/year)
- 13% of the patients have BRVO (one patient needs 6 vials/year)
- 26% of the patients have DME (one patient needs 8 vials/year)
- 3% of the patients have mCNV (one patient needs 1 vials/year)

Patient exposure is estimated according to the following calculations:

Across the indications AMD, CRVO, BRVO, DME and mCNV the mean number of vials that a patient needs per year is:

$$0.52\times7 + 0.06\times6 + 0.13\times6 + 0.26\times8 + 0.03\times1 = 6.89$$

If X is the total number of vials used (sold) then the number of patient years (NPY) is:

$$X/(0.52\times7 + 0.06\times6 + 0.13\times6 + 0.26\times8 + 0.03\times1) = NPY$$

0.52×NPY is the number of patient years treated for AMD

0.06×NPY is the number of patient years treated for CRVO

0.13×NPY is the number of patient years treated for BRVO

0.26×NPY is the number of patient years treated for DME

0.03×NPY is the number of patient years treated for mCNV

Post-Authorization (Non-Clinical Trial) Exposure

- Cumulative worldwide sales volume of aflibercept from first launch until 30 NOV 2019 was 31,286,095 vials. Patient exposure and cumulative number of vials sold, during this reporting period, are based on two different cut-off-dates due to publicly availability, i.e. for Regeneron Pharmaceuticals Inc. 30 SEP 2019 (USA), and for Bayer AG 30 NOV 2019 (rest of the world). Cumulative sales volume of aflibercept in the United States was 12,311,752 vials and in the rest of the world 18,974,343 vials.
- In the reporting period 7,590,564 vials have been sold (see Table 5-2).

Post-authorization (Non-clinical Trial) Exposure, Calculation for Indication

Age Related Macular Degeneration: The estimated amount of sold aflibercept corresponds to an cumulative exposure of approximately 2,361,215 patient-years until 30 NOV 2019 and

an overall exposure of approximately 572,873 patient-years for the reporting period in the post marketing setting for the indication AMD (see Table 5-2).

Central Retinal Vein Occlusion: The estimated amount of sold aflibercept corresponds to a cumulative exposure of approximately 272,448 patient-years until 30 NOV 2019 and an exposure of approximately 66,101 patient-years for the reporting period in the post marketing setting for the indication CRVO (see Table 5-2).

Branch Retinal Vein Occlusion: The estimated amount of sold aflibercept corresponds to a cumulative exposure of approximately 590,304 patient-years until 30 NOV 2019 and an exposure of approximately 143,218 patient-years for the reporting period in the post marketing setting for the indication BRVO (see Table 5-2).

Diabetic Macular Edema: The estimated amount of sold aflibercept corresponds to a cumulative exposure of approximately 1,180,607 patient-years until 30 NOV 2019 and an exposure of approximately 286,436 patient-years for the reporting period in the post marketing setting for the indication DME (see Table 5-2).

Myopic Choroidal Neovascularization: The estimated amount of sold aflibercept corresponds to a cumulative exposure of approximately 136,224 patient-years until 30 NOV 2019 and an exposure of approximately 33,050 patient-years for the reporting period in the post marketing setting for the indication mCNV (see Table 5-2).

Table 5-2: Sales Figures in Number of Vials and Patient Exposure in Patient Years by Indications

Previous Period: 01 DEC 2017 to 30 NOV 2018*						
Number of Vials	Patient Years/Indication					Total Patient Years
	AMD	CRVO	BRVO	DME	mCNV	
6,646,784	501,644	57,882	125,411	250,822	28,941	964,700

Current Period: 01 DEC 2018 to 30 NOV 2019*						
Number of Vials	Patient Years/Indication					Total Patient Years
	AMD	CRVO	BRVO	DME	mCNV	
7,590,564	572,873	66,101	143,218	286,436	33,050	1,101,678

*Postmarketing exposure numbers from last PSUR period were corrected as inadvertently distributed Procedure Packs (do not contain Eylea vials) were included in the exposure calculation.

This corresponds approximately to an overall cumulative exposure to aflibercept of 4,540,798 patient-years until 30 NOV 2019 and an overall exposure of 1,101,678 patient-years for the reporting period.

Compared to the previous period, the number of patient exposure in patient years, increased by approximately 14.2%.

5.3 Post-authorization Use in Special Populations

No new safety relevant information on post-authorization use of aflibercept in special populations is available.

5.4 Other Post-authorization Use

There has been no information on specific patterns of post-authorization use considered relevant for the interpretation of safety data.

6. Data in Summary Tabulations

The data in the Summary Tabulations (STs) appended to this report are based on those reports that were received by the company and registered in the global safety database at the time of data lock point. This may include cases that have not undergone complete processing, and therefore include events for which the MedDRA coding process has not been finalized.

Adverse events are sorted by primary system organ class and include only diagnoses and not the associated symptoms.

The seriousness of adverse events/reactions in the STs corresponds to the seriousness assigned to events/reactions in the ICSRs.

According the Good Pharmacovigilance Practice, Module VI, special situations (lack of drug effect, exposure during pregnancy, exposure from breast milk, overdose, abuse, off-label use, misuse, medication error, occupational use and lack of therapeutic efficacy) should be captured as adverse events and coded via MedDRA terminology. This is done by Bayer since 05 NOV 2012.

6.1 Reference Information

MedDRA Version 22.1 was used for adverse event coding for all new cases in all appended line listings and summary tabulations.

6.2 Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

A **cumulative** summary tabulation of all serious adverse events (SAEs) from all aflibercept studies is given in **Appendix 3a.**

The term “clinical trial” refers to interventional clinical trials.

In case of ongoing masked clinical trials, treatment is unmasked only for cases with serious unexpected ADRs (SUSARs) in all line listings and summary tabulations. For all other cases reported from ongoing masked studies, treatment is kept masked.

Possible medication types for SAEs from clinical trials include “verum”, “comparator”, “placebo”, “masked”, “additional study medication”, “study medication not given”, and “unknown”. In case a medication type is not display in a column, this means that no SAE with

the respective medication type is entered in the database. The category "additional study medication" refers to study medications that are not identical to the PBRER/PSUR drug. The category "unknown" refers to study medications that are not identical to the PBRER/PSUR drug and for which the field "study medication type" has the value "unknown" or is empty.

6.3 Interval Summary Tabulations of Serious Adverse Events from Clinical Trials

Following PSUR # 7 (reporting period: 01 DEC 2016 to 30 NOV 2017) the PRAC Rapporteur requested a separate listing of Summary Tabulations of Serious Adverse Events from Clinical Trials **for the reporting interval.**

An **interval** summary tabulation of all serious adverse events (SAEs) from all aflibercept studies is given in **Appendix 3b.**

6.4 Cumulative and Interval Summary Tabulations from Post-marketing Data Sources

Cumulative and interval summary tabulation of all spontaneous ICSRs, and adverse reactions derived from non-interventional studies, and other solicited sources for aflibercept are given in **Appendix 3c.**

Columns "Spontaneous, including regulatory authority and literature": Serious and non-serious events are included. All events from spontaneously reported cases are included, regardless of the causal relationship assessment for the individual event.

Columns "Non-interventional post-marketing studies and other solicited sources": Serious adverse reactions are included. Non-serious reactions and unrelated events are not included.

7. Summaries of Significant Safety Findings from Clinical Trials during the Reporting Interval

This section presents relevant interventional clinical studies sponsored by Bayer AG (and its affiliates) or by Regeneron which were completed and analyzed, or ongoing during the reporting period.

Non-interventional studies are addressed in chapter 8.

Post-authorization safety studies that were completed or ongoing during the PBRER/PSUR interval are not addressed in this section: They are included in the table in **Appendix 4** and referred to in chapter 8.

Relevant ongoing Bayer AG and Regeneron sponsored interventional studies are tabulated in **Appendix 5a.**

An overview of completed studies (approved Clinical Study Report during the reporting period) can be found in **Appendix 5b.**

7.1 Completed Clinical Trials

The section on completed clinical trials refers to relevant interventional studies.

A tabulated overview of completed clinical trials can be found in **Appendix 5b.**

The following study was completed during the reporting period:

- VENERA study (Trial No. 19652); Sponsor Bayer AG

VENERA study (Trial No. 19652); Sponsor Bayer AG

VENERA was a multicenter, single-arm, non-randomized and open-label phase 3 study evaluating the efficacy, safety and tolerability of intravitreal aflibercept in Japanese patients with neovascular glaucoma (NVG).

The primary objective was to assess the efficacy of IVT administration of aflibercept on the change in intraocular pressure (IOP) in patients with NVG. The primary efficacy variable was the change in IOP from baseline to Week 1 of IVT administration of aflibercept in NVG patients. The secondary efficacy variable was proportions of subjects who had improved NVI grade from baseline to Week 1. The secondary objective was to assess the safety and tolerability of IVT administration of aflibercept in patients with NVG. This study focused on short-term efficacy at Week 1 after a single dose of aflibercept and patients were followed-up to Week 5 for safety assessment. NVG patients have a high probability of permanent vision loss if IOP is not properly controlled. To provide benefit to the patients in the study, the concomitant use of topical IOP-lowering drug therapy was required from screening, and only patients who did not achieve control of IOP before baseline with conventional therapy were assigned.

A total of 17 subjects were screened, and 16 subjects were assigned and received the study treatment. Of 16 subjects who received the study treatment, all subjects had IOP measurement at both baseline and Week 1 (completed treatment). Fifteen subjects completed the follow-up period; whereas, 1 subject did not complete the follow-up due to subject withdrawal. All of the 16 treated subjects were included in the per protocol set (PPS), full analysis set (FAS) and the safety analysis set (SAF), and these 3 analysis sets were identical.

All of the 16 assigned subjects were Asian (Japanese) and most of them (12 subjects, 75.0%) were male. The age of the subjects ranged from 43 to 82 years, with a mean and standard deviation (SD) of 65.6 ± 12.9 years. The baseline weight was 66.3 ± 12.16 kg, the baseline height was 163.27 ± 9.71 cm, and the baseline body mass index (BMI) was 24.85 ± 3.96 kg/m2. The study was conducted at 7 study centers in Japan.

Efficacy results

Primary efficacy variable

The IOP (mean ± SD) was 34.1 ± 6.7 mmHg at baseline and 25.8 ± 8.0 mmHg at Week 1. The change of IOP from baseline to Week 1 was -8.3 ± 7.3 mmHg with a two-sided 95% CI

of -12.2 to -4.4 mmHg (p = 0.0004). This study was regarded as success, as the upper limit of the CI was less than zero (pre-defined threshold).

Secondary efficacy variables

The proportion of subjects with improvement in NVI grade (at least 1 NVI grade decrease) at Week 1 was 81.3% (13/16 subjects, 95% CI: 54.4% to 96.0%).

Exploratory efficacy variables

IOP

IOP and change in IOP from baseline to each visit:

The IOP (mean ± SD) decreased to 25.8 ± 8.0 mmHg at Week 1 from baseline (34.1 ± 6.7 mmHg) (change from baseline: -8.3 ± 7.3 mmHg). The IOP further decreased to 22.6 ± 7.9 mmHg (change from baseline: -11.6 ± 7.5 mmHg) at Week 2 and 18.6 ± 7.8 mmHg (change from baseline: -15.5 ± 8.8 mmHg) at Week 5.

Proportion of subjects who controlled IOP (≤ 21 mmHg) at each visit:

The proportion of subjects with a controlled IOP (≤21 mmHg) was 43.8% (7/16 subjects, 95% CI: 19.8% to 70.1%) at Week 1. The proportion increased up to 56.3% (9/16 subjects) at Week 2, and further increased to 86.7% (13/15 subjects) at Week 5.

NVI

NVI and change in NVI grade from baseline to each visit:

From baseline to Week 1, 6 of 16 subjects (37.5%) gained 1 NVI grade decrease, and 7 of 16 subjects gained at least than 1 NVI grade decrease, which led to a decrease in the proportion of the subjects with a higher NVI grade (from 25.0% to 12.5% in grade 3, and 6.3% to 0.0% in grade 4). At Week 5, 5 of 16 subjects (33.3%) gained 1 NVI grade decrease, and 8 of 16 subjects gained at least 1 NVI grade decrease from baseline, resulting in 80.0% of the subjects (12/15 subjects) with grade 0 and each 1 of 15 subject (6.7%) with grade 1, 2 and 3.
Proportion of subjects who had improved NVI grade from baseline to each visit:

The NVI grade was improved in most of the subjects (13/16 subjects, 81.3%) at Week 1. The improvement of NVI grade continued until Week 5 (13/15 subjects, 86.7%).

NVA (neovascularization of the angle)

Proportion of subjects who had improved NVA grade from baseline to Week 1:

The proportion of subjects with improvement in NVA grade from baseline to Week 1 was 50.0% (8/16 subjects, 95% CI: 24.7% to 75.3%).

NVA and change in NVA grade from baseline to each visit:

From baseline to Week 1, 2 of 16 subjects (12.5%) gained 1 NVA grade decrease, and 6 of 16 subjects (37.5%) gained at least 1 NVA grade decrease, which led to decrease in the proportion of the subjects with a higher NVA grade (from 56.3% [9/16 subjects] to 31.3% [5/16 subjects] in grade 3). At Week 5, 4 of 15 subjects (26.7%) gained 1 NVA grade decrease, and 6 of 15 subjects (40.0 %) gained at least 1 NVA grade decrease, resulting in 60.0% of the subjects (9/15 subjects) with grade 0, 1 of 15 subject (6.7%) with grade 1 and 5 of 15 subjects (33.3%) with grade 3 or 4. One subject (6.3%) showed the deterioration of NVA grade (changing from Grade 3 to Grade 4) at Week 2, and another subject showed the similar deterioration of NVA grade at Week 5 (2 subjects [13.3%] were totally categorized into Grade 4).

Proportion of subjects who had improved NVA grade from baseline to each visit:

The NVA grade was improved in 8 of 16 subjects (50.0%) at Week 1. The improvement of NVA grade continued until Week 5 (10/15 subjects, 66.7%).

Safety evaluation

Safety variables were similar to those of aflibercept clinical trials for other diseases, i.e. adverse events (AEs), physical examination, vital signs (body temperature, blood pressure and pulse rate), clinical laboratory findings (hematological test, blood biochemical examination and urine test), and ophthalmic examinations (indirect ophthalmoscopy, slit-lamp microscopy and gonioscopy). Visual acuity testing, which is used to evaluate visual functions in patients with glaucoma, and applanation tonometry, which is used to evaluate IOP after IVT injection, were also to be performed as a safety evaluation.

At least one TEAE was observed in 6 subjects (37.5%). TEAEs which were considered study drug-related by the investigator occurred in 1 subject (6.3%), and injection procedure-related TEAEs occurred in 2 subjects (12.5%). The maximum intensity of the TEAEs was moderate (2 subjects, 12.5%) or mild (4 subjects, 25.0%); there were no subjects experienced severe TEAEs. The serious TEAE was observed only in 1 subject (6.3%). TEAEs with outcome of death, and TEAEs leading to permanent discontinuation of the study drug were not reported in this study. The most frequently reported events were events belonging to the SOC “Eye disorders”, which were reported in 4 subjects (25.0%). In this SOC, eye pain was the most frequent TEAE reported in 4 subjects (25.0%).

At least one ocular TEAE in the study eye was observed in 4 subjects (25.0%). Ocular TEAEs in the study eye which were considered study drug-related by the investigator were not reported. The IVT injection procedure-related TEAEs in the study eye occurred in 2 subjects (12.5%). The maximum intensity of the ocular TEAEs in the study eye was moderate (1 subject, 6.3%) or mild (3 subjects, 18.8%); there were no subjects experienced severe TEAEs. The serious ocular TEAEs in the study eye were not observed. All ocularTEAEs in the study eye were related to the SOC “Eye disorders”. In this SOC, eye pain was the most frequent ocular TEAE reported in 4 subjects (25.0%). In addition, corneal erosion and eye pruritus were observed in 1 subject (6.3%) each.

Ocular TEAEs in the fellow eye were not observed.

Non-ocular TEAEs occurred in 3 subjects (18.8%). As a non-ocular TEAE, nasopharyngitis, pneumonia, and headache were reported in 1 subject (6.3%) each.

Study drug-related TEAEs occurred in 1 subject (6.3%); headache was observed in 1 subject (6.3%). There was no study drug-related ocular TEAE in the study eye and the fellow eye.

Serious TEAE occurred in 1 subject. This patient experienced pneumonia (MedDRA PT) with intensity of moderate, considered not related to the study drug. There were no serious ocular TEAEs.

There were no notable changes in laboratory parameters and vital signs for the study population as a whole.

Overall conclusions

Considering all the efficacy and safety results in this study, aflibercept is beneficial for the treatment of patients with NVG as it offers clinically meaningful improvements in efficacy; seen in the first week on treatment and continued until the end of the observation period - paired with well-established and tolerable safety profile and a possibility to prevent disease progression.

7.2 Ongoing Clinical Trials

The section on ongoing clinical trials refers to relevant interventional studies. AZURE is a PAES and PASS study. VIOLET (Trial No.17613) is a PAES and PASS study. Other PASS studies are addressed separately in chapter 8.

A tabulated overview of ongoing clinical trials can be found in **Appendix 5a.**

The following studies were ongoing during the reporting period:

In adult subjects:

- AZURE study (Trial No. 16598); Sponsor: Bayer AG (PAES study)
- VIOLET (Trial No. 17613); Sponsor: Bayer AG (PAES study)
- ARIES study (Trial No. 17508); Sponsor: Bayer AG
- CENTERA study (Trial No. 17514); Sponsor: Bayer AG
- PANORAMA (VGFTe-OD-1411) – Sponsor: Regeneron Pharmaceuticals, Inc.

In pediatric subjects:

- FIREFLEYE study (Trial No. 20090); Sponsor Bayer AG
- BUTTERFLEYE (VGFTe-ROP-1920): Sponsor: Regeneron Pharmaceuticals, INC

AZURE study (Trial No. 16598); Sponsor: Bayer AG

AZURE is a post-approval efficacy study from the European Medicines Agency (EMA) to assess in a population neovascular AMD patients every-other-month dosing versus a regimen with gradually extended treatment intervals and no maximum limit to the treatment interval. This phase-3b PAES compares a fixed dosing regimen of 2 mg aflibercept administered every 8 weeks ("2Q8 group") to a flexible extended regimen of 2 mg aflibercept ("extended dosing group") in patients with neovascular AMD who have completed at least 1 year of treatment with aflibercept. First patient first visit was on 29 SEP 2015. A total of 330 patients are planned to be enrolled.

As of 30 NOV 2019, 470 patients have been screened and 336 patients have been randomized and received treatment.

To date, no new safety signals were derived from this study.

VIOLET study (Trial No. 17613); Sponsor: Bayer AG

As a condition for approval, the European Medicines Agency (EMA) has required a study to collect further data regarding second year of treatment in DME patients including information on treatment cessation and restart.

This Phase 3b, open-label, randomized, active-controlled, parallel-group study is being conducted to evaluate the efficacy, safety, and tolerability of three different treatment regimens of 2 mg aflibercept administered by intravitreal injections to subjects with diabetic macular edema (DME) after at least 1 year of treatment with 5 initial monthly injections followed by injections every 2 months. As of 30 NOV 2019, a total of 500 subjects were enrolled and 463 were randomized to one of three dosing regimens: fixed-dosing regimen every 8 weeks (2Q8fix, 155 subjects) with no monitoring visits between treatment visits (reference arm), a flexible-dosing regimen with gradually extended dosing interval (≥ 8 weeks, no upper limit) according to the current EU label (2Q8ext, 154 subjects) with no monitoring visits between treatment visits, or a *pro re nata* dosing regimen (2PRN, 154 subjects) with monthly monitoring. The 52 weeks primary endpoint results showed similar and small mean increases from baseline in all 3 treatment arms with mean changes of 0.4 ± 6.7 letters in the 2Q8fix arm, 0.5 ± 6.7 letters in the 2Q8ext arm, and 1.7 ± 6.8 letters in the 2PRN arm and demonstrated that the 2Q8ext and 2PRN arms were both non-inferior to the 2Q8fix arm. The safety profile was similar to the one observed for other indications. The study is ongoing until week 100.

ARIES study (Trial No. 17508); Sponsor: Bayer

This is a multicenter, randomized, open-label, active-controlled, parallel-group, Phase 3b/4 study in subjects with neovascular AMD (nAMD) to assess the non-inferiority of a 2-mg IVT aflibercept Treat and Extend (T&E) dosing regimen initiated after the first 8-weekly treatment interval (3 initial monthly doses followed by 1 dose 2Q8; then treatment individualization) to a 2-mg IVT aflibercept T&E dosing regimen per label (3 initial monthly doses followed by 5 doses 2Q8; treatment individualized after year 1).

The primary objective of the study is to assess whether 2 mg IVT aflibercept administered in an early-start T&E regimen (initiated after the first 8-weekly treatment interval) is non-inferior to 2 mg IVT aflibercept administered in a late-start T&E regimen (initiated at the end of Year 1, per label) in subjects with nAMD. The primary efficacy variable is the change in BCVA as measured by the ETDRS letter score from Week 16 to Week 104.

The study is conducted in 39 sites in 8 countries: 5 sites in Australia, 3 in Canada, 2 in France, 8 in Germany, 4 in Italy, 3 in Spain, 5 in the UK, and 9 in Hungary. A target of approx. 383 patients was to be screened and 259 patients randomized. Randomization was done at the week 16 visit in a 1:1 ratio into the early-start T&E regimen arm versus the late-start T&E regimen study arm.

According to the randomization the treatment intervals may be extended based on the visual and anatomic outcomes from week 16 (early T&E arm) or week 52 (late T&E arm) on.

As of 30 NOV 2019, the study has fully enrolled, (i.e. a total of 443 subjects were enrolled, with 271 subjects randomized (at week 16, 135 subjects to the early start T&E, and 136 subjects to the late-start T&E group). As of week, 104, 287 patients were treated with aflibercept and were included in the SAF. Of the 287 treated subjects, 16 subjects were treated during the initiation phase but not randomized to a treatment arm after the initiation phase. At Week 16, a total of 271 subjects were randomized stratified by visual outcomes from baseline to Week 16 (<8 or ≥8 letters gain in BCVA) to receive treatment under one of the 2 dosing regimens. A total of 23 subjects (9 in the early-start T&E arm and 14 in the late-start T&E arm) were mis-stratified due to data entry errors in the interactive web/voice response system. All subjects from the SAF were also included in the FAS (N=269) with the exception of the 16 subjects who were treated but not randomized and 2 additional subjects, one in each treatment arm, who had Week 16 but no post-Week-16 BCVA data. Of the 269 subjects included in the FAS, 59 subjects in total were excluded from the PPS (N=210) due to being injection intensive between Week 16 and Week 52, violation of in- or exclusion criteria, or a treatment duration shorter than 52 weeks. and 269 patients comprised the FAS. 132 patients were treated in the Early Start T&E group and 134 in the Fixed Q8 group. Baseline BCVA (SAF) was 60.8 (±12.0) and 60,0 (±12.6) for the two treatment groups respectively. The mean change in BCVA from Week 16 (i.e. time point of randomization to the two treatment groups) and Week 104 was -2.1 $\pm$ 11.4 letters for the Early start T&E treatment arm and --0.4 $\pm$ 8.4 letters in the late-start T&E treatment arm with a mean of 12(±2.3) and 13 (±1.8) aflibercept injections, respectively Non-inferiority of the early-start T&E regimen to the late-start T&E regimen was demonstrated by the main analysis of the primary efficacy variable (change in BCVA as measured by the ETDRS letter score from Week 16 to Week 104).

The safety profile of aflibercept was similar in both treatment arms. No new safety signals were derived from this study and aflibercept was well tolerated. The final clinical study report is under preparation.

CENTERA study (Trial No. 17514); Sponsor: Bayer

This is an international, multi-center, prospective, interventional, single-arm cohort, phase 4 study in adult subjects with a diagnosis of macular edema secondary to CRVO who have previously had not been treated with any systemic or IVT anti-vascular endothelial growth factor treatments. Intravitreal aflibercept will be administered to the study eye at specific intervals, with the possibility to extend the treatment interval based on visual and anatomic outcomes as judged by the treating investigator.

The primary objective is to determine the efficacy and durability (treatment interval) of 2mg intravitreal aflibercept in a Treat and Extend (T&E) regimen over a period of 76 weeks using protocol-defined visual and anatomic criteria in subjects with macular edema secondary to central retinal vein occlusion.

The study is conducted in approximately 40 sites in Australia, Canada, Denmark, France, Germany, Italy, Spain, and UK. It was planned to enroll 160 subjects in this study. Subjects were to receive the first treatment at the baseline visit on Day1. The treatment phase comprises an initiation phase followed by a T&E phase. During the T&E phase all subjects will be treated with IVT aflibercept using a T&E approach.

As of 30 NOV 2019, the study has fully enrolled 162 patients receiving at least 1 study treatment. To date, no new safety signals were derived from this study.

PANORAMA Study (Trial Nr. VGFTe-OD-1411), Sponsor: Regeneron Pharmaceuticals Inc.

PANORAMA Study (Trial Nr. VGFTe-OD-1411) –

Sponsor: Regeneron Pharmaceuticals Inc.

The PANORAMA study is a phase 3, double-masked, randomized study of the efficacy and safety of IVT aflibercept for the improvement of moderately severe to severe non-proliferative diabetic retinopathy (NPDR).

The primary objective of the study is to assess the efficacy of intravitreal (IVT) aflibercept compared to sham treatment in the improvement of moderately severe to severe NPDR.

Eligible patients were enrolled into 1 of 3 treatment groups in a 1:1:1 ratio and will be treated as follows through week 48: 1) 2Q8 aflibercept IVT after 5 initial monthly doses; 2) 2Q16 aflibercept IVT after 3 initial monthly doses and 1 8-week interval; and 3) sham treatment. In year 2 (beginning at week 56), all dosing will continue as indicated except in the 2Q8 group which will be treated with a flexible dosing regimen.

The primary outcome measure of the study is the proportion of patients who have improved by ≥2 steps from baseline on the DRSS in the combined 2Q8 and 2Q16 groups at week 24, and in each group separately at week 52. Enrollment is complete with 402 subjects randomized.

At week 24 a significant proportion of patients in the combined aflibercept dosing groups had a ≥2 step improvement from baseline on the DRSS compared to patients receiving sham injections (58% vs 6%). At week 52, 80% and 65% of patients in the 2Q8 and 2Q16 dosing groups, respectively, had a ≥2 step improvement, compared to patients receiving sham injections (15%). In addition, there was a 82-85% reduction in the number of patients developing a vision-threatening complication (VTC, defined as proliferative diabetic retinopathy [PDR]/anterior segment neovascularization [ASNV]) and a 68-74% reduction in the number of patients developing center-involved diabetic macular edema (CI-DME) in the 2Q8 and 2Q16 aflibercept dosing groups compared to sham treatment. At week 100, the results seen at week 52 results were largely maintained with 50% and 62% of patients in the 2Q8→PRN and 2Q16 dosing groups, respectively having a ≥2 step improvement, compared to 12.8% patients receiving sham injections. There was a 77-83% reduction in the number of patients developing a VTC and a 68-76% reduction in the number of patients developing CI-DME over 100 weeks in the 2Q8→PRN and 2Q16 aflibercept dosing groups compared to sham treatment. No new safety signals were identified in this study. The final clinical study report (CSR) is currently being finalized.

FIREFLEYE study (Trial No. 20090); Sponsor Bayer AG

The FIREFLEYE study is a phase 3., multicenter, randomized, 2-arm, open-label clinical study to assess the efficacy, safety and tolerability of 0.4 mg IVT aflibercept per treatment-requiring eye versus laser photocoagulation in subjects with treatment-naive retinopathy of prematurity (ROP). A minimum of 102 preterm infants are planned to be randomized to achieve at least 102 subjects evaluable for the primary analysis. Subjects will be randomized 2:1 to receive treatment with an IVT injection of aflibercept 0.4 mg/0.01 mL (approximately 68 subjects) or laser photocoagulation (approximately 34 subjects). Subjects randomized to aflibercept will receive a single IVT injection of 0.4 mg aflibercept/0.01 mL per eligible eye at baseline. Thereafter, if required, up to additional IVT injections of aflibercept 0.4 mg/0.01 mL (at intervals of at least 28 days) may be administered in case predefined retreatment criteria are met, or rescue treatment with laser may be performed as per predefined protocol criteria. Subjects in the laser treatment arm may be retreated with laser or rescued with aflibercept as per predefined criteria. Retreatment(s) with the subject's randomized treatment, or rescue treatment (laser for the aflibercept arm; aflibercept for the laser arm) are allowed if the specified criteria are met during the 23-week treatment period.

The primary efficacy endpoint is the proportion of patients with absence of active ROP and unfavorable structural outcomes at 24 weeks after starting study treatment.

Secondary efficacy endpoints include the requirement for intervention with a second treatment modality from baseline to week 24, the recurrence of ROP from baseline to week 24, and the exploration of the new ROP activity scale proposed by the International Neonatal Consortium. Secondary objectives of this study is to assess the safety and tolerability of aflibercept, the treatment burden of aflibercept and laser and to describe the systemic exposure to aflibercept. The study population will consist of male and female preterm infants with treatment-naïve ROP Zone I Stage 1 plus, 2 plus, 3 non-plus or plus, or Zone II Stage 2

plus or 3 plus or aggressive posterior retinopathy of prematurity (AP-ROP) according to the International Classification for ROP. Subjects are eligible for study inclusion if their gestational age at birth is < 32 weeks or birth weight is <1500 g, and if their weight at the time of study treatment is at least 800 mg. The first patient was treated on 26 SEP 2019. As of 30 NOV 2019, 21 subjects were randomized and treated (aflibercept: 14, laser: 7). To date, no new safety signals were derived from this study.

A Phase 3b study (Study 20275; extension study) is planned to assess the long-term outcomes of patients who received study intervention in the ongoing 20090 phase 3 study. All treated patients from the ongoing FIREFLEYE study (20090) must be offered participation in a follow-up Study 20275 (FIREFLEYE NEXT) until they are 5 years of age to assess ocular effects, clinical and neurodevelopmental outcomes (no study treatment will be administered). The Sponsor plans to provide data at the time of marketing authorization application on structural abnormalities at 1 year of chronological age from at least 50% of the subjects enrolled into follow-up Study 20275.

BUTTERFLEYE Study (VGFTe-ROP-1920), Sponsor: Regeneron Pharmaceuticals, Inc,

The BUTTERFLYEYE study is a Phase 3 Randomized, Controlled, Multi-Center Study to Assess the Efficacy, Safety, and Tolerability of Intravitreal Aflibercept Compared to Laser Photocoagulation in Patients with Retinopathy of Prematurity

The study consists of screening/baseline (1 or 2 visits), a treatment period (including potential retreatment and rescue treatment), and a final visit at week 52 of chronological age. The study also includes an optional fluorescein angiography (FA) sub-study, which includes optional FA at baseline, and mandatory FA at week 52 of chronological age.

The primary objective of the study is to assess the efficacy of aflibercept compared to laser in patients diagnosed with ROP.

The primary endpoint is the proportion of patients with absence of active ROP and of unfavorable structural outcomes at week 52 of chronological age, as determined by the Investigator. For patients with both eyes enrolled in the study, both eyes must meet the endpoint. Unfavorable structural outcomes are defined as retinal detachment, macular dragging, macular fold, or retrolental opacity.

As of 30 NOV 2019, one patient has been enrolled and treated in this study.

7.3 Long-term Follow-up

No new safety relevant information on long-term follow up has become available during the reporting period.

7.4 Other Therapeutic Use of Medicinal Product

During the period of this PBRER/PSUR there have not been any significant findings from other programs that would change the positive benefit risk profile of aflibercept.

7.5 New Safety Data Related to Fixed Combination Therapies

There were no clinical activities with combination therapies in this reporting period.

8. Findings from Non-Interventional Studies

Post-authorization safety studies that are ongoing during the PBRER/PSUR interval are specifically indicated and included in the table in **Appendix 4**.

For details on the ongoing second PASS to measure the effectiveness of the Eylea Educational Material in the EU please refer to section 16.5.

No relevant safety information or information with potential impact in the benefit-risk assessment became available in the reporting period from non-interventional studies.

18636 - Dot et al (2019) (12) described the 1-year interim results of the APOLLON study, a 2-year real-world observational, prospective trial into the outcomes of DME patients treated with aflibercept. Patients who were treatment naïve (n=77) had higher baseline BCVA scores (62.7 letters) than previously treated patients (n=70; 60.0 letters). At 12 months, after a mean of 7.6 injections for all patients, the change in BCVA was greater in treatment naïve patients than in previously treated patients (+7.8 letters versus +5.0 letters, no p-value given). The mean change in CRT from baseline to Month 12 was -121 µm in the treatment naïve group and -141 µm in the previously treated group (no p-value given). Ocular AEs were reported in 54.1% of patients – the most common being cataract (4.4%) and diabetic retinal edema (3.1%)

16641 - This study was a regulatory Japanese post-marketing study (J-PMS) or PASS, to reconfirm the clinical usefulness and, in particular, the safety profile of aflibercept. This was a prospective, non-interventional, multicenter post-authorization 2-year safety study of patients with a diagnosis of macula edema secondary to CRVO. The selection of aflibercept treatment as well as the decision to use aflibercept according the Japanese Package Insert was made by investigator discretion prior to enrolling patients in this study. Patients were followed for a time period of 2 years or until it was no longer possible (e.g. lost to follow-up) within the 2-years. In total, 300 patients were recruited. For each patient, data were collected as defined in the electronic case report form (eCRF) at the initial visit, follow-up visits and final visit by routine clinical visits (as per investigator's routine practice). The physician was to enter the records of the study variables under real-life practice conditions of all patients enrolled in this study.

A total of 396 patients were enrolled, of whom the case report forms were collected with the data locked for 378 patients. Of the 378 patients, 377 patients were included in the safety analysis set, after exclusion of 1 patient who received no doses of aflibercept. Of these patients in the safety analysis set, 360 patients were included in the effectiveness analysis set, after exclusion of 17 patients (for the reasons of un-assessable best corrected visual acuity [decimal acuity, ETDRS] or central retinal thickness). The investigator or a delegate used the electronic CRF to document study data with procedures that followed routine practice. Data sources were patient medical records that were available in paper or electronic form, any

results obtained by examinations and assessments done in routine practice, or any information obtained by the patient or other treating physicians.

Safety results: among 377 patients in the safety analysis set, 27 adverse events occurred in 22 patients (5.8%). Serious adverse events were 2 events of retinal vein occlusion, 1 event each of glaucoma, cataract, malignant glaucoma, cataract operation, pneumonia bacterial, mesothelioma malignant, facial paralysis, cardiac failure, myocardial infarction, familial amyloidosis, and death. There were 20 ocular adverse events reported, including 4 events of intraocular pressure increased; 2 events each of glaucoma, ocular hypertension, and retinal vein occlusion; and 1 event each of cataract, conjunctivitis allergic, corneal infiltrates, posterior capsule opacification, retinal hemorrhage, vitreous hemorrhage, malignant glaucoma, intraocular pressure decreased, retinal laser coagulation, and cataract operation. There were 5 adverse reactions in 5 patients (1.3%). Specifically, these adverse reactions were 3 events of intraocular pressure increased and 1 event each of retinal vein occlusion and malignant glaucoma. There were no non-ocular adverse reactions reported. In terms of the conditions identified in the safety specification for aflibercept, i.e., arterial thromboembolic events (i.e., nonfatal stroke, nonfatal myocardial infarction, vascular death), intraocular inflammation, intraocular pressure increased, retinal tear, retinal detachment and traumatic cataract, the following adverse events were reported: 4 cases of intraocular pressure increased, 2 of ocular hypertension and 1 of myocardial infarction. Of these, 3 cases of intraocular pressure increased were adverse reactions. These results were consistent with the safety profile of aflibercept described in the labeling.

Effectiveness results - The mean number of IVT-AFL injections was 4.0±2.5 over the 2-year period. The percentage of cases with “Improved” or “Maintained” visual acuity at 2 years of Aflibercept treatment was 87.8%. The mean visual acuity (converted to logMAR values) improved from 0.752 ± 0.535 (n=213) at baseline to 0.609 ± 0.561 (n=214) at 2 years of Aflibercept treatment. The mean central retinal thickness was 558.9 ± 229.8 μm (n=110) at baseline and decreased to 335.4 ± 166.6 μm (n=131) at 2 years of Aflibercept treatment. Out of 116 cases of non-ischemic CRVO at baseline, 0 cases had progression to ischemic CRVO at 6 months of Aflibercept treatment, and 2 cases had progression to ischemic CRVO at 2-years of aflibercept treatment. There were no new safety concerns observed in this study, and the safety results were consistent with other aflibercept RVO studies, although the number of treatments were lower and visual acuity gains were thus consequently smaller than reported in RCTs.

17416 - This study was a regulatory Japanese post-marketing study (J-PMS) or PASS, to reconfirm the clinical usefulness and, in particular, the safety profile of aflibercept. This was a prospective, non-interventional, multicenter post-authorization 2-year safety study of patients with a diagnosis of myopic CNV (mCNV). The selection of aflibercept treatment as well as the decision to use aflibercept according the Japanese Package Insert was made by investigator discretion prior to enrolling patients in this study. Patients were followed for a time period of 2 years or until it was no longer possible (e.g. lost to follow-up) within the 2-years. In total, 300 patients were recruited. For each patient, data were collected as defined

in the electronic case report form (eCRF) at the initial visit, follow-up visits and final visit by routine clinical visits (as per investigator's routine practice). The physician was to enter the records of the study variables under real-life practice conditions of all patients enrolled in this study. No notable safety concerns specific to mCNV patients treated with aflibercept were observed in the pivotal clinical trial. Thus, additional safety information related to the drug in real practice was collected by a special drug use investigation (AMD), since the number of Japanese patients receiving treatment with the drug in the pivotal clinical trial was small. To assess at least one major common adverse event with an incidence of 1% or more in mCNV, a sample size of 300 cases is necessary (95% power). The investigator or a delegate used the eCRF to document study data. The procedures follow a routine practice. Data sources were the patients' medical records that were available in paper or electronic form, besides any results obtained by examinations and assessments done in routine practice or any information obtained by the patient or other treating physicians.

Safety: among the 348 patients in the safety analysis set, 17 adverse events occurred in 12 patients (3.4%). Serious adverse events were 2 events each of macular hole and retinal detachment, and 1 event each of intraocular inflammation, prostate cancer, and quadriplegia. A total of 13 ocular adverse events were reported. Specifically, these events were 3 events of macular hole, 3 events of iritis, 2 events each of retinal detachment and retinoschisis, and 1 event each of intraocular inflammation, conjunctivitis allergic, and ocular hypertension. A total of 8 adverse reactions occurred in 7 patients (2.0%). Of these, 6 events were ocular adverse reactions, specifically, 3 events of iritis, 2 events of retinoschisis, and 1 event of ocular hypertension. Non-ocular adverse reactions were 1 event each of headache and asthenia. No serious adverse reactions were reported.

In terms of the conditions identified in the safety specification for aflibercept, i.e., arterial thromboembolic events (i.e., nonfatal stroke, nonfatal myocardial infarction, vascular death), intraocular inflammation, intraocular pressure increased, retinal tear, retinal detachment and traumatic cataract, the following adverse reactions were reported: intraocular inflammation in 4 patients (iritis in 3 patients, intraocular inflammation in 1 patient), intraocular pressure increased in 1 patient (ocular hypertension), retinal tear and retinal detachment in 7 patients (macular hole in 3 patients, retinal detachment in 2 patients, and retinoschisis in 2 patients). Adverse reactions were intraocular inflammation (iritis) in 3 patients, intraocular pressure increased (ocular hypertension) in 1 patient, and retinal tear and retinal detachment (retinoschisis) in 2 patients. These results were consistent with the safety profile of aflibercept described in the labeling.

Effectiveness: the percentage of cases with "Improved" or "Maintained" visual acuity during the first 1 month of Aflibercept therapy was approximately 91.4%. The visual acuity (logMAR scale) improved from 0.607 ± 0.452 (n=209) at baseline to 0.443 ± 0.450 (n=209) at 1 year of Aflibercept therapy. The central retinal thickness decreased from 332.8 ± 110.9 μm (n=120) at baseline to 268.4 ± 79.1 μm (n=136) at 1 year of Aflibercept therapy. There were no new safety concerns observed in this study, and the safety results were consistent with the aflibercept mCNV MYRROR RCT.

16469: This prospective, company sponsored, 4-month, observational, multi-center study documents observational data on subjects under routine treatment of wet age-related macular degeneration(wAMD), macular edema secondary to RVO, diabetic macular edema (DME) and myopic choroidal neovascularization (mCNV) with Eylea®. The standard observation period of 4 months for each subject from the date of first intravitreal injection of Eylea® in Korea. This study was a company sponsored and single-arm prospective cohort observational study of subjects seeking treatment with Eylea® for wAMD, RVO, DME, and mCNV which are approved for marketing authorization and is considered a PASS. The subjects were included in this study by investigators who are prescribing Eylea® routinely in their clinical practice. The decision for treatment with intravitreal aflibercept was made by the treating ophthalmologist prior to and independent of study inclusion. All decisions in terms of diagnostic procedures, treatments and management of the disease were fully dependent on mutual agreement between the patient and the investigator. No study drug was provided by Bayer. All data required for the aims of this study was collected during routine visits or by phone. It was planned to include a total of 3,750 patients in Korea, the number which considers 20% drop out, although the minimum regulatory requirement for recruitment was 3,000. The given reexamination period is 6 years from time of product approval and the recruitment period starts from the time of actual product launch (expected 1Q 2014). If the Eylea® treatment was terminated prior to 4 month or 8-month, AE tracking was conducted up to 90 days after last study injection. Patients were followed for 4 months after the start of Eylea® treatment and for 8 months based on investigator's decision. Statistical methods Statistical analyses were of explorative and descriptive nature. All analyses were performed for the total study population (overall analysis). Subjects taking at least one injection of Eylea® and AE monitoring were included in the safety analysis.

Safety: during the entire reporting period, AE incidence was 2.84% (90/3,169 subjects, 113 cases). Among them, the incidence of ADRs whose causality with the study medication could not be excluded was 1.70% (54/3,169 subjects, 62 cases). SAE incidence was 0.35% (11/3,169 subjects, 15 cases). Of them, the incidence of SAEs whose causality with the study medication could not be excluded was 0.09% (3/3,169 subjects, 3 cases). Incidence of ocular-related AEs was 1.80% (57/3,169 subjects, 67 cases). Among them, incidence of ocular-related ADRs SAEs whose causality with the study medication could not be excluded was 1.20% (38/3,169 subjects, 41 cases).

Effectiveness: BCVA analysis in wAMD subjects showed that the mean was 0.62 ± 0.42 at baseline, 0.47 ± 0.39 at 4 months, and 0.45 ± 0.30 at 8 months. The mean BCVA at 4 months compared with baseline was 0.15 ± 0.31, which was statistically significant ($p < 0.0001$). In DME subjects, results showed it was 0.58±0.36 on average at the Baseline; 0.35±0.26 on average at Month 4; and 0.36±0.33 on average at Month 8. BCVA at Month 4 compared to the Baseline decreased by 0.27±0.22 on average, which was statistically significant ($p<0.0001$). In the wAMD subjects, the eyes of which the VA was maintained or improved were 93.25% (1,588/1,703 subjects) at Month 4 after injection of Eylea and 92.35% (881/954 subjects) at Month 8 after injection of Eylea®. In the DME subjects, the eyes of which the VA was maintained or improved were 100% at Month 4 and Month 8 after injection of Eylea®

(28/28 subjects and 6/6 subjects, each). 93.25% (1,588/1,703 subjects) at Month 4 after injection of Eylea and 92.35% (881/954 subjects) at Month 8 after injection of Eylea®. In the DME subjects, the eyes of which the VA was maintained or improved were 100% at Month 4 and Month 8 after injection of Eylea® (28/28 subjects and 6/6 subjects,

Prunte et al (2019) (13) reported on the ASTERIA study, a 4-year retrospective and prospective, observational study to explore the outcomes of eyes with nAMD treated with aflibercept T&E. After 1 year of T&E treatment patients gained a mean of 8.4 ± 14.4 letters (n=139, mean number of injections=8.8) and at 2 years patients gained a mean of 5.0 ± 11.4 letters (n=95, mean number of injections in year 2=6.3). The last maintained injection interval at 2 years was 65.9 ± 28.3 days (40% of patients had an interval of <8 weeks). There were no serious AEs to aflibercept

9. Information from Other Clinical Trials and Sources

No relevant safety information with potential impact on the benefit-risk assessment became available in the reporting period from any other clinical trials.

9.1 Other Clinical Trials

Not applicable.

9.2 Medication Errors

For the evaluation of new data on the potential risk of medication error and misuse please refer to section 16.3.5.

Please also refer to the regional **Appendix R06** on the numbers of Preferred Terms (PT) in '[SMQ] Medication errors [Narrow]' reported with serious or non-serious adverse reaction(s) from post-authorization sources for AFLIBERCEPT 01 DEC 2018 to 30 NOV 2019.

10. Non-Clinical Data

No relevant safety information with potential impact on the benefit-risk assessment of Eylea 2mg became available in the reporting period from any non- clinical trial/study source.

11. Literature

A standardized search in the literature databases MEDLINE, EMBASE, BIOSIS, Derwent Drug File, Science Citation Index, and Chemical Abstracts was performed for articles relating to aflibercept covering the period of this report. Retrieved abstracts and/or full texts were reviewed for important efficacy and safety findings. Adverse reactions deriving from published individual case reports are included in the summary tabulations in **Appendix 3c**.

Publications referring to signals and risks are presented and discussed under the relevant topics in chapter 15 and 16 of this PBRER/PSUR.

Articles containing relevant safety findings are presented below. The bibliography of these articles is given at the end of this document.

11.1 Newly Identified Information on Safety

Geographic atrophy (GA)/macular atrophy (MA):

Following the last PSUR#8 the MAH was requested to conduct a cumulative review on the topic macular/geographic atrophy. In the final PSUR Assessment Report it was stated that *.."regarding the "geographic atrophy" / "macular atrophy" signal which emerged in the last PSUSA from literature, based on new articles published during the review period, Eylea may have a contributory role. Regarding "macular atrophy" / "geographic atrophy" a cumulative review of post-marketing data should be provided in the next PSUR, along with a complete analysis of the cases, including medical history, the number of aflibercept injections before the event, aflibercept's indication, concomitant treatment(s), the onset latency and the outcome."* As per PRAC request a cumulative review on this topic was conducted and can be found in **Appendix 6.** Overall, from the totality of data evaluated, incidental detection of GA/MA in a closely-monitored population in which GA/MA is expected to commonly occur, possibly in conjunction with unmasking of pre-existing atrophy with reduction of macular edema, is considered to be the most likely explanation for the GA/MA events reported during treatment with aflibercept. The results of the review do not support the assumption of a causal effect of IVT aflibercept in the development of GA/MA.

A cumulative review of literature on this topic (as of 01 OCT 2019) was included in the overall topic evaluation (**Appendix 6**). All relevant articles received during this reporting period are covered in the cumulative review presented in Appendix 6. No further relevant publication was identified until the DLP of this PSUR.

Most relevant articles pertaining to GA/MA received only during this reporting period include one randomized trial and observational studies:

Randomized trial

The RIVAL study (Gillies MC, Hunyor AP, Arnold JJ, Guymer RH, Wolf S, Pecheur FL, et al. Macular Atrophy in Neovascular Age-Related Macular Degeneration: A Randomized Clinical Trial Comparing Ranibizumab and Aflibercept (RIVAL Study). Ophthalmology. 2019.) (14) was a randomized, partially masked, multicenter trial that investigated differences in the development of MA over 24 months between treat-and-extend ranibizumab and aflibercept in patients aged 50 years or older with active, treatment-naive subfoveal CNV secondary to neovascular AMD. Two hundred seventy-eight patients were included in the analysis (ranibizumab 0.5 mg, N=141; aflibercept 2.0 mg, N=137). Mean change in square root area of MA from baseline to month 24 was +0.36 mm (95% CI, 0.27-0.45 mm) for ranibizumab and +0.28 mm (95% CI, 0.19-0.37 mm) for aflibercept (treatment difference,

+0.08 mm [95% CI, -0.05 to 0.21 mm]; P=0.24). The proportion of patients with MA increased from 7% (10/141) to 37% (43/117) for ranibizumab and from 6% (8/137) to 32% (35/108) for aflibercept from baseline to month 24. The average number of injections received per year was similar between both groups.

The authors noted that natural history studies of untreated patients have reported faster growth rates than those observed in this study, and concluded that there was no statistical difference between ranibizumab and aflibercept in the development of MA in neovascular AMD patients treated over 24 months and that both treatments achieved similar visual acuities and retinal thickness improvements with similar numbers of injections and comparable safety results.

Observational Studies:

The identified observational studies included between 30 and 197 eyes; the mean number of injections ranged from 7 to 20 and follow-up duration was up to 4 years. The frequency of new GA/MA or GA/MA progression (as per endpoint definition of the respective study) during the observational period ranged from 10-53%. Most of the studies included patients treated with any anti-VEGF agent (not only aflibercept) and evaluated effects of anti-VEGF agents as a class. None of the reviewed studies included a non-anti-VEGF comparator group.

Six studies were identified that evaluated whether development or growth of GA/MA correlated with the number of anti-VEGF injections. Of these, 5 studies found no correlation (15-19), one reported a negative correlation (20).

Some reviewed studies compared GA/MA incidence or progression rates between different anti-VEGF agents. One study received during this reporting period is a 12-month study in 30 mCNV eyes which observed more pronounced thinning of the foveal choroid but no statistically significant difference in progression of chorioretinal atrophy (21). Three studies found no difference in GA/MA incidence or progression rates between different anti-VEGF (16-18).

In multiple regression analyses, patient age and duration of underlying disease rather than treatment with anti-VEGF agents were found to be the strongest risk factors for development of GA/MA (15, 19).

MAH comment:

Development of GA is a possible natural course of AMD irrespective of any treatment, and this association confounds all of the above studies. Relevant publications identified during the reporting period did not raise a new safety concern for Eylea. No correlation was found regarding the number of injections to the contrary one publication showed a negative correlation with more atrophy development in patients treated with less injections. In addition. no difference was observed between the anti VEGF agents.

For the comprehensive cumulative review please refer to **Appendix 6**.

Retinal artery occlusion, retinal perfusion:

Consigli (22) et al. observed a 5,7% reduction of the calibers of retinal arteries in 12 eyes of 9 patients with DME (mean diameter 87,2µm at baseline, 82µm one week after the third injection). The authors discuss the results of this pilot study and state that it is unclear whether the reduction in artery diameter is a result of the pharmacodynamic anti-VEGF properties or result of the generally improved retinal hemostasis following anti-VEGF treatment.

Ciloglu (23) measured peak-systolic velocity (PSV), end-diastolic velocity (EDV) and resistive index (RI) one week and one month after aflibercept injection or dexamethasone implant in 47 patients with CRVO or BRVO.

In the CRVO group, they found a significant decrease in flow parameters in the ophthalmic artery and the central retinal artery after both dexamethasone implants and anti-VEGF injection without any significant difference between injection type. There was no difference in RI values.

In the BRVO group, there was no change in the flow parameters for the optic artery, but Vmax and Vmin values for the CRA were significantly decreased compared to the pre-injection with anti-VEGF. The authors conclude that intravitreal anti-VEGF and dexamethasone implant may induce retinal arteriolar vasoconstriction in patients with retinal vein occlusion.

Company comment: Anti-VEGF treatment may be associated with reduced NO-production and vasoconstriction. The clinical impact of potential vasoconstriction cannot be concluded from this publication.

Muralha et al (24)observed 18 cases of transitory central artery occlusion (TCRAO) in a series of 4,069 anti-VEGF injections (807 patients). TCRAO was defined as a sudden optic disc pallor and lack of pulsation of the central retinal artery, associated with unilateral painless loss of vision occurring immediately after the injection, lasting a few minutes. The mean IOP varied from 18.1 ± 2.20 mmHg, before the intravitreal injection, to 20.2 ± 1.75 mmHg just after the AE. When comparing mild and severe cases, the last one presented higher cup/optic disc ratio (p=0.03), positive carotid doppler test (p=0.01) and lower number of prior injections (p=0.01). The authors conclude that TCRAO is a rare adverse event with a tendency to occur more often in eyes with diabetic macular edema, after the first or second intravitreal injection of anti-VEGF, predominantly in female and elders over 60 years-old. Positive carotid Doppler test and higher cup/optic disc ratio could predict more severe cases.

Company comment: transient IOP increase is known to occur following intravitreal injection. The CCDS states that “in all cases, both the intraocular pressure and the perfusion of the optic nerve head must therefore be monitored and managed appropriately.”

Mursch-Edlmayr et al. (25) examined 20 patients with nAMD receiving aflibercept with laser speckle flowgraphy (LSFG) 10, 30 and 45 minutes after aflibercepts injection. In the injected eyes, mean blur rate (MBR, i.e. a relative measure of perfusion and the main outcome parameter of LSFG) within the major vessels of the ONH (optic nerve head) as well as at the

entire ONH region decreased significantly ($p < 0.001$). No change in MBR was observed in the fellow eye. Choroidal blood flow was maintained stable in both eyes. Decreased MBR was still observed after 30 and 45 minutes when IOP had normalized. The authors hypothesize a pharmacological effect for this observation.

Company Comment: transient increase of intra-ocular pressure is known to occur following intravitreal injection and may transiently affect retinal perfusion. A vasoconstrictive effect due to VEGF depletion after 30 minutes of injection remains questionable.

Clinical effects of aflibercept in the retina with significantly reduced perfusion were analyzed by Feltgen et al. (26) They compared the clinical outcomes of CRVO patients from the studies COPERNICUS and GALILEO depending on the retinal perfusion state at baseline defined by retinal capillary non-perfusion (RNP, i.e. non-perfusion in 10 or more disc areas) and macular non-perfusion (MNP). Patients with baseline RNP and MNP showed an equal increase in BCVA following aflibercept treatment compared to patients without RNP or MNP. Moreover, in this study (30), aflibercept treated eyes showed significant reductions in the proportion of subjects having RNP and MNP status at baseline by week 24 whereas the proportion with RNP/MNP for sham treated eyes remained at baseline levels. Similarly, in the VIBRANT study, the proportion of BRVO patients with baseline perfused status significantly increased by week 24 over laser treated patients.

Schmidt-Erfurth et al (27) presented a post-hoc analysis of the randomized controlled Bayer-sponsored VIVID-DME trial. Visual outcomes were compared between subgroups of patients either with or without central macular ischemia at baseline as assessed by capillary loss in fluorescein angiography. At weeks 52 and 100, BCVA outcomes in patients with DME treated with IVT-AFL (N=163) were superior to those of patients treated with laser photocoagulation (N=75), regardless of baseline macular ischemia. Treatment effect of both IVT-AFL combined treatments versus laser photocoagulation was not substantially affected by baseline ischemia status. Worsening of central ischemia was rare in all treatment groups. While differences were not statistically significant, macular ischemia resolved more frequently in patients undergoing treatment with IVT-AFL compared to laser (at week 100: 54.5% vs 47.1%, respectively). The authors concluded that functional outcomes post IVT-AFL treatment in patients with DME were unaffected by baseline macular ischemia status, and that IVT-AFL treatment did not adversely affect ischemia status.

Wykoff et al (28) evaluated changes in retinal perfusion status with intravitreal aflibercept injection (IAI) and laser treatment in the phase 3 VISTA study of patients with diabetic macular edema (DME). Retinal perfusion status was evaluated by fluorescein angiography based on the presence or absence of retinal non-perfusion (RNP) in quadrants intersecting at the optic nerve head. At week 100, the proportion of eyes with improvement in retinal perfusion in the laser control, 2q4, and 2q8 groups was 14.6%, 44.7%, and 40.0%, respectively. The proportion of eyes that experienced worsening in retinal perfusion at week 100 in the laser control, 2q4, and 2q8 groups was 25.0%, 9.0%, and 8.6%, respectively. The authors conclude that regular IAI dosing can not only slow worsening of retinal perfusion

associated with diabetic retinopathy but also may be able to improve retinal perfusion in some cases by decreasing zones of RNP.

Gao et al. (29) published results from a retrospective study evaluating the occurrence of retinal artery occlusion in a large tertiary care retina practice: A total of 16,686 unique patients received 125,108 anti- VEGF injections during the study period. Twelve patients developed a retinal artery occlusion (eight cases of central RAO and four cases of branch RAO) within 90 days of injection, resulting in an incidence of 1/1389 (0.072%). Four events occurred in 52,964 aflibercept injections (0.008%). The incidence was higher in patients with hypertension and retinal vein occlusion. The authors conclude that in the absence of a control it is unknown whether RAO was related to the intravitreal injection procedure, injected drug or comorbidities of these patients. Larger population-based studies may help confirm these findings and elucidate other underlying risk factors.

Company Comment: the company concurs with the authors that the study does not allow conclusion on a causal association with the anti-VEGF treatment.

Gupta et al. (30) evaluated the impact of intravitreal aflibercept on retinal non-perfusion (RNP) in eyes with proliferative diabetic retinopathy (PDR) with no macular edema. They analyzed 40 subjects with treatment naive PDR and substantial RNP (defined as > 20 disc areas). For the entire study sample the mean total RNP area at month 12 (280 ± 143 mm2) was increased but not significantly (p=0.12) when compared with baseline (242 ± 169 mm2). Ischemic index (ISI), however, was significantly (p=0.009) increased at month 12 (34 ± 17) compared with baseline (27 ± 16). The area of retinal neovascularization (NV) was significantly decreased at month 12. The authors concluded that despite dramatic reductions in the area of neo-vascularization, there was no significant reduction of RNP area with aflibercept among the enrolled PDR eyes with extensive RNP.

Company comment: The clinical relevance of these findings remains limited. The CLARITY study was conducted as an investigator led study evaluating aflibercept therapy in PDR patients, see also literature section on efficacy findings (Ramu et al). The study showed a significant increase in BCVA in the aflibercept treated PDR patients compared to patients treated with PRP at 52 weeks.

Overall company conclusion:

Anti-VEGF treatment may result in vasoconstriction due to reduced NO production. In line with this pathomechanism two publications reported vasoconstriction following intravitreal aflibercept injection. On the other hand, clinical data demonstrate that patients with ischemic retinal disease benefit equally from anti -VEGF treatment. Therefore, the clinical relevance of vasoconstrictive effects due to the anti-VEGF therapy appears to be remote.

Increase of IOP after injection may also affect retinal perfusion. This is appropriately addressed in the CCDS which states that “in all cases, both the intraocular pressure and the perfusion of the optic nerve head must therefore be monitored and managed appropriately.”

Hence it is concluded that the data from above publication do not warrant a change in the CCDS.

Changes in retinal nerve fiber layer, ganglion cell-inner plexiform layer, and choroidal thickness

Kim et al (31) investigated changes in retinal nerve fiber layer, ganglion cell-inner plexiform layer, and choroidal thickness in the macular area in patients with neovascular age-related macular degeneration who received repeated intravitreal ranibizumab and aflibercept treatments. This retrospective study included 90 eyes of 90 treatment-naive patients from a single center. Fifty eyes were treated with intravitreal injections of aflibercept, and 40 were treated with intravitreal injections of ranibizumab. Unaffected fellow eyes (71 eyes) were used as controls. The dosage was one injection per month for 3 consecutive months as an initial treatment. The patients were examined monthly for 6 months following the initial injection. Additional intravitreal injections were given reactively in an optical coherence tomography-guided pro re nata protocol. Measurements of the retinal nerve fiber layer, ganglion cell-inner plexiform layer, full retina, and choroidal thickness were simultaneously obtained via swept-source optical coherence tomography in the nine Early Treatment Diabetic Retinopathy Study subfields. Results showed that the retinal nerve fiber layer thickness in the nine Early Treatment Diabetic Retinopathy Study subfields did not differ significantly among the three study groups (aflibercept vs. ranibizumab vs. control). The ganglion cell-inner plexiform layer thickness was significantly reduced in the aflibercept group, while the choroidal thickness was reduced in both the aflibercept and ranibizumab groups. The authors conclude that long-term vascular endothelial growth factor inhibition by an anti-vascular endothelial growth factor agent that is trapped by neuronal and retinal pigment epithelium cells may adversely affect the function of physiological vascular endothelial growth factor and harm retinal cells and vessels.

MAH comment:

The clinical relevance of these findings in a small scale, single center and retrospective study covering a short observation period of 6 months remains equivocal. Fifty patients received 3.7 aflibercept injections in mean within the follow up period of 6 months. Aflibercept treatment resulted in improved BCVA. No deterioration or relevant impact on clinical safety was reported. These findings may be evaluated in the context of above topic on atrophy development during anti VEGF therapy. From the aflibercept postmarketing or clinical trial data over longer observation periods no clear causality can be established regarding the development of clinically relevant retinal damage and (macular) atrophy.

Post-injection pain

Two articles regarding post injection pain were identified**:**

Bilgin et al. conducted a study to compare the pain scores of the patients during intravitreal injection of ranibizumab and aflibercept based on patient feedback. Seventy-two eyes of 72 patients, who had not previously undergone any intravitreal injection procedures, were

included in this study. Thirty-eight patients received ranibizumab, and 34 patients received aflibercept injections. The pain was measured by visual analog scale (VAS). Patients were asked to rate their pain experienced during the injection between 0 (no pain) and 10 (worst pain ever felt) on VAS just after the injection. The study showed that VAS pain scores in ranibizumab and aflibercept groups were 3.28 ± 2.45 and 4.20 ± 2.30, respectively. There was a significant difference in average VAS pain scores between groups (P = 0.04). Authors concluded that VAS pain scores in aflibercept group were found to be significantly higher than the scores in the ranibizumab group (Bilgin et al. Assessment of patient pain experience during intravitreal ranibizumab and aflibercept injection. Middle East African Journal of Ophthalmology (2019) 26:2 (55-59) (32).

Ertan et al. conducted a study with the aimed to compare pain scores of patients during intravitreal aflibercept, ranibizumab or dexamethasone implant injection procedures. The study included 162 eyes of 162 patients, who received intravitreal ranibizumab, aflibercept or dexamethasone implant injections at our clinic. Following the injection, patients were asked to rate their pain from 0 (no pain) to 10 (worst pain) using a visual analogue pain score survey (VAS). VAS was evaluated according to age, sex, indication for the injection, number of previous intravitreal injections, and lens status in the study eye. Results showed that the mean VAS in the ranibizumab, aflibercept or dexamethasone implant groups was 3.38±2.31, 3.82±2.46, and 3.61±2.94, respectively. Female patients reported a higher average pain score than male patients (p = 0.02). Also, phakic patients reported a higher average pain score than pseudophakic patients (p = 0.01). Pain did not significantly correlate with indication for the injection, number of injections, and injection drugs (p>0.05). The authors concluded that pain associated with intravitreal injection is generally mild and associated with sex, age, and lens status. There was no significant difference in pain between intravitreal injections of dexamethasone implant, ranibizumab or aflibercept (Ertan et al. Comparison of pain during intravitreal dexamethasone, ranibizumab and aflibercept injection. Clinical & experimental optometry (2019) (33).

MAH comment:

Injection site pain and eye pain are listed ADRs for Eylea. No new safety concern was raised from these publications.

Intravitreal silicone

Thompson compared the incidence of silicone oil microdroplets in the vitreous of eyes with 6 or more intravitreal injections of the same anti-VEGF drug (34). It was a prospective cross-sectional study of 115 consecutive eyes receiving one of three anti-VEGF drugs for treatment of choroidal neovascularization, diabetic macular edema or macular edema from venous occlusive disease. The control group were 36 fellow eyes of patients receiving intravitreal injections with no prior intravitreal injections. The anterior and mid-vitreous were examined by slit lamp biomicroscopy with dilated pupil and ocular saccades to detect one or more silicone microdroplets in the vitreous. Each of the 3 anti-VEGF drugs was delivered with a different syringe type produced by same manufacturer (Becton Dickinson). Bevacizumab was

delivered with 0.3 ml polypropylene insulin syringes, ranibizumab with 1.0 polypropylene tuberculin syringes and aflibercept with 1.0 ml polycarbonate syringes. Silicone oil is used in small quantities to help lubricate the barrel of each of the three Becton Dickinson syringes. Results showed that silicone microdroplets were detected in 38/50 eyes (76%) receiving bevacizumab, 3/33 eyes (9.1%) receiving ranibizumab, 0/11 eyes (0%) receiving ranibizumab in silicone-free prefilled syringes, 7/21 eyes (33.3%) receiving aflibercept and 0/36 control eyes (0%). The difference in incidence of silicone microdroplets was significant when comparing bevacizumab to ranibizumab (P<.001), to ranibizumab prefilled syringes (P<.001), to aflibercept (P=.001), and to control eyes (P<.001). The difference in incidence of silicone microdroplets was also significant comparing aflibercept to ranibizumab (P=.025), to ranibizumab prefilled syringes (P=.03) and to controls (P<.001). There were no significant differences between ranibizumab, ranibizumab prefilled syringes and controls. The number of silicone oil microdroplets, when present, were greater in eyes receiving bevacizumab compared to ranibizumab and aflibercept. The authors concluded that silicone microdroplets in eyes receiving multiple bevacizumab and aflibercept injections are more common than previously reported. The syringe type influences the likelihood of silicone microdroplets.

Gal et al. evaluated the incidence and characteristics of silicone oil droplets in the vitreous cavity by B-scan ultrasonography in eyes following intravitreal anti-VEGF injections in an observational consecutive study (35). Patients undergoing intravitreal anti-VEGF injections (Bevacizumab, Ranibizumab or Aflibercept) in either eye, as well as treatment naive eyes were recruited. All patients prospectively underwent contact B-scan ultrasonography, findings were recorded and graded. 30 decibel reduction test was performed to identify the droplets and differentiate them from other vitreal opacities. Forty eyes of 30 patients were included. Included eyes exhibited at least one echogenic particle in the vitreous cavity consistent with silicone oil droplets following intravitreal anti-VEGF injections. In 25 (64%) eyes, silicon droplets were identified by ultrasonography. Correlation between the echogenic findings to anti-VEGF agent, duration and number of intravitreal injections was assessed. Clinically visible silicon droplets were noted in 5 (12%) of patients. The authors concluded that intravitreal silicone oil droplets are a complication of intravitreal injections and appear very echogenic within the vitreous cavity using ultrasonography. The incidence of these echogenic findings was found to be higher than previously reported. No significant association was identified to a specific anti-VEGF agent.

Sivertsen et al describe an abrupt increase in the incidence of symptomatic silicone oil droplets following intravitreal anti-VEGF injections compounded in insulin syringes, and the absence of further cases after changing to silicone-free syringes (36). The study was designed as a prospective registry study at the Department of Ophthalmology and approved by the Institutional data protection officer at Oslo University Hospital, Norway. Aflibercept, ranibizumab, and bevacizumab were compounded at the hospital pharmacy using insulin plastic syringes (BD Micro-Fine Plus) and a validated aseptic production procedure in accordance with European regulations. All episodes of symptomatic intravitreal silicone oil droplets were registered in a pre-approved internal quality register at the Department of Ophthalmology, Oslo University Hospital. Concurrently, a silicone-free procedure for

compounding of the three anti-VEGF drugs was developed. The new procedure introduced silicone-free syringes with limited dead-space (Injekt-F, Braun) and a 33G x 9 mm low dead-space needle (company: TSK). Once the procedure was finalized and validated, all injections were performed using the new compounding procedure. Results: 48 cases in 45 patients (3 bilateral) of symptomatic, non-resolving floaters after intravitreal anti-VEGF injections were registered. The first case occurred after an injection on 18 MAY 2018, the last on 30 OCT 2018. The presence of silicone droplets was confirmed ophthalmoscopically in each case. There was a 2:1 ratio of cases between bevacizumab and aflibercept injections, and no cases after ranibizumab injections. Four months after changing the compounding procedure from insulin syringes to silicone-free syringes no new cases had been registered. From May through October 2018, 6403 injections of bevacizumab, 6167 injections of aflibercept, and 448 injections of ranibizumab were performed, which represents an approximate 14:14:1 bevacizumab/aflibercept/ranibizumab ratio. During this period 0.4% of injections resulted in symptomatic silicone oil droplets in the vitreous. The authors conclude that starting in May 2018, a cluster of symptomatic silicone droplets cases following intravitreal anti-VEGF-injections were observed. The likely origin of the silicone was the silicone oil lubrication used in the insulin syringes. Of note was that these syringes had been in use for several years with only sporadic incidents. The silicone-coated syringes were replaced in November 2018; from November 2018 to March 2019 no further cases of symptomatic silicone droplets occurred. The change in compounding procedure eliminated the risk of symptomatic silicone pearls in the vitreous. The study suggests silicone-free syringes are preferable to silicone-containing insulin syringes for intravitreal anti-VEGF injections.

MAH comment:

Insulin syringes normally have a staked needle as it is the case with the insulin syringe used in the last publication by Sivertsen. Insulin syringes are not recommended to be used for IVT aflibercept injections. In the Eylea label the recommended syringe for IVT injection is a 1 ml Luerlock syringe. The dead space of the Luer part of the syringe is considered beneficial to capture /trap and thereby decrease the potential silicone injected into the eye.

The impact of intravitreal silicone and particularly in the context of the devolvement of intraocular inflammations (IOI) was investigated in 2016 (see PSUR# 6). Few cases with IVT silicone with Eylea were reported and no causality could be established to the development of IOI or other relevant clinical findings. Vitreous floaters as a potential consequence of IVT silicone is a listed ADR for Eylea.

No new signal was derived from these publications.

Corneal irritations:

Goldhardt et al (37) investigated the effect of repetitive intravitreal (IV) anti-VEGF injections on corneal nerves (CN). In a retrospective case-control study CN parameter were compared between eyes in 39 individuals who received anti-VEGF injections in one eye only and compared CN parameters between 50 eyes of 50 individuals with a history of IV anti-VEGF injections and 80 eyes of 80 individuals without a history of injection. Paired and independent t test methodologies were used to compare nerve parameters, and multivariable linear regression analysis was performed to control for potential confounders. Results showed that in 39 patients (own controls), eyes with a history of IV injection had lower CN length density, total length, nerve fibers, bifurcations, and branches ($P < 0.005$) compared to the fellow eyes without injection. Similar findings were seen in the eyes of 50 individuals with a history of injection compared to 80 individuals without injection. A history of IV injections and ethnicity remained significantly associated with the CN length density and explained 32% of the variability ($R = 0.56$). It was concluded that decreased CN parameters in eyes with a history of anti-VEGF injections were found compared to eyes without such a history.

Muto et al evaluated the effect of intravitreal aflibercept injection on the corneal endothelium in patients with diabetic or cystoid macular edema caused by retinal vein occlusion (38). Forty-six eyes of 44 consecutive patients (27 men, 17 women; age range: 55-88 years) were evaluated. All participants initially received a single intravitreal injection of aflibercept (2 mg in 0.05 mL), followed by pro re nata use and underwent central corneal specular microscopy before the injection and at 1, 3 and 6 months after the first injection during a 6-month follow-up period. The endothelial cell density (ECD), average cell size (AVG), standard deviation of cell size (SD), coefficient of variation of cell size (CoV), maximum of cell size (MAX), minimum of cell size (MIN) and percentage of hexagonal cells (Hex%) were analyzed and the central corneal thickness (CCT) was measured. Results showed no significant differences in the ECD, AVG, SD, CoV, MIN, Hex% and CCT between measurements obtained before and 1, 3 and 6 months after the first injection. The MAX measured before injection differed significantly from the values measured at 1, 3 and 6 months after the first injection ($P=0.033$). An average of 1.43±0.58 intravitreal aflibercept injections were administered per patient. The authors concluded that the study findings indicate that the intravitreal administration of aflibercept (2 mg) might very slightly alter the corneal endothelium within 6 months of the first injection.

Verrecchia et al. performed a prospective study to evaluate changes in the corneal surface and tear film induced by IVT injections, and its impact on quality of life (39). 40 eyes of 40 patients were included, who had unilateral IVT injections of Ranibizumab, Aflibercept or Dexamethasone. Patients were assessed during two consultations: One before injection, with a clinical exam (presence of keratitis evaluated by Oxford classification), an automated evaluation of corneal surface using Lacrydiag® and the achievement of an OSDI score (ocular surface disease index). These exams were repeated one day after injection, with a pain scale measurement. The primary outcome was the difference in the OSDI score before and after IVT. Secondary outcomes were to determine whether injections impact the ocular

surface, comparing the injected eye and the fellow eye (control eye). Results showed a mean change in OSDI score of + 25.5 +/- 1.6 (p= 0.05). Superficial Keratitis was observed in 60% of case in the injected eye, and 10% in the fellow eye (p<0.001). Mean pain scale was 5.5/10 during the day after IVT. The tear film meniscus was lower in the injected eye than in the fellow eye (1.15mm vs 2.30mm) (p=0.05), measures of automated break up time was similar in the two groups. Other measurements made with Lacrydiag® (automated break up time and interferometry in the injected eye/fellow eye) were not statistically significant. The authors concluded that repeated intravitreal injections induced clinical discomfort in patients and altered their quality of life by modifying the corneal surface. These side effects could lead to poor compliance and a lack of motivation for these long-term treatments.

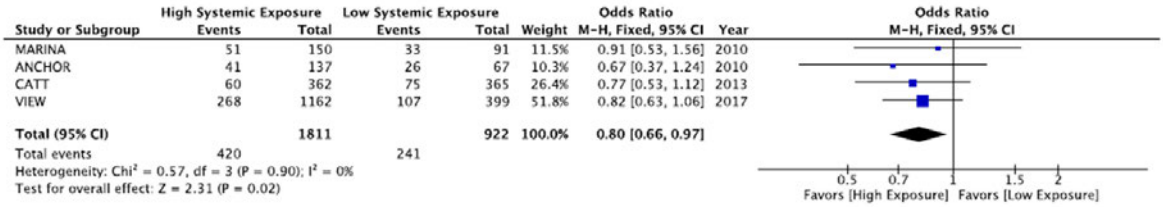
MAH comment:

Corneal irritations such as corneal abrasion, erosion, punctate keratitis, corneal epithelium defect, and corneal edema are listed ADRs of Eylea. Furthermore, Regeneron Pharmaceuticals conducted as a postmarketing safety study in the US on the effects of repeated intravitreal aflibercept injection on the corneal endothelium in patients with age-related macular degeneration (RE-VIEW study, study ID VGFTe-AMD-1124). Eylea therapy for 52 weeks had no apparent corneal endothelial toxicity evaluated by specular microscopy in N=154 patients treated for neovascular age-related macular degeneration (see also PSUR#8, section 11)

AMD progression in fellow eye

Avery et al presented an abstract on a metanalysis to address the question whether anti-VEGF treatment for AMD lowers the risk of neovascularization in the fellow eye (40). It is stated that as pharmacokinetic studies have demonstrated ranibizumab to have less systemic exposure following IVI than bevacizumab or aflibercept, it was considered the lower systemic exposure agent when compared to these agents, and the higher systemic exposure agent when compared to sham arms. ANCHOR, MARINA, CATT, VIEW 1, VIEW 2 studies were reviewed. When comparing the arms with more systemic exposure to anti-VEGF agents to arms with less or no systemic exposure, a decreased risk of fellow eye nAMD was found with greater systemic anti-VEGF exposure, odds ratio 0.80 (0.66-0.97), p=0.02 (Table 11-1)

Table 11-1: Higher/Lower systemic exposure agents and AMD events in fellow eye



The authors suggest that this study provides evidence of the biologic plausibility that following IVI, anti-VEGF agents escape the eye at concentrations sufficient to potentially have effects on distant organs, such as fellow eyes.

MAH comment:

The above abstract is all information available on this publication. The abstract does not detail what events were considered for the evaluation for AMD occurrences in the fellow eye. Furthermore, it is of note, that fellow eyes may have been treated with active anti VEGF therapy during the studies which may limit the relevance of this evaluation. For example, in the Bayer / Regeneron sponsored VIEW studies considered for this analysis a total of N=406 patients in the arms randomized to receive aflibercept therapy in the study eye also received anti VEGF therapy in the fellow eye. 146 patients randomized to receive ranibizumab in the study eye also received fellow eye anti VEGF therapy during the VIEW study duration.

In the VIEW studies AMD development/progression in the fellow eye was not systematically analyzed. However, no difference in AE reporting regarding PTs related to AMD development/progression (PT age related macular degeneration, PT macular degeneration) was noted (see Table 11-2 below).

Table 11-2: Number of subjects with ocular treatment-emergent adverse events of fellow eye by preferred term (Safety Analysis Set), VIEW 1/VIEW 2 studies 96 weeks

MedDRA labeling grouping (LG) Preferred term MedDRA Version 14.0	R 0.5 mg Q4 N=595 (100%)	VTE 2.0 mg Q4 N=613 (100%)	VTE 0.5 mg Q4 N=601 (100%)	VTE 2.0 mg Q8 N=610 (100%)	VTE total N=1824 (100%)	TOTAL N=2419 (100%)
Age-related macular degeneration	44 (7.4%)	41 (6.7%)	36 (6.0%)	46 (7.5%)	123 (6.7%)	167 (6.9%)
Macular degeneration	27 (4.5%)	19 (3.1%)	30 (5.0%)	27 (4.4%)	76 (4.2%)	103 (4.3%)

In addition, BCVA (ETDRS letters) were measured in the fellow eye over the study duration, no relevant change from baseline was noted in the fellow eye in any treatment arm.

Overall, systemic exposure of aflibercept after IVT injection in AMD patients was low to undetectable. Systemic effects are deemed very unlikely to be sufficient to have an effect on fellow eye AMD disease progression.

AE comparison aflibercept versus ranibizumab in Korea

Ha et al (41) compared the AEs reported for aflibercept and ranibizumab and determined signals using data from the Korean Institute of Drug Safety & Risk Management-Korea Adverse Event Reporting System Database (KIDS-KD). AEs were collected between 2007 and 2016 and differences in patient demographics, report type, reporter, causality, and serious-AEs between aflibercept and ranibizumab were compared. Metrics including proportional reporting ratio (PRR), reporting odds ratio (ROR), and information component (IC), were used to compare signals with the AEs on the drug labels in the United States of America and Korea. The database retrieval identified a total of 32 aflibercept and 103 ranibizumab AEs. The proportion of AEs that were reported spontaneously was higher with aflibercept (50.5%) use than ranibizumab (4.9%), whereas the AEs reported by post-marketing surveillance were higher with ranibizumab (46.6%) use than aflibercept (31.3%). The percentage of AEs in patients >60 years old, reports by consumers, and the ratio of SAEs to AEs associated with aflibercept (84. %, 9.4%, and 75.0%, respectively) were higher than those of ranibizumab (77.7%, 1.9%, and 19.4%, respectively).

For aflibercept 3 signals (PRR >2, Chi square>4, more than 3 AEs reported) were identified: endophthalmitis, muscae volitantes, and conjunctivitis. Among the 3 conjunctivitis was found not to be listed in the US PI as ADR. For ranibizumab 8 signals were detected: retinal disorder, drug ineffective, endophthalmitis, retinal detachment, retinal hemorrhage, vision abnormal, conjunctivitis, and muscae volitantes. Among these, medicine ineffective was not listed in the label.

Overall, endophthalmitis (OR 6.96, 95% CI 2.74-17.73) was more likely to be reported in patients with aflibercept than in patients without aflibercept, whereas medicine ineffective (OR 18.49, 95% CI 2.39-143.29) and retinal disorder (OR 7.03, 95% CI 1.60-30.96) were more likely to be reported in patients with ranibizumab than in patients without ranibizumab.

MAH comment:

In the Korean database 3 mined safety observations were identified for aflibercept concerning endophthalmitis, muscae volitantes (vitreous floaters), and conjunctivitis. Vitreous floaters and endophthalmitis are listed ADRs for Eylea. Conjunctivitis is not considered an ADR with Eylea. During the postmarketing period few cases were reported (0.04 events per 10 000 sold vials) and no signal arose during the clinical trial program. Of note, conjunctival hyperemia is listed in the CCDS and events reported as conjunctivitis may present as hyperemia. No new safety concern arises from this publication.

Pharmacovigilance in ophthalmology in Switzerland:

Karrer et al. analyzed the most frequently reported ocular adverse drug reactions within the last 25 year in Switzerland (42). This was a retrospective cohort study using registry data (WHO Global ICSR database, VigiBase™) with a base cohort consisting of all ADRs associated with the system organ class term“ eye disorders”[1] .A focus of the analyses was on new ocular drugs licensed in Switzerland in the past 15 years, the majority of which are anti-VEGF agents approved in Switzerland since the middle of the last decade. They reviewed individual case safety reports (ICSRs) submitted in Switzerland between January1991 and June 2016. ADRs were analyzed with respect to reporting rate per year, age and sex of the patient, and reported symptoms. Patients were grouped based on their age by decade and reported symptoms were described according to MedDRA terminology.

Results: three VEGF inhibitors account for the majority of ocular disorders notified in Switzerland since their approval: overall a total of 99 (3.5%) ICSRs with anti VEGFs were reported, 57(57.6%) represented patients treated with ranibizumab, 33 (33.3%) with aflibercept and 10 (10.1%) with bevacizumab. The first ICSRs pertaining to VEGF inhibitors were reported in 2006, but most ADRs were reported between 2012 and 2016 (76 ICSRs corresponding to 76.8% of patients). A total of 159 reactions were notified, comprising106 (66.7%) related to ranibizumab, 42 (26.4%) to aflibercept and 11 (6.9%) to bevacizumab.

For ranibizumab, an inverse significant disproportionality (ROR <1.00) was identified in connection with retinal haemorrhage (ROR 0.14, 95% CI 0.04–0.55; p = 0.005) and uveitis (ROR 0.13, 95% CI 0.03–0.63; p = 0.012). Bevacizumab showed a significant disproportionality for visual impairment (ROR4.67, 95% CI 1.08–20.16; p = 0.04), and no other ROR showed a significant correlation with the respective data. Aflibercept showed the greatest number of significantly disproportional RORs: retinal haemorrhage (ROR 10.36, 95%CI2.65–40.50;p<0.001), blindness (ROR3.73,95% CI 1.08–12.96; p = 0.04), and uveitis (ROR 6.91, 95% CI 1.64–29.13; p = 0.01) were significantly more frequently reported in association with aflibercept than with the other two VEGF inhibitors.

MAH comment:

These results of this database review for cases in Switzerland were based on very small numbers. Thus, a total of 33 cases with aflibercept with overall 9 events of retinal hemorrhage, six events of blindness, and 6 events of uveitis with aflibercept were evaluated. Large scale randomized clinical trials comparting aflibercept with ranibizumab in AMD patients (VIEW1 and VIEW 2 studies) did not show any meaningful differences in the occurrence of blindness, retinal hemorrhage and uveitis between the treatment arms. Blindness and retinal hemorrhage can be considered symptoms of the underlying disease and are clinical features of all approved Eylea indications. During this reporting period a cumulative evaluation on retinal hemorrhages and the use of Eylea was conducted (see **Appendix 7**). Based on the data reviewed no causality to Eylea could be established.

Anti-VEGF drug levels in breast milk after intravitreal injection:

Juncal et al. (43) investigated the concentrations of ranibizumab and aflibercept and their impact on VEGF-A levels in breast milk of lactating patients after intravitreal injection. This prospective, multi-center study performed in Canada included lactating patients who required intravitreal anti-VEGF therapy for any retinal disease from October 2017-2018. Three patients were enrolled. Patient 1 was a treatment-naïve 37-year-old nursing a 16-month-old child who was diagnosed with mCNV for which ranibizumab was recommended. Breastfeeding was discontinued prior to injection and there was no breast milk pumping outside of study visits. Patient 2 was a 37-year-old nursing a 1-month old child who was diagnosed with mCNV and had received one intravitreal ranibizumab injection 4 weeks prior to baseline. She continued receiving ranibizumab therapy and was regularly breastfeeding throughout treatment. Breast milk was collected at baseline (1h before injection) and on days 1-7, 14, 21 and 28 post-injection. in patients 1 and 2. Patient 3 was a treatment-naïve 24-year-old diagnosed with DME. She gave birth to a child 1 week prior to baseline and decided not to breastfeed. She was started on treatment with intravitreal aflibercept. Breast milk was collected at baseline (1h before injection) and on days 1-4, after which samples could not be obtained due to the lack of additional breast milk production. There was no breast milk pumping or breastfeeding outside of study visits. Free ranibizumab and aflibercept levels were measured using an enzyme-linked immunosorbent assay. The lower limit of quantitation (LLOQ) of the ranibizumab and aflibercept assays were 1.6ng/ml and 5ng/ml, respectively. VEGF-A concentrations were measured with an immunoassay (R&D Systems Kit-LXSAHM-01) using the Luminex® platform. Samples were run in duplicates for analysis. In patient 1, ranibizumab was detected starting on day 3 (34.7ng/ml), with generally increasing levels over time. VEGF-A demonstrated a reduction from 22.8ng/ml at baseline to 12.3ng/ml on day 1 and down to 4.9ng/ml on day 28. In patient 2, who was continuously breastfeeding, ranibizumab levels remained below the LLOQ throughout all study time points, and VEGF-A concentrations remained mostly unchanged. In patient 3, aflibercept was detected on day 4 (10.9ng/ml), while VEGF-A levels were reduced from 10.6ng/ml at baseline to 4.9ng/ml on day 1.

The authors conclude that based on the results found with patients 1 and 3, both ranibizumab and aflibercept reach the breast milk with a corresponding reduction in VEGF-A levels. Because aflibercept was only detected on day 4 and ranibizumab starting on day 3, while VEGF A levels were reduced on day 1, they hypothesize that both drugs likely reached the breast milk by day 1 and initially bound with free VEGF present in the breast milk. It is stated that because these assays only detect free drug, free ranibizumab and aflibercept levels could have remained below the LLOQ during the first days. Ranibizumab detection was stated to be influenced by whether the patient was continuously breastfeeding or not. In patient 1 who discontinued breastfeeding, free drug continued to reach the breast milk and kept on accumulating for several days, accounting for the increasing levels observed with time. In patient 2, who continued to breastfeed, all samples were negative for the presence of ranibizumab at the assay's level of detection likely because the drug in the breast milk was

constantly excreted and ingested by the infant and never accumulated sufficiently to be above the LLOQ. The authors conclude that although this study demonstrates a correlation between decreasing VEGF-A and increasing anti-VEGF levels in human breast milk, the consequences to the infant are unknown. Authors acknowledged that the study is limited by the small sample size explained by the fact that such patients present relatively infrequently. Another limitation is given that VEGF levels in the breast milk may vary according to the gestational age at birth and period of lactation. VEGF concentrations in the breast milk are known to decrease in the first 30 days post-partum, so it is possible that some of the reduction in VEGF-A levels observed in these patients are related to reduced production.

Company comment:
This publication included very limited information on drug levels in breast milk in patients being treated with aflibercept (n=1). No robust data is yet available. As per CCDS label text Eylea therapy is not recommended during breast feeding and states: *It is unknown whether aflibercept is excreted in human milk. A risk to the breast-fed child cannot be excluded. Eylea is not recommended during breast-feeding. A decision must be made whether to discontinue breast-feeding or to abstain from Eylea therapy.*

11.2 Newly Identified Information on Efficacy

A standardized search in the literature databases MEDLINE, EMBASE, BIOSIS, Derwent Drug File, Science Citation Index and Chemical abstracts was performed for publications relating to Aflibercept covering the period of this report. Retrieved abstracts were reviewed for efficacy and effectiveness.

The benefit–risk profile of EYLEA remains positive over the review period of 01 DEC 2018 to 30 NOV 2019. A total of 66 publications including conference presentations and posters and manuscripts discussed efficacy and safety in five approved indications several off label investigations.

The following information on the efficacy/effectiveness of Eylea has become available during the PSUR/PBRER interval:

nAMD

Augsburger *et al* (2019) (44) retrospectively compared the efficacy of anti-VEGFs in patients with nAMD at one eye clinic in Switzerland. Patients treated with T&E regimens using ranibizumab (n=191) or aflibercept T&E (n=419) experienced comparable improvements over time in logMAR where a greater proportion of patients treated with either ranibizumab T&E or aflibercept T&E experienced clinically relevant VA gains (>0.2 logMAR) than patients treated with ranibizumab PRN (no p-value given). The authors concluded that ranibizumab T&E led to greater VA improvements than PRN and had a longer injection interval than aflibercept T&E.

Baillif *et al* (2019) (45) reported the interim 2-year results of a real-world, 4-year study into the effectiveness and safety of aflibercept administered using regular (3 loading doses

followed by 2q8) or irregular dosing (with and without the loading doses and aflibercept every <2 or >2 months). At 24 months, the change in BCVA from baseline was +4.9 letters in the regular cohort (n=70) and +4.0 letters in the irregular cohort with the 3 loading doses (n=142; *P*<0.05 vs. baselines for both groups). There was a decrease of 2.5 letters in the irregular cohort that didn't have the 3 loading doses (n=40), but it wasn't statistically significant. The mean number of injections was 8.8 (all cohorts), 10.6 (regular cohort), 9.3 (irregular cohort with 3 loading doses) and 7.8 (irregular cohort without 3 loading doses). The most common ocular AEs were lack of response (6.3%), vitreous floaters (2.7%), lacrimation increased (1.7%) and VA reductions (1.5%).

Bhandari *et al* (2019) (46) compared the outcomes of eyes treated with either ranibizumab (n=499) or aflibercept (n=466) in the Fight Retinal Blindness! registry. The mean VA and type of CNV at the start of treatment was similar between the two groups, but the authors noted that ranibizumab was preferred for older patients. Eyes received a median of 18 injections with either treatment over a median of 21 visits over the 3 years. The crude mean VA change at 3 years was similar between the groups (ranibizumab: +1.5 letters, 95% CI: 0, 3.1 vs. aflibercept: +1.6 letters, 95% CI: -0.2, 3.3; *P*=0.97). There were more switches from ranibizumab to aflibercept than vice versa (*P*<0.001), but the proportion of eyes discontinuing treatment before 3 years in each group was similar (*P*=0.21).

Boyer *et al* (2019) (47, 48) reported the 12-month interim data for a prospective, 24-month, single-masked study into the ability of aflibercept to prevent the conversion of AMD into nAMD. By 12 months, 4/63 (6.3%) eyes treated with aflibercept 2q12 converted from intermediate AMD to nAMD compared with 6/64 (9.4%) of eyes treated with sham (*P*=0.50). The proportion of eyes with OCT angiography-determined subclinical CNV at any point over 12 months was 2/7 (25%) in the aflibercept group and 3/10 (30%) in the sham group (*P*=0.18). No new safety signals were identified. The authors concluded that aflibercept could not be used as a prophylactic treatment against conversion to nAMD.

Bro and Hagg (2019) (49) retrospectively explored the effects of switching from aflibercept or ranibizumab to bevacizumab due to policy decisions. Mean BCVA in eyes treated with ranibizumab (n=93) was 68.3 letters (95% CI: 61.3, 66.4) before the switch and 62.2 letters (95% CI: 59.3, 65.1) after the switch to bevacizumab. In aflibercept treated eyes (n=19), the mean BCVA prior to the switch was 68.2 letters (95% CI: 63.4, 73.1) and 67.7 letters (62.8, 72.6) after switching to bevacizumab (no p-value given). The authors concluded that patients with nAMD could be switched to bevacizumab without significant decreases in VA.

Brynskov *et al* (2019) (50) reported on the 10-year RWE with aflibercept and ranibizumab for nAMD in a single treatment center in New Zealand. A total of 1,971 eyes received ranibizumab, 1,804 eyes received aflibercept and 903 eyes received both drugs over the 10-year window. Patients received a mean of 5.4 injections in the first year and 4.0–4.3 yearly thereafter. At baseline, 29% of patients had a BCVA of ≥70 letters which increased to 31-37% until Year 9. 8% had a BCVA loss of ≥3 lines at the first follow-up, which increased to 34% after 10 years. 12.6% of eyes were still receiving treatment after 10 years. The authors noted that baseline BCVA was an important prognostic factor in BCVA gains.

Cabrera *et al* (2019) (51) retrospectively explored the efficacy of aflibercept as a first-line treatment for nAMD in 14 Spanish centers. 116 patients with newly-diagnosed nAMD received a mean of 7.6 aflibercept injections over the 52-week study period. At 12 months, VA improved significantly by a mean of 10.5 letters (P<0.001) and 39.7% of patients gained ≥15 letters (95% CI: 30.8, 48.6). CRT significantly decreased by a mean of -99.9 µm (P<0.001) and mean PED height at 12 months was 214.5µm, being seriously-vascularized and fibrovascular in 13 cases (35.1%). No treatment-related AEs were reported during the study.

Cahill *et al* (2019) (52) reported the 96-week results from HAWK and HARRIER, which assessed the efficacy and safety of brolucizumab (3 or 6 mg, q8 or q12) versus aflibercept (2q8) in nAMD. Brolucizumab was non-inferior to aflibercept in mean BCVA change from baseline at 48 weeks (the primary endpoint) but was superior in key anatomical outcomes. The visual and anatomic improvements were sustained with brolucizumab over 96 weeks with a significant proportion of patients remaining on q12 dosing (no p-values given). The ocular and non-ocular AE rates were comparable between the two drugs.

Carrasco *et al* (2019) (53) carried out a meta-analysis to explore the real-world effectiveness and treatment burden of aflibercept and ranibizumab. At Week 52, the mean VA gain was 5.30 ETDRS letters in patients who reported an average of 7.10 aflibercept injections and 8.65 visits. In comparison, ranibizumab treated patients experienced a mean VA gain of 4.24 ETDRS letters with an average of 5.88 injections and 10.10 visits. After correcting for age differences and baseline VA, the mean VA gain was 6.57 letters for patients treated with aflibercept and 4.42 letters for patients treated with ranibizumab (no p-value given). The cost-effectiveness analysis showed that aflibercept was a more effective treatment option with an incremental gain in QALYs (4.918 vs. 4.880) and an incremental cost-effectiveness ratio (ICER) of €27, 087 per QALY.

Chang *et al* (2018) (54) compared the anatomic outcomes in the first 16 weeks of the HAWK and HARRIER studies. At 16 weeks in the HAWK study, mean change in CST from the baseline was -161.4 µm for 6 mg brolucizumab and -133.6 µm for 2q8 aflibercept (P=0.0016). In HARRIER, the mean CST change to 16 weeks was -174.4 µm with 6 mg brolucizumab and -134.2 µm for 2q8 aflibercept (P<0.0001). At 16 weeks, fewer patients receiving brolucizumab had IRF, SRF (subretinal fluid) and sub-RPE fluid compared with aflibercept. The authors concluded that brolucizumab treatment demonstrated better anatomical outcomes than aflibercept with respect to retinal thickness and fluid status at 16 weeks.

Chou *et al* (2019) (55) retrospectively assessed the factors that affect treatment choices in Taiwan. Of the 159 treatment applications that were reviewed, 123 were for aflibercept and 43 were for ranibizumab; however only 71.5% of applications for aflibercept were reimbursed compared with 69.9% for ranibizumab. Age (P<0.01), laterality (P=0.05), presence of RPE detachment (P<0.01), history of hypertension, coronary heart disease, and cerebral vascular accidents (P=0.01) were factors that were associated with choosing aflibercept over ranibizumab. The authors concluded that more patients and ophthalmologists chose to treat nAMD with aflibercept rather than ranibizumab, despite there being no significant differences in efficacy or clinical outcomes.

Dhingra *et al* (2019) (56) retrospectively assessed the outcomes of eyes treated with ranibizumab or aflibercept at a single center. Following 3 loading doses, both drugs were administered q8 for the first 12 months followed by PRN or T&E regimens in the second year. At 12 months, when all patients had received 8 injections, the VA improved significantly from baseline in eyes treated with ranibizumab (n=112; +10 letters; $P<0.0001$) or aflibercept (n=86; +8 letters; $P<0.0001$). The VA in all eyes was unchanged up to Month 24 irrespective of RPN or T&E regimens; however, VA gains of ≥15 letters were seen more often in T&E eyes (35.5% with ranibizumab and 28.8% with aflibercept, no p-values given). CMT reductions were comparable across treatments (-148.5 µm with ranibizumab and -135.2 µm with aflibercept; no p-value given) but aflibercept treatment led to a significantly greater reduction in IRF at 24 months than ranibizumab ($P<0.0001$).

Dugel *et al* (2019) (57) reported the 48-week results from the HAWK and HARRIER studies, which compared brolucizumab with aflibercept in 1,817 patients with untreated nAMD. At Week 48, brolucizumab at 3 or 6 mg (q8 or q12) was non-inferior to aflibercept (2q8) with respect to BCVA change from baseline. At Week 16, fewer eyes treated with 6 mg brolucizumab had disease activity than those treated with aflibercept in HAWK (24.0% vs. 34.5%; $P=0.001$) and HARRIER (22.7% vs. 32.2%; $P=0.002$). From baseline to Week 48, brolucizumab treatment led to greater reductions in CST than aflibercept in HAWK ($P=0.001$) and HARRIER ($P<0.001$) and retinal fluid outcomes favored brolucizumab over aflibercept (no p-values given). AE rates were comparable between the two treatments. The authors concluded that although brolucizumab was non-inferior to aflibercept in visual function at 48 weeks, it offered greater benefits in anatomic outcomes.

Eleftheriadou *et al* (2018) (58) reported the outcomes of a retrospective, single-center, non-randomized, interventional case series analysis using aflibercept for nAMD. Data from 108 eyes were included over a three-year follow-up period (mean patient age: 80.6 ±8.3 years). At 3 years, the mean VA gain was 6.6 ± 15.4 letters, and the change in CSMT was -77.9 ± 101.4 µm with an absence of macular fluid in 71% of eyes (no p-values given). The mean total number of injections was 15.9 ± 6.1 by Year 3. The authors concluded that good long-term morphological and functional outcomes can be achieved with aflibercept in nAMD in a clinical setting.

Gale *et al* (2019) (59) prospectively assessed the effect of switching from aflibercept to ranibizumab in 100 patients with persistent/recurrent nAMD (SAFARI study). There was a significant change in median CSRT from baseline of -30.75 µm (95% CI: -59.50, -20.50; $P<0.0001$) to Day 90, and improvements were observed in other OCT parameters. 55% and 59% of patients gained >0 ETDRS letters from baseline to Day 90 and Day 180, respectively. No new safety signals were observed over the 6-month study. The authors concluded that patients with nAMD who experienced a suboptimal response to aflibercept may benefit from switching to ranibizumab.

Gemenetzi *et al* (2019) (60) reviewed the medical records of nAMD patients at Moorfields Eye Hospital, UK who were treated with aflibercept for at least two years. Out of 1,003 eyes, 200 had experienced at least one extended >10-week treatment interval and were included in

the analysis. The mean patient age was 78 years, mean follow-up time was 3.4 years; in Year 1 the mean number of injections was 8, in Year 2 it was 5. The mean VA at baseline was 54 ETDRS letters and the mean VA at the first visit of the stable phase was 62 letters and at the last follow up it was 58 letters (no p-values given). 52% of eyes had IRF at the last follow-up. The authors concluded that aflibercept eyes treated at intervals of >10 weeks had active and stable phases of treatment and noted that IRF may not be a crucial prognostic factor for VA changes.

Gillies *et al* (2019) (61) reported the 12-month interim analysis of the RIVAL study, which compared T&E ranibizumab (n=127) and aflibercept (n=121) in patients with nAMD. From baseline to Month 12 the mean change in BCVA was +7.2 for ranibizumab and +4.9 for aflibercept (letter score difference of 2.3; 95% CI, -0.1 to 4.7; *P*=0.06). The mean number of injections to month 12 was 9.7 in both treatment groups. The authors concluded that neither ranibizumab nor aflibercept were superior in terms of VA gains and injection burden.

Gomi *et al* (2019) (62) prospectively evaluated the QoL of Japanese patients with nAMD treated with aflibercept for 12 months in the real world. At 12 months, 446 patients had received a mean of 4.6 aflibercept injections. The mean improvement from baseline in the NEI-VFQ-25 composite score at this time point was 4.6 (*P*<0.0001); for the subscale scores, the mean change was ≥4 (minimally important difference) for general health and mental health (*P*<0.0001). There was a significant improvement from baseline in mean BCVA at 12 months of -0.1 logMAR (*P*<0.0001), and the mean change in NEI-VFQ-25 score was greatest in patients with improved BCVA (≤-0.3 logMAR or ≥15 letters; no p-value given).

Grassi *et al* (2019) (63) reported on the outcomes of anti-VEGFs administered at a new intravitreal injection center in Italy. 197 patients with unilateral disease received a mean of 7 ±2.2 aflibercept or ranibizumab injections, and BCVA improved by a mean of 9 ± 16.4 letters with a macular thickness decrease of 102 ± 163.8 µm (no p-values given). No significant differences were noted between patients treated with aflibercept or ranibizumab (P>0.05).

Hara *et al* (2019) (64) retrospectively investigated the characteristics of nAMD patients who developed tachyphylaxis following repeated aflibercept injections. 313 treatment naïve eyes that achieved resolution soon after starting aflibercept were followed for 12 months. 28 patients (8.9%) developed tachyphylaxis (defined as an absence of improvement or worsening of CRT within 1 month after more than 2 repeated monthly aflibercept injections when the exudative change remained). The mean number of injections was 10.5 ± 7.8 and the mean interval until tachyphylaxis was 20.9 ± 14.0 months. There was a significant difference in the AMD subtypes between the group with tachyphylaxis and the group without it (*P*=0.0029), with PCV (n=14) and no classic CNV (n=14) being the only subtypes in the eyes with tachyphylaxis.

Hasan *et al* (2019) (65) retrospectively explored the outcomes of 183 nAMD patients who received fixed doses of aflibercept (2q8) for 2 years. The baseline VA was 0.64 and the final VA at 24 months was 0.48 LogMAR, corresponding to a gain of 8 letters (no p-value given). CMT reduced by 108 µm by 24 months (no p-value given). No patients developed any

complications related to the injections. The authors concluded that a fixed dosing protocol achieved significant visual gains in patients with no macular structural damage and improves the capacity of the clinic.

Heinke *et al* (2019) (66) carried out a prospective clinical to assess the impact of aflibercept on patients with CNV due to nAMD. Patients received aflibercept 2q8 (following 3 loading doses) for one year. Patients gained 2.47 letters after 3 months and 9.29 letters after 12 months of treatment ($P<0.001$). Mean CRT decreased from 370.38 µm at baseline to 300.76 µm at 12 months ($P<0.001$). The injections were well-tolerated and no serious local or general AEs were recorded. Baseline VA was the most important predictor of final VA after treatment ($r=-0.421$; $P<0.01$). The subtype of CNV, patient's sex, lens status and exposure to prior therapy did not correlate with final VA or CRT.

Holz *et al* (2019) (67) reported the 96-week results from HAWK (n=1775) and HARRIER (n=1048) that investigated the efficacy and safety of brolucizumab versus aflibercept. In both studies, brolucizumab was non-inferior to aflibercept at Week 48 and vision gains were maintained to Week 96. Compared with aflibercept, brolucizumab treatment led to greater reductions in CST from baseline to Week 16 and 48, which was maintained at Week 96 (HAWK: $P=0.0010$ [Bro 3 mg vs. Afl]; $P=0.0057$ [Bro 6 mg vs. Afl]; HARRIER: $P<0.0001$). The proportions of patients with IRF and/or SRF at Week 96 in HAWK were 31% with Bro 3 mg ($P=0.0344$) and 24% with Bro 6 mg ($P=0.0001$) vs. 37% for Afl; and in HARRIER were 24% for Bro 6 mg ($P<0.0001$) vs. 39% for Afl.

Hong *et al* (2018) (68) carried out a retrospective audit using a pharmacy database to compare visual outcomes of nAMD patients receiving aflibercept or ranibizumab. 112 eyes were treated with ranibizumab and 235 eyes were treated with aflibercept for a duration of one year (mean injections of 8 for ranibizumab and 7.2 for aflibercept). At 12 months, the gains in VA were comparable between the two treatments (4.5 letters for ranibizumab and 4.0 letters for aflibercept; $P>0.05$), but there was a greater improvement in VA for patients treated with ranibizumab compared with aflibercept following the initial three loading doses (4.8 vs 3.9 letters; $P>0.05$).

Jakobsen *et al* (2019) (69) investigated the effect of three monthly injections of aflibercept on retinal oxygen saturation in nAMD (n=76), dry AMD (n=30) and normal eyes (n=43). Patients with nAMD and dry AMD had higher retinal arteriolar oxygen saturation compared with normal eyes (94.3% vs. 95.2% vs. 92.6%, respectively, $P=0.04$). An increased retinal venular oxygen saturation level was associated with negative structural treatment outcomes after aflibercept loading doses ($P=0.03$). The authors concluded that changes in retinal venular oxygen saturation associate independently with initial aflibercept treatment responses in nAMD.

Kim *et al* (2019) (70) retrospectively evaluated disease reactivation following aflibercept or ranibizumab treatment in 179 patients with stage II–III type 3 neovascularization with dry macula. The first reactivation was noted in 145 eyes at a mean of 6.6 months after the third anti-VEGF injection. In the eyes that experienced early reactivation (n=94), the subfoveal

choroidal thickness was notably thicker and the proportion of women affected was greater than in the non-early reactivation group (n=85; no p-value given). There was no difference between ranibizumab and aflibercept in terms of reactivation.

McAllister *et al* (2019) (71) reported the 96-week outcomes of the HAWK and HARRIER studies, highlighting the achievement of dryness. The cumulative incidence rate (%) of sustained dryness was greater for brolucizumab compared to aflibercept at Week 48 (≥2/≥3 visits) HAWK [Bro 3 mg, 82.9/77.1; Bro 6 mg, 86.4/79.1; Afl, 76.4/67.6]; HARRIER [Bro 6 mg, 91.5/85.9; Afl-81.2/72.7] (no p-values given). The 50th percentile for sustained dryness was achieved earlier for brolucizumab, with most achieving dryness at ≥2/≥ 3 visits by Week 8/8 in HAWK and Week 4/4 in HARRIER compared to aflibercept (≥ 2/≥ 3 visits: HAWK, Week 8/12; HARRIER: Week 8/8) (no p-values given). The authors concluded that patients treated with brolucizumab were more likely to achieve sustained dryness than those treated with aflibercept.

Mehta *et al* (2019) (72) carried out a retrospective study of visual and anatomic outcomes following aflibercept treatment for five years. 100 consecutive eyes with nAMD were treated at a single center in the North East of England, using fixed dosing in Year 1 and PRN thereafter. Stability of vision was achieved by 69% of patients at 5 years and 65% of OCT investigations were dry at the last follow-up (no p-values given). The authors noted that this real-world study demonstrated the long-term efficacy of aflibercept.

Pavel *et al* (2019) (73) retrospectively compared the outcomes of eyes treated with bimonthly ranibizumab (n=112) or aflibercept (n=86) at a single center. At 12 months, all eyes received 8 injections, and VA improved significantly compared to baseline (+10 letters with ranibizumab and +8 letters with aflibercept; $P<0.0001$ for both compared with baseline). Maximal VA was achieved at 3 months with aflibercept and 6 months with ranibizumab, and the proportion of eyes gaining ≥15 letters was 25% with ranibizumab and 20.9% with aflibercept (the difference was not statistically significant). Complete macular dryness (observed after 3 injections, which remained dry at 12 months) was seen more frequently with aflibercept (40%) than with ranibizumab (32%) (no p-value given).

Nishikawa *et al* (2019) (74) investigated the 4-year visual outcomes of 98 AMD patients in clinical practice. Patients received 7.0 ± 0.1 aflibercept injections during the first year and 8.0 ± 7.4 injections in the following three years. LogMAR at baseline, Year 1 and Year 4 was 0.28, 0.14 ($P=0.033$) and 0.22 ($P=0.697$), respectively, and vision gains did not differ between AMD subtypes (typical AMD, PCV and RAP; $P=0.513$). The presence of external limiting membrane, absence of vitreoretinal adhesion and thicker choroid at baseline were associated with better logMAR values at Year 4 ($P=7.34 \times 10^{-6}$, 0.01 and 0.028, respectively). The authors concluded that these features were predictive of long-term outcomes with aflibercept.

Sakurada *et al* (2019) (75) assessed the relationship between genetic variants of nAMD and response to aflibercept over 12 months. 83 patients with nAMD and 83 with PCV were genotyped and received three monthly aflibercept injections; additional treatment was needed

for 67.5% of patients during the follow-up period. T allele frequency at ARMS2 A 69S (rs10490924) and C allele frequency at CFH (rs1329428) were significantly lower in patients who didn't need retreatment than in those who did (P=1.4 x 10^{-5} and 5.9 x 10^{-3}, respectively). The number of additional injections needed also correlated with certain genotypes, although none were associated with visual outcomes at 12 months.

Tarakcioglu *et al* (2019) (76) retrospectively explored the records of eyes with nAMD that were treated with aflibercept or ranibizumab, and graded their anatomic responses. 74.3% (110 eyes), 12.2% (18 eyes) and 13.5% (20 eyes) of eyes showed good, intermediate and poor anatomic responses between Months 3 and 12, respectively. Aflibercept treatment led to better anatomic outcomes than ranibizumab for both early and late treatment periods (P=0.02 and P=0.03). Both CNV area and presence of a PED were predictors of treatment response.

Theodoropoulou *et al* (2019) (77) retrospectively reviewed 157 eyes that were treated with a hybrid T&E aflibercept regimen at Bristol Eye Hospital, UK. After the 3 loading doses patients with no signs of disease activity entered a PRN regimen, and the remaining patients were treated with T&E. After at least 12 months of follow-up 27 patients (17.2%) needed no more than the 3 loading doses of aflibercept. Of the 130 patients that were treated with T&E, the mean VA gain was 8 letters which was maintained to 24 months. 18.9% of eyes had a 15-letter gain and 5.4% lost >15 letters by 24 months. 32 eyes (22.8%) achieved a treatment interval of ≥10 weeks, while 12% achieved ≥12 weeks.

Traine *et al* (2019) (78) carried out an observational 4 year study into the outcomes of nAMD patients (n=231) receiving T&E aflibercept. Mean BCVA increased from 59.8 letters at diagnosis to 65.8 letters after the loading phase and to 65.5 letters at 12 months. After 4 years, mean BCVA was 63.4 letters (+3.6 gain from baseline; P>0.05). Patients received a mean of 7.7 ± 1.2 injections and 4.4 ± 1.6 clinic visits in Year 1, and 4.4 ± 1.9 injections and 4.3 ± 1.3 clinic visits per year thereafter. By 2 years of follow-up, 46.9% of patients reached a treatment interval of 12 weeks.

Vazquez-Alfageme *et al* (2019) (79) retrospectively assessed the incidence of RPE tears in eyes with nAMD treated with aflibercept and ranibizumab. After a mean of 34.0 ± 9.1 months follow-up, 3.2% of 500 eyes treated with aflibercept experienced a tear compared with 2.3% of 300 eyes treated with ranibizumab (P=0.52). 29 eyes with RPE tears were followed for a mean of 30.76 months, which had a baseline VA of 50.7 ± 19.3 letters and at VA of 36.1 ± 26.1 letters at the end of the follow-up. The mean number of injections was 7.3 at 12 months and 13.9 at the study end. The authors confirmed that the rate of RE tears was comparable between aflibercept and ranibizumab.

Veritti *et al* (2019) (80) prospectively evaluated the 12-month outcomes of aflibercept administered at a fixed dose according to the label or via a PRN regimen. VA improved from baseline to 12 months in both study groups and at Month 4 the fixed regimen was equivalent to the PRN regimen (mean difference: 1.75 ETDRS letters, 95% CI: -1.42, +4.92), however at Month 12 the PRN regimen failed to show non-inferiority to fixed dosing (mean difference:

4.83 ETDRS letters, 95% CI: +1.37, +8.29). All patients in the fixed group received 7 injections, whereas the PRN arm received a mean of 5.5. ± 1.6 injections.

Yong *et al* (2019) (81) explored the effects of a high dose (0.7 mg ranibizumab and 2.8 mg aflibercept) and a regular dose (0.5 mg ranibizumab and 2.0 mg aflibercept) regimen on nAMD patients. The mean BCVA as well as anatomic outcomes did not differ between the high and regular dose cohorts at 1 month and 24 months after the loading injection (no p-value given). However, in both the regular dose and high dose groups the final CMT and GC-IPL thickness were significantly thinner than at baseline (no p-value given). The authors concluded that the decreased GC-IPL thickness resulted from transsynaptic degeneration of ganglion cell dendrites with photoreceptor loss or that the retinal photoreceptors were chronically hypoperfused and ischemic from microvascular choroidal damage.

PCV:

Ao *et al* (2018) (82) reported the 96-week results of the PLANET study in which patients with PCV were randomized to receive aflibercept monotherapy of aflibercept + active rescue PDT. After 2 years of treatment, mean BCVA change with aflibercept was non-inferior to aflibercept + rescue PDT (in patients overall [+10.7 vs. +9.1 letters, n=318] and in those requiring rescue treatment [+2.6 vs. +0.0 letters, n=54]; no p-value given). Mean CST was comparable between aflibercept monotherapy and aflibercept + rescue PDT groups (no p-value given) and both cohorts received 8.1 injections from baseline to Week 52 and 4.6 injections from Week 52 to 96. The most frequent ocular AEs were conjunctival hemorrhage (6.4% of aflibercept monotherapy group) and dry eye (6.8% of aflibercept + PDT group). The authors concluded that aflibercept monotherapy was effective for most PCV patients.

Chang *et al* (2019) (83) reported the results of 89 Japanese patients diagnosed with PCV enrolled in the HAWK study. Patients were treated with 3 or 6 mg brolucizumab q12 (or q8 where needed) or 2 mg aflibercept at q8. Mean change in BCVA from baseline to Week 48 was 11.4 ETDRS letters (SE: 2.6) for 3 mg brolucizumab, 10.4 ETDRS letters (SE: 1.5) for 6 mg brolucizumab and 11.6 ETDRS letters (SE: 1.4) for 2 mg aflibercept. The BCVA gains were maintained to Week 96. Compared with aflibercept, fewer brolucizumab patients had fluid present at Week 96 (no p-value given).

Ozawa *et al* (2019) (84) retrospectively reviewed the medical charts of 100 treatment-naïve eyes of patients with PCV to explore the dynamic changes of the choroid during anti-VEGF treatment (aflibercept or ranibizumab). Both pachyvessels in the choroid (P=0.008) and pachychoroid (P=0.002), and dynamic changes in choroidal vascular diameter (CVD) and central choroidal thickness (CCT) were related to exudative changes in PCV (no p-value given). Basal levels of CVD and CCT when patients had no exudative changes after anti-VEGF treatment differed between eyes with or without initial pachyvessels and pachychoroid with these definitions determined by treatment outcomes, suggesting involvement of regulatory mechanisms other than VEGF-related in the basal choroidal condition. In contrast, CVD increase preceded CCT increase and recurrent exudative changes and could be treated with anti-VEGF treatments, suggesting that dynamic changes in CVD may regulate CCT and

exudative changes most likely in response to VEGF. Dynamic CVD change may be a biomarker of disease activity.

DME:

Baker *et al* (2019) (85) reported the outcomes of a randomized clinical trial that was conducted at 91 sites in the US and Canada that investigated the visual outcomes of DME patients treated with aflibercept, laser or observation (aflibercept was administered in the laser and observation groups following a loss of at least 10 letters from baseline). At 2 years, 16%, 17% and 19% of eyes experienced at least a 5-letter VA decrease in the aflibercept (n=205), laser (n=212) and observation groups (n=208), respectively (P=0.79 for aflibercept versus laser and P=0.79 for aflibercept versus observation). APTC events occurred in 7%, 5% and 3% of patients in the aflibercept, laser and observation groups, respectively. The authors concluded that there was no significant difference in vision loss at 2 years in DME patients whether managed with aflibercept, laser or observation.

Dot *et al* (2019) (12) described the 1-year interim results of the APOLLON study, a real-world observational, prospective trial into the outcomes of DME patients treated with aflibercept. Patients who were treatment naïve (n=77) had higher baseline BCVA scores (62.7 letters) than previously treated patients (n=70; 60.0 letters). At 12 months, after a mean of 7.6 injections for all patients, the change in BCVA was greater in treatment naïve patients than in previously treated patients (+7.8 letters versus +5.0 letters, no p-value given). The mean change in CRT from baseline to Month 12 was -121 µm in the treatment naïve group and -141 µm in the previously treated group (no p-value given). Ocular AEs were reported in 54.1% of patients – the most common being cataract (4.4%) and diabetic retinal edema (3.1%).

Jack *et al* (2019) (86) performed a retrospective data-warehouse query for all eyes receiving aflibercept or ranibizumab for DME between March 2013 and October 2018 in a real-life setting. Over the observation period 1,117 eyes received only aflibercept, 691 eyes received ranibizumab (741 eyes received both and were excluded from the analysis). There were no significant differences in VA changes from baseline between the two treatments (p-value not given) and the authors concluded that aflibercept and ranibizumab are equivalent in terms of functional outcomes.

Lukic *et al* (2019) (87) carried out a retrospective, real-life cohort study to assess the outcomes of 92 patients who received aflibercept for DME. At 12 months, patients had received a mean of 6.92 injections, 33.67% of patients gained ≥15 ETDRS letters and 55.55% of eyes had a decrease in CFT of ≥100 µm. At baseline the mean VA was 59.7 and at 12 months it was 69.6 letters (P<0.0001); similar outcomes were observed in CFT which decreased from 431 µm at baseline to 306 µm at 12 months (P<0.0001). The authors concluded that there was a significant improvement in VA and anatomic outcomes in a real-life setting.

Mahmood *et al* (2019) (88) exported anonymized data from an electronic patient record system to explore outcomes of DME patients treated with anti-VEGFs. 1,153 patients were

included in the analysis who had received a mean of 6 injections (range of 5–8) over a 12-month follow-up period. Over this period, VA improved by 5 letters, with worse baseline VA associated with the greatest improvements ($P<0.001$). The authors concluded that the results reflected prior real-life studies and that there was possibly a ceiling and floor effect with anti-VEGFs.

Ozsaygili *et al* (2019) (89) prospectively investigated the effects of aflibercept on 273 treatment-naïve DME patients who were grouped into age bands (Group 1: 40–50 years; Group 2: 51–60 years; Group 3: 61–70 years; Group 4: >70 years). After 3 monthly injections of aflibercept, the mean reductions in CFT were -256.4 ± 110.9, -197.4 ± 96.4, -189.4 ± 110.8 and -186.2 ± 118.9, in Groups 1, 2, 3 and 4, respectively (the changes of CFT were significantly different between the groups; $P=0.003$). The ages of patients were correlated with the mean reduction of CFT and mean improvement of VA for the whole study group (r = -0.183, $P=0.002$ for CFT; r= -0.682, $P<0.001$ for VA, Pearson correlation). The authors concluded that aflibercept was more effective in younger patients with treatment-naïve DME.

Plaza-Ramos *et al* (2019) (90) retrospectively compared the outcomes of eyes with DME treated with PRN regimens using aflibercept (n=91) or ranibizumab (n=122). At Month 12, VA improved from 0.55 to 0.4 logMAR in the ranibizumab group and 0.48 to 0.4 logMAR in the aflibercept group ($P=0.864$). No differences between the two drugs were observed in terms of CMT, CMV and glycosylated hemoglobin. The mean number of injections was 5.56 ± 2.10 in the ranibizumab group and 6.07 ± 1.99 in the aflibercept group.

Stratton *et al* (2019) (91) compared the outcomes of aflibercept of DME patients who had received prior cataract surgery with those who had not. Anonymized data was extracted from an electronic patient record system of 21 UK centers. Patients who had undergone cataract surgery were older and had worse baseline VA than those who had not undergone surgery. At 12 months of aflibercept treatment, the change in VA did not differ between the psuedophakic and phakic groups (6 letters vs. 5 letters; $P=0.091$). In a regression analysis, change in VA was associated with age (4 more letters gained in those <65 years compared with those aged ≥75 years; $P=0.0008$), baseline EDTRS letters (those with <50 letters at baseline gained 19 more letters than those with a baseline of >80; $P<0.0001$). Each aflibercept injection was also associated with a gain of 0.4 letters ($P=0.03$).

Stratton *et al* (2019) (92) retrospectively explored data from 3,151 eyes with DME from 21 UK centers. Significant variation in dosing with aflibercept was observed between centers, with the time for 50% of eyes to receive 5 injections ranging from 16–44 weeks. At 12 months, the proportion who had received at least 5 injections was between 62% and 93%. Younger patients and those with worse vision at baseline were more likely to experience VA improvements and each additional aflibercept injection increased the chance of improvement of 10 or more letters by 5% (no p-value given). The authors concluded that the audit showed a high level of heterogeneity in aflibercept treatment protocols and outcomes.

Talks *et al* (2019) (93) carried out an audit of 21 centers that were using aflibercept to treat patients with DME and compared outcomes of those that used 3 loading doses with those that

used 5 loading doses. At 12 months, the improvement in VA was 5 (range: -1 to 12) in the 3-dose group (n=763) and 5 (range: 0 to 12) in the 5-dose group (n=367). Regression analysis showed that improvement in VA was associated with age (*P*=0.003) and baseline ETDRS letter score (*P*<0.0001), but not the number of injections (*P*=0.07) or protocol (*P*=0.60).

RVO

Ao *et al* (2018) (94) analyzed a randomized 10% longitudinal data sample of Pharmaceutical Benefits Scheme (PBS) prescriptions of patients initiating VEGF therapy for RVO. 681 patients completed a year of treatment and 36% received aflibercept, while 60% had BRVO and 45% had CRVO (5% had treatment for both conditions). In the first year of treatment 29% of patients received 9 prescriptions, 35% received 6–8, 28% received 3–5 and 8% received <3. The distribution of prescriptions was similar between BRVO and CRVO (no p-value given). The authors concluded that over 2/3 of patients did not achieve resolution of RVO and almost 1/3 required ≥6 injections in the second year.

Gkika *et al* (2019) (95) retrospectively analyzed the outcomes of treatment-naïve patients with macular edema due to CRVO who received T&E aflibercept in a single clinic. A total of 245 patients received a mean of 7 injections and their mean VA improved from a baseline of 50 letters to 60 letters (mean follow up was 227 days) (no p-value given). The authors concluded that this real-life data suggests the T&E regimen is effective for the treatment of macular edema secondary to CRVO, requiring fewer aflibercept injections and reducing the treatment burden.

Scott *et al* (2019) (96) carried out a pre-planned secondary analysis of the Study of Comparative Treatments for Retinal Vein Occlusion 2, which was a randomized clinical trial involving 346 patients from 66 private clinics or academic centers in the US. Significant improvements occurred from baseline to month 6 in the composite score of the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) in both the aflibercept (mean change of 7.5; *P*<0.001) and bevacizumab (mean change of 6.1; *P*<0.001) cohorts. At Month 6 there were no differences in composite or subscale scores between the two treatments.

Unapproved or exploratory studies

Benner *et al* (2019) (97) retrospectively reviewed charts of patients who received aflibercept during the recall of aflibercept that began on February 28, 2018. At a single university-based practice, affected vials were used in 320 patients without any known cases of inflammation, but bevacizumab was used as an alternative for those who preferred to switch. During the period of analysis, bevacizumab was used in 81 injections, aflibercept in 49 and ranibizumab in 2. At the second visit, patients who had received bevacizumab were transitioned back to aflibercept. In both switched and maintained patients the change in VA was 0 letters (*P*=0.253) and the median change in CST was +3 µm for switched and -6 µm for maintained patients (*P*=0.085). The authors concluded that the switch to bevacizumab did not have a deleterious effect on patients and saved $153,900.

DR – Note: EYLEA is not approved for the DR without DME indication in the EMA and EU regions. In the US, EYLEA is approved for the treatment of non-proliferative DR without DME.

Halim *et al* (2019) (98) graded fundus images from the CLARITY study that were obtained from DR eyes treated with aflibercept. From the 232 eyes that were analyzed, there were 88 that exhibited neovascularization of the optic disc (NVD) and 355 had neovascularization elsewhere (NVE). The total number of NVD and NVE lesions was reduced in the aflibercept arm of the study compared with panretinal photocoagulation at 12 weeks (OR 0.26; $P<0.001$) and 52 weeks (OR 0.27; $P<0.001$). The authors concluded that aflibercept was a better treatment than panretinal photocoagulation at both time points and at all disease locations.

Ramu *et al* (2019) (99) reported on a sub-study of CLARITY that explored the effect of PRP and aflibercept on visual outcomes in PDR patients. Of 232 patients, 90 had received bilateral PRP at baseline, of which 43 were randomized into a 'repeat PRP' arm. Of 83 patients who were PRP-naïve at baseline, 43 were randomized into a 'new PRP arm' and 39 into an aflibercept arm 'no PRP'. There was a significant decrease in BCVA in the 'repeat PRP' arm ($P=0.0346$) and the 'new PRP' arm ($P=0.0017$) and a significant increase in BCVA in the 'no PRP' arm ($P<0.0001$) at 52 weeks. The authors concluded that aflibercept had a clear advantage over PRP.

Toraih *et al* (2019) (100) evaluated a panel of circulating hyperglycemia-related long non-coding RNAs (lncRNAs) in patients with 130 patients with diabetes (with and without DR) treated with aflibercept. A month after aflibercept injection significant reductions in CMT and VA were seen in the DR cohorts ($P=0.001$ and $P<0.001$, respectively). The 4 lncRNAs were overexpressed in the plasma of DR patients compared with controls, but their levels did not correlate with the severity of retinopathy or drug response.

Pearce *et al* (2019) (101) reanalyzed fundus images of 55 eyes from patients with proliferative diabetic retinopathy (PDR) who were treatment-naive and had received aflibercept in the CLARITY Phase IIb non-inferiority study. Images from baseline, Week 12 and Week 52 were analyzed. At Week 12, 48/55 (87.3%), 36/43 (83.7%) and 0/32 (0%) patients who had deep hemorrhages (DH), intraretinal microvascular abnormalities (IRMA) and venous beading (VB), respectively, had improved. Between Week 12 and Week 52, 18 of 55 patients with DH showed further improvements, 21 had no change, and 10 worsened. In patients with IRMA, 14 showed further improvements, 9 had no change and 15 worsened, and in patients with VB, none improved, 30 had no change, and 2 worsened. The authors concluded that in patients with PDR, aflibercept appears to improve DH and IRMA after just 3 injections, but that once injections are reduced, these parameters can deteriorate again.

Lemaitre *et al* (2019) (102) conducted an observational, descriptive and ambispective study into the off-label use of anti-VEGFs in two French centers. Patients were enrolled who were treated with ranibizumab or aflibercept for the following indications: neovascular glaucoma, macular neovascularization secondary to retinal inflammation, idiopathic choroidal neovascularization in young patients, exudation secondary to macular telangiectasia,

exudation secondary to macroaneurysm and rubeosis iridis. After 3 months of treatment, significant improvements in BCVA and significant reductions in CRT were observed (no p-value given). In neovascular glaucoma a decrease of IOP was noted from 37.5 mmHg to 28.8 mmHg one month after injection (no p-value given). In iris or pre-retinal neovascularization, the regions of neovascularization disappeared after one injection.

Muralha *et al* (2019) (24) prospectively assessed the incidence of transitory central retinal artery occlusion (tCRAO) in 807 patients with retinal diseases who received 4,069 anti-VEGF injections. 18 patients (0.44%) presented with tCRAO, of which 14 were graded as mild cases and 4 severe. The mean age of the affected patients was 65.3 ± 8.93 years and it was more frequent in females (61.1%). 5 of the affected patients had nAMD, 9 had DME 3 had RVO and 1 had myopic macular degeneration. tCRAO occurred after a single injection in 7 of the patients, after 2 injections in 6 patients and after >3 injections in 3 patients.

Vedantham *et al* (2019) (103) retrospectively investigated the outcomes of 46 eyes that received aflibercept for high risk pre-threshold ROP, threshold ROP and aggressive-posterior ROP. Aflibercept led to the regression of ROP in all 46 eyes one week after the first injection. 15 eyes (32.6%) achieved complete vascularization with no recurrence of ROP at varying time intervals up to 64 weeks and did not require a secondary intervention. In 81.8% of Zone I ROP eyes, aflibercept facilitated the continuation of retinal vascular development following ROP regression, resulting in less extensive laser during treatment of ROP recurrence.

Summary of Newly Identified Information on Efficacy and Effectiveness:

Recent publications add to the growing body of evidence corroborating the positive benefit-risk profile of Eylea. Within the current observation period, there continues to be exponential growth in the volume and scope of published studies with EYLEA. A significant proportion of papers and studies evaluated the duration of treatment or frequency of treatment and their relationship to visual and/or anatomic outcomes. EYLEA is the standard of care in multiple regions of the world, and this is reflected in important trials, which incorporate EYLEA as the positive control arm, the reference standard, in pivotal nAMD PIII trials of other investigative therapies. Multiple publications report on the Hawk and Harrier (Cahil M, Chang A, Dugel P, Holz F, McAllister I), two such trials, which evaluated the efficacy and safety of brolucizumab, an intravitreal anti-VEGF antibody SC fragment, administered with a complex dosing regimen with rescue-eligible extension to every 12-week dosing after 16 weeks from baseline. These cohorts were compared to EYLEA administered every 8 weeks following the monthly loading dose phase. In these trials, the proportion of subjects achieving and maintain a every12 week dosing regimen by week 48 (57% and 52%, respectively) were comparable to outcomes already shown by EYLEA, where, in the ALTAIR PIV study (Ohji et al (104)), approximately 58-60% reached an intended every12week dosing interval at 52weeks, and maintained 60% or more every 12 week dosing with over 40% reaching every 16 weeks (Ohji *et al*. (105)) Moreover, brolucizumab treated groups did not show superior visual outcomes in the reported aggregated visual acuity data for both groups of the subjects achieving every 12-week posology and those requiring rescue and return to every 8 weeks, compared with EYLEA in either study. Study outcomes for the 96week timepoint show that the proportion

maintained Q12 week dosing remain less (~38-46%) than that reported for aflibercept (~60%). Recent publications highlight anatomic outcomes (CST or decrease in SRF and or IRF) showing that the aggregate data for Q8/Q12w dosed brolucizumab showed statistically better reductions. The importance of this finding is diminished as results for the individual fluid regions (SRF vs IRF) were not shown. Currently the presence of subretinal fluid has been shown in multiple studies to be associated with better visual outcomes, while in contrast, presence of IRF is associated with worse visual outcomes. Thus, the clinical significance of these findings in HAWK/HARRIER is unknown at this time. Eleftheriadou et al (2018) (58) showed vision gains comparable to pivotal RCTs with aflibercept treatment over a 3-year period in nAMD patients: At 3 years, the mean VA gain was 6.6 ± 15.4 letters, and the change in CSMT was -77.9 ± 101.4 µm with an absence of macular fluid in 71% of eyes with the mean total number of injections of 15.9 ± 6.1.

Important learnings from real-world evidence type of studies were published, from both Bayer sponsored observation studies and others recently published. These studies confirm the importance of adequate treatment intensity early with less intensity in the later years and their association to better visual outcomes in DME, while those in nAMD showed the importance of regular treatments in maintaining the robust vision gains generally achieved in the first year.

Several nAMD observation studies established the relevance of regular versus irregular posology of treatment with EYLEA. APOLLON observation trials confirmed the importance of the initial monthly loading doses and the importance of regular treatment, defined as >6 injections within the first 12 months, and its association with better visual outcomes. The Asteria observational trial confirmed the beneficial effect of EYLEA for DME subjects and the benefit of sufficient numbers of loading doses and associated visual acuity gains.

Exploratory studies or unapproved indication studies are providing emerging evidence of potential efficacy and beneficial effects of aflibercept treatment for other retinal diseases. The PANORAMA study (Brown (106)), a double-masked, randomized, Phase III trial in non-proliferative retinopathy (NPDR) patients examined whether aflibercept administered every 8week after 5 initial monthly doses or following a every 16 week after 3 monthly and one 8week interval dose improved the diabetic retinopathy severity scale score at week 24 and at 52 weeks compared to sham treatment. Overall, of EYLEA patients, achieved and maintained a >2-step improvement in DRSS scores in the majority of subjects compared to the low proportions observed in sham. The proportion of patients with a ≥2-step improvement in DRSS score was significantly greater with aflibercept 2q8 and 2q16 versus sham at Week 52 (80% and 65% versus 15%, $P<0.0001$ for both). The proportion of patients who developed vision-threatening complications or center-involved DME was significantly lower with aflibercept 2q8 and 2q16 than with sham (3% and 4% vs. 20%; $P<0.001$ for both). Halim et al, and Ramu et al confirmed in the CLARITY study of aflibercept treatment in DR that aflibercept was a better treatment than panretinal photocoagulations at 12weeks and 52 weeks, showing statistically reduced neovascularization and statistically better visual outcomes than PRP.

In summary, the benefit risk profile of EYLEA remains positive, based on the prior randomized clinical trial results and the prior and current review of this year's ever-increasing volume of published prospective, retrospective, and observational studies across multiple approved and unlicensed indications. These treatment benefits are seen in both treatment naïve patients as well as those switched from ranibizumab and/or bevacizumab. Proactive dosing using a treat-and-extend or fixed bimonthly dosing regimen generally results in better treatment outcomes than PRN dosing. Several studies illustrated the importance of an intensive early treatment phase (typically 3 monthly injections in neovascular age-related macular degeneration and 5 monthly injections in diabetic macular edema). Audits of electronic medical records showed substantial differences among treatment centers in terms of patient demographics and disease characteristics as well as treatment regimens.

12. Other Periodic Reports

No other PBRER/PSURs have been prepared for aflibercept for ophthalmological indication by other parties during the report interval.

13. Lack of Efficacy in Controlled Clinical Trials

During the PBRER/PSUR interval there have been no reports of lack of efficacy from aflibercept clinical trials which could have a direct impact on subjects' safety.

14. Late-Breaking Information

December 2019: Physicians in Israel were concerned with intraocular inflammations following the injection of Eylea with 3 particular batches (KT03900, KT033KP, KT037VV). The Ministry of Health in Israel distributed a local DHCPL asking HCPs to avoid using these 3 batches until all quality investigations are completed. Not more than 5 cases of intraocular inflammation were received per batch, cases were spread across the months, some cultures returned negative and some were positive for different microorganisms (Staph. epi, unspecified Streptococcus, Streptococcus viridans, Granulitacella adiacens). No further intraocular inflammation case from any other country worldwide was received from other batches coming from the same drug product batch. To date, no quality deficit of any of the 3 batches could be confirmed by Bayer or its filling facility. In the meantime, the Israeli Ministry of Health concluded their sterility investigations without any findings and communicated that the batches can continue to be used (January 2020).

Overall, to date no product related safety concern could be identified that would have led to the development of intraocular inflammations. The global reporting rate of intraocular inflammation rate remained stable, no increase was observed. These findings are considered local occurrences and do not change the positive benefit risk assessment of Eylea.

Otherwise no further potentially important safety, efficacy and effectiveness findings have arisen after the data lock point of this PBRER/PSUR which would alter the evaluations of risks, or the integrated benefit-risk evaluation for aflibercept.

15. Overview of Signals: New, Ongoing, or Closed

A tabulation of signals ongoing and closed during the reporting interval can be found in Table 15-1 .

Table 15-1: Tabular Summary of Safety Signals (ongoing/closed)

Signal Term	Date detected	Status (ongoing or closed)	Date closed (for closed signals)	Source or trigger of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
Cluster of intraocular inflammations in the United States of America	05 SEP 2017	closed	12 SEP 2019	Single cases	An increase in intraocular inflammation (IOI) cases was observed in the USA in Q3/2017 through Q1/2018. A potential link to 2 co-distributed Becton Dickinson syringe batches was observed in US. No Eylea product deficit was detected. Syringe quality investigations was completed during this repprting period. IOI reporting rates ex-USA remained stable.	Review of global and US specific IOI cases and reporting rates US batch quality reviews. Syringe quality investigations.	In US Regeneron Pharmaceuticals informed FDA and sent voluntary letters to Eylea prescribers to inform about potential link between increase in intraocular inflammations and 2 batches of Becton Dickinson syringes. Bayer voluntarily informed Health Authorities in Rest of the World about increase in IOIs in US. Quality investigations of syringe completed during reporting period, no root cause identified.

Table 15-1: Tabular Summary of Safety Signals (ongoing/closed)

Signal Term	Date detected	Status (ongoing or closed)	Date closed (for closed signals)	Source or trigger of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
Artery Dissection/Aneurysm	Signal validated 07 JAN 2019 (based on PRAC meeting minutes from meeting 26-29 NOV 2018)	closed	14 FEB 2019	PRAC signal	On 16 MAY 2019 PRAC requested MAHs of VEGF inhibitors for intravitreal administration: to submit by 31 JUL 2019, a cumulative review of all cases of artery dissections and aneurysms with their respective products.	Cumulative review of clinical trial data, literature, and single cases.	Signal refuted by MAH and PRAC, no action necessary.

15.1 Specific Topics to be reviewed

15.1.1 Analysis of Fatal Cases

A total of 2099 new PSUR qualifying fatal cases were received during the current reporting period and are discussed in this section. Table 15-2 provides an overview on the number of fatal cases by reporting source and causality assessment.

Table 15-2: New fatal PSUR Qualifying Cases by Reporting Source and Case Causality

Reporting Source	Case Causality[a]		Total
	Not related	Related	
Spontaneous/literature	4	50	54
Interventional study	38	1	39
Solicited postmarketing sources	--	2,006	2,006
Total	**42**	**2,057**	**2,099**

[a] A case is "related" if at least one event (not necessarily the fatal event) is assessed as related by the investigator/reporter and/or the MAH.

Of the 2,099 PSUR qualifying fatal cases, 1,976 (94%) were reported from the USA and 123 cases (6%) from other countries, with 5 or more cases reported from Canada (50 cases), Poland (14 cases), Japan (9 cases), Great Britain (8 cases), Australia (7 cases), South Africa (6 cases), Italy (5 cases) and Switzerland (5 cases). The vast majority of fatal cases were derived from solicited postmarketing sources (2006 of 2099 fatal cases; 96%) and here particularly from the US reimbursement / patient support program ("EYLEA4U"; 1875 cases).

EYLEA4U is a Regeneron-sponsored US-only patient support program providing patients and healthcare providers with reimbursement and product support. Annual enrollment into this program during the reporting interval was in excess of 250,000 patients. Physicians can enroll patients in the EYLEA4U program to assist in confirming they have appropriate insurance coverage to receive Eylea. When a new patient is enrolled, a benefit investigation is conducted to confirm coverage. This can be at the request of an HCP or routine annual reverification of benefits. As part of this process, the MAH may learn from the HCP that there is no further need for insurance coverage because the patient has died. Per the established process, follow-up is requested to confirm the patient's exposure to Eylea and to obtain additional details on the patient's death (date and cause). Safety reports originating from this program are considered solicited for pharmacovigilance case processing and reporting. Often no explicit causality assessment is provided by the reporter and the case information is too limited for a conclusive company assessment. The small number of cases that reported a cause of death that was expressly assessed by the reporter as causally related to aflibercept, are discussed in more detail below.

Table 15-3 displays the number of cases per indication for use of aflibercept and reporting source.

Table 15-3: Fatal PSUR Qualifying Cases, by Indication and Reporting Source

Product Indication	Reporting Source			Total
	Spontaneous/ Literature	Interventional study	Solicited postmarketing sources	
Age-related macular degeneration*	18	8	1340	**1,366**
Diabetic macular edema§	7	11	345	**363**
Unspecified retinal vein occlusion	3	--	186	**189**
Central retinal vein occlusion	2	2	21	**25**
Branch retinal vein occlusion	2	--	13	**15**
Diabetic retinopathy without macular edema	--	11	7	**18**
Other#	2	6	18	**26**
Not reported/unknown	20	1	76	**97**
Total	**54**	**39**	**2,006**	**2,099**

* Including not further specified macular degeneration and choroidal neovascularization.
§ Including cases reporting diabetic retinopathy in conjunction with macular edema as the indication.
# Other indications reported more than once included vitreous haemorrhage (8), unspecified retinal/macular edema (6), retinal neovascularization (2) and cataract (2).

The indication of use of aflibercept was reported for 2,002 of the 2,099 cases (95%). Reported indications included AMD/macular degeneration in 1366 cases (68% of cases with known indication), DME in 363 cases (18%), RVO (CRVO, BRVO or unspecified) in 229 cases (11%) and diabetic retinopathy without mention of macular edema in 18 cases (1%). The indication for aflibercept was unknown in 97 cases (5%). Except for a lower proportion of cases with unknown indication (5% in the current reporting interval vs. 39% in the previous reporting interval), no relevant differences were observed in the distribution between the indications when compared to the previous reporting period. Regeneron retrained vendor staff of the reimbursement program and updated the data collection form to improve the medical documentation on fatal cases derived from the reimbursement program. This led to the receipt of additional indication information for cases than had been reported in prior years.

Table 15-4 (reporting period) and Table 15-5 (cumulative since launch) display the distribution of fatal cases from postmarketing sources (i.e., excluding reports from interventional trials) per indication together with the corresponding reporting rates, based on indication-specific patient exposure estimates (see section 5.2). Numbers from the last year's PSUR No. 8 are included in Table 15-4 for comparison. The overall reporting frequency of fatal cases for the current reporting interval is similar to the previous reporting period. Considering the lower number of cases with unknown indications compared to the previous reporting interval, the distribution of fatal cases across indications is very similar to the previous year and no meaningful differences between the reporting periods are apparent.

Table 15-4: Number and Reporting Rate of Fatal Cases from Postmarketing Sources, by Indication – Current and Previous Reporting Periods

Product Indication	Current reporting period			Previous reporting period (PSUR No 8)	
	Number of cases (%)	Patient exposure in patient-years	Reporting rate per 10,000 pt-yrs	Number of cases (%)	Reporting rate per 10,000 pt-yrs
Age-related macular degeneration[a]	1,358 (65.9%)	572,873	23.7	827 (42.3%)	15.9
Diabetic macular edema[b]	352 (17.1%)	286,436	12.3	232 (11.9%)	8.9
CRVO, BRVO, unspecified RVO	227 (11%)	209,319	10.8	128 (6.5 %)	6.7
Diabetic retinopathy w/o macular edema	7 (0.3%)	33,050	NA	2 (0.1%)	NA
Other	20 (1.0%)	NA	NA	14 (0.7%)	NA
Not reported/unknown	96 (4.7%)	NA	NA	753 (38.5%)	NA
Total	**2,060 (100%)**	**1,101,678**	**18.7**	**1,956 (100%)**	**19.6**

Table 15-5: Number and Reporting Rate of Fatal Cases from Postmarketing Sources, by Indication – Cumulative

	Number of cases	%	Patient exposure in pt-years	Reporting rate per 10,000 pt-yrs
Age-related macular degeneration*	4,439	71.0%	2,361,215	18.8
Diabetic macular edema[b]	914	14.6%	1,180,607	7.7
CRVO, BRVO or unspecified RVO	569	9.1%	862,752	6.6
Diabetic retinopathy w/o macular edema	17	0.3%	NA	NA
Other	75	1.2%	NA	NA
Not reported/unknown	237	3.8%	NA	NA
Total	**6,251**	**100.0%**	**4,404,574**	**14.2**

[a] Including not further specified macular degeneration and choroidal neovascularization.
[b] Including cases reporting diabetic retinopathy in conjunction with macular edema as the indication.

Cause of Death

In the following, cases are presented and discussed according to the reported cause of death, which was grouped as cardiovascular, non-cardiovascular or unknown. Pursuant to a corresponding request in the PSUR Assessment Report for previous PSUR No. 8, cases with a known cause of death and "with no predisposing factors" are highlighted.

Cases reporting a cardiovascular cause of death

A total of 38 new PSUR qualifying cases with fatal outcome reported a cardiovascular cause of death, including 15 spontaneous reports, 13 cases from interventional studies, 8 cases from solicited postmarketing sources and 2 cases from published studies. These cases concerned 26 male and 7 female patients; gender was not reported in 5 cases. Patient age was known in

33 cases and in those cases ranged from 41 to 94 years (median, 72 years). The reported death causes were (acute) myocardial infarction (14 cases), ischemic, hemorrhagic or unspecified cerebrovascular accidents (10 cases), cardiac/cardio-respiratory arrest (4 cases), (congestive) heart failure (3 cases), aortic aneurysm rupture (2 cases), not further specified cardiac disorder (2 cases), pulmonary embolism (1 case) and not further specified infarction (1 case); the remaining case reported multiple cardiovascular and non-cardiovascular events (2019-186376; see below).

Time to onset from first administration to onset of the fatal event was known in 26 of the 38 cases and in those cases ranged from approximately 4 months to more than 3 years (median, 19 months). Time to onset from the last dose to onset of the fatal event was known in 29 cases and in those cases ranged from the day of administration to almost 2 years (median, 57 days). The total number of administered injections was known in 19 cases and ranged from 2 to 23 injections (median, 7 injections).

Any medical history or comorbidity was reported in 23 of the 38 cardiovascular death cases and each of these cases included (mostly multiple) risk factors for the reported cardiovascular event, most frequently diabetes mellitus (17 cases), hypertension (15 cases), heart failure (7 cases), hyper-/dyslipidemia (5 cases), coronary artery disease or prior myocardial infarction (5 cases), and/or arrhythmia (5 cases). In one additional case, presence of diabetes mellitus was evident from the indication for use of aflibercept (DME), although diabetes was not coded as a comorbidity. In further 2 cases, no medical history or comorbidities were reported, but concomitant drugs included antiplatelet agents, thereby suggesting the presence of cardiovascular risk factors.

The reporter considered the fatal event(s) unrelated to aflibercept in 21 of the 38 cases and did not provide a causality assessment in further 15 cases. The fatal event was considered related to aflibercept in 2 cases:

- [redacted]: A spontaneous report from a physician of a 53-year-old male patient who died from myocardial infarction almost 2 years after initiation of aflibercept for DME and 13 days after administration of the last dose. Relevant comorbidities included diabetes mellitus and malignant hypertension.
- [redacted]: A case identified in a clinical trial publication describing an 81-year-old patient who died from myocardial infarction 10 weeks after his 9th injection of aflibercept in the indication CRVO. Risk factors included concurrent atrial fibrillation, congestive heart failure, diabetes mellitus and hypertension, a previous myocardial infarction and a 25 pack-year smoking history.

Company comment: The reporters did not explain why they considered the myocardial infarction to be causally related to aflibercept in either case. Multiple, significant risk factors were reported and sufficiently explain the event in both cases.

Three reports of fatal cardiovascular events concerned patients who were younger than 50 years old; these cases were reported from different clinical trials in the indication diabetic retinopathy:

- [redacted]: A 41-year-old female patient who experienced fatal myocardial infarction 12 days after her 5th aflibercept dose. Pertinent medical history included diabetes mellitus, hypertension, congestive heart failure, hypercholesterolemia and hypokalemia.
- [redacted]: A 47-year-old female patient who experienced acute kidney injury and intraventricular hemorrhage approximately 6 weeks after her 5th aflibercept dose. Pertinent medical history included inadequately controlled diabetes mellitus, hypertension and hypercholesterolemia.
- [redacted]: A 43-year-old female patient who experienced fatal diabetic ketoacidosis, septic shock, myocardial infarction, cerebrovascular accident and cardiac arrest, with the onset date of all events reportedly 11 days after her 7th aflibercept dose. The patient's relevant medical history included diabetes mellitus, hypertension and a not further specified abscess.

Company comment: Each of the above patients had multiple risk factors for the reported fatal event(s). The investigator considered the fatal events unrelated to aflibercept in each of these cases, citing the patients' respective comorbidities as an alternative explanation in each case.

Cases reporting a cardiovascular cause of death with no reported predisposing factors

The PSUR Assessment Report for previous PSUR No. 8 included a request to highlight cases "with no predisposing factors". As summarized above, predisposition for cardiovascular events was evident from the available case information in 26 of the 38 cardiovascular death cases. In the remaining 12 cases, no predisposing factors for cardiovascular death were reported in addition to advanced patient age (median age in 10 cases reporting patient age: 81 years) and mostly male gender (9 of 11 cases where gender was reported). In the given postmarketing pharmacovigilance setting and in view of the demographic characteristics of the patients, lack of information on comorbid conditions and risk factors is assumed to be more likely due to incomplete case information rather than proof of true absence of these factors. There is ample indication of such missing information and underreporting of predisposing factors in the analyzed case set, for example:

- Time to onset from first administration to onset of the fatal event was not reported in 8 of the 12 cases with no reported predisposing factors as compared with 4 of the 26 cases where predisposing factors were identifiable. Case information was similarly incomplete in regard to the number of administered aflibercept injections (unknown for 9/12 cases with no reported predisposing factors);
- Reporting of predisposing comorbidities was likely incomplete. For example, hypertension was reported as a comorbidity in only 15/38 cases (39%), whereas the

general population prevalence of hypertension in the concerned age group is approximately twice as high (107) (108);

- Similarly, concomitant treatments appear to have been incompletely reported: despite access to IVT aflibercept therapy, only 14 of the 26 cases (54%) with identifiable predisposing factors and none of the 12 cases without identifiable predisposing factors reported any concomitant medications. Several cases reporting diabetes mellitus or hypertension as comorbidities did not report corresponding medication.

The fatal event in the 12 cases without identifiable additional predisposing factors for cardiovascular events was assessed by the reporter as unrelated to aflibercept in 6 cases; no causality assessment was provided in the other 6 cases. None of the 12 cases stated that alternative causes for the fatal event were absent or ruled out, or that, in the view of the reporter, the fatal event was causally related to aflibercept.

Overall, no unexpected patterns or clusters were identified during from review of the cases describing death of patients from cardiovascular causes that would give reason to assume a causal role of aflibercept in the patients' demise.

Cases reporting other (non-cardiovascular) causes of death

A total of 30 deaths citing non-cardiovascular causes were newly received during the reporting interval, including 14 cases from interventional studies, 7 spontaneous reports, 8 cases from solicited postmarketing sources and 1 literature report. These cases concerned 11 male and 16 female patients; gender was not reported in 3 cases. Patient age was known in 29 cases and in those cases ranged from 36 to 101 years (median, 81 years). The reported death causes were various malignancies in 8 cases, pulmonary or non-pulmonary infection or sepsis in 8 cases, renal failure in 3 cases, injuries/accidents in 2 cases, and single cases of various gastrointestinal, neurological, metabolic or poorly specified disorders.

Predisposing factors for the reported fatal event(s) in addition to age were apparent in 20 of the 30 cases, for example underlying COPD or cerebral disease in patients who died from pulmonary infections or aspiration pneumonia; diabetes, immunosuppressive medications or recent surgery in patients who died from non-pulmonary infections; diabetes or potentially nephrotoxic drugs in patients who died from renal failure; or prior (other) malignancy / chemotherapy treatment in patients who died from a malignancy.

Time to onset from first administration to onset of the fatal event was known in 22 of the 30 cases and in those cases ranged from approximately 1 month to more than 2 years (median, 13 months). Time to onset from the last dose to onset of the fatal event was known in 19 cases and in those cases ranged from the day of administration to more than 2 years (median, 48 days). The total number of administered injections was known in 15 cases and ranged from 1 to 19 injections (median, 6 injections).

In 3 cases, the reporter considered the fatal non-cardiovascular event to be related to aflibercept. One of these cases concerns a 75-year-old female who died from lung cancer approximately 2 years 3 months after initiation of aflibercept for AMD (2019-038878); a

second case describes an 85-year-old female who died from acute kidney injury approximately 3.5 months after initiation of aflibercept for AMD (2019-066232). Both of these cases are too poorly documented for meaningful assessment (e.g., no exact information on the nature of the reported event, unknown medical history, no information on possible predisposing factors such as smoking history or drug exposure), and the reporters did not provide their reasoning for assuming a causal relationship to aflibercept in either case. The third case describes ischemic colitis; fatal outcome of this event appears to have been coded erroneously (2019-032359; see above).

Three reports of fatal non-cardiovascular events concerned patients younger than 50 years; these cases were reported from clinical trials:

- [redacted]: A 36-year-old female patient who died from septic shock and multiple organ dysfunction syndrome 10 months after starting and 7 months after ending aflibercept for treatment of CNV. The patient's medical history included heart transplant and concomitant treatment included an immunosuppressant. The suspected root cause of sepsis was not reported.
- [redacted]: A 42-year-old female patient who died from renal failure approximately 3.5 months after her 19th dose of aflibercept for treatment of proliferative diabetic retinopathy. Relevant medical history included diabetes mellitus, hypertension and hypercholesterolemia. No further information on the nature or possible cause of the patient's kidney disease was available.
- [redacted] A 46-year-old female patient who died from a coma approximately 8 weeks after her 7th dose of aflibercept for treatment of proliferative diabetic retinopathy. Medical history included diabetes mellitus, hypertension and hypercholesterolemia. The assumed cause of coma was not reported.

Company comment: In-depth assessment of these cases is impeded by limited information on the nature and context of the respective fatal event, although possibly predisposing factors are identifiable in all cases. The investigator considered the fatal events unrelated to aflibercept in each of these cases.

Cases reporting a non-cardiovascular cause of death with no reported predisposing factors

As summarized above, one or more predisposing factors for the reported fatal event(s) were identifiable in 20 of the 30 cases reporting a non-cardiovascular cause of death. In the remaining 10 cases, no predisposing factors other than advanced patient age (age range in these 10 cases, 72-101 years; median: 85 years) were identifiable. None of these 10 cases mentions that risk factors or alternative causes for the reported fatal event were absent or ruled out. As discussed above for the cardiovascular death cases without identifiable predisposing factors, these cases are incompletely documented overall and in the given postmarketing pharmacovigilance setting, lack of information on the presence of disease-specific risk factors is assumed to be more likely due to incomplete case information than evidence of their true absence.

Overall, no unexpected patterns or specific concerns arise from review of the cases reporting non-cardiovascular causes of death.

Cases with unknown cause of death

In 2,030 of the 2,099 new fatal cases (97%), the cause of death was not specified. Of these 2030 cases, 12 cases were from interventional studies, 28 were spontaneous reports, and 1,990 cases originated from solicited postmarketing sources, including 1,866 cases from the US reimbursement program. Of these 2,030 cases:

- 26 cases report one or more adverse events that could plausibly explain the patient's demise, although no adverse event was expressly reported as fatal. These events include various malignancies (6 cases), cerebrovascular accident (5 cases), (acute) myocardial infarction (3 cases), other/unspecified heart disease (3 cases), renal disease or failure (3 cases), infection/sepsis (2 cases), trauma/injury (2 cases), general health deterioration (2 cases) and single mentions of various pulmonary, neurological or hematological events. The cases concern 10 male and 15 female patients (gender unknown in 1 case) aged 57 to 97 years (median, 81 years). Almost all of these cases mention risk factors for the reported events as medical history such as diabetes, hypertension, and/or underlying cardiac or renal disease.
- Further 51 cases report adverse events other than "death" that however would usually not be expected to have a fatal outcome, such as ophthalmological events, unspecific complaints such as headache or dyspnea, and aflibercept medication errors such as dose omissions or off-label use. These cases concern 26 male and 24 female patients (gender unknown in 1 case) aged 52 to 99 years (median, 84 years).
- In the remaining 1,953 cases, "death" (1,951 cases) or "sudden death" (2 cases) is the only coded adverse event. Most of these cases (1,926 cases) originate from solicited postmarketing sources, in particular the US reimbursement program (1,821 cases). In accordance with good pharmacovigilance practices for organized data collection schemes, adverse events – including information on a patient's death – are captured in these programs and processed by the MAH irrespective of the cause of death or any assumed causal role of aflibercept. Most of these cases provide no more information than patient age and gender, limited treatment data and the information that the patient passed away, with no suspicion of drug-induced death. In most cases, further information or a causality comment could not be obtained from the prescriber despite repeated follow-up efforts. Of these 1,953 cases, 763 concerned male patients and 904 female patients; gender was not known in 286 cases. Patient age was known in 1,944 cases and in those cases ranged from 29 to 108 years (median, 86 years). Medical history or comorbidities were coded in 443 (23%) of these cases; most frequently this was diabetes mellitus (373 cases, mostly inferred from the indication DME). Other more commonly reported medical history / comorbidities in this case group included hypertension (74 cases), cardiovascular diseases (e.g., coronary artery disease, myocardial infarction, cerebrovascular accident, cardiac arrhythmias;

42 cases), dyslipidemias (43 cases), malignancies (29 cases), pulmonary disease (13 cases) and renal disease/failure (11 cases).

In 13 of the 2,030 cases (0.6%) with unspecified cause of death, the reporter considered the patient's death causally related to aflibercept. No reasoning for this assessment was provided in any of these cases; default conservative assessment or documentation errors thus cannot be ruled out in this small fraction of cases. Time to onset and number of injections were not reported in most of these 13 cases. Indication was reported in 10 of these cases and was mostly AMD (8 cases). The very limited information in these cases does not allow for meaningful case assessment.

Fifteen of the 2,030 cases with unspecified cause of death concern patients younger than 50 years of age (range, 29-49 years). Indication for aflibercept was DME in 14 of these cases and AMD in 1 case. Medical history / comorbidities (other than diabetes mellitus) were reported only in 1 case and in this case included multiple cardiovascular diseases and risk factors. Time from first and last dose prior to the patient's demise was reported in 6 cases and in those cases ranged from 8 months to 2 years and from 25 days to 10 months, respectively. The total number of aflibercept injections, reported in 14 of the 15 cases, ranged from 1 to 18 (median, 8 injections). None of these deaths was assessed as related to aflibercept by the reporter. The very limited information in these 15 cases does not allow for meaningful case assessment; however, the presence of diabetes mellitus in most cases implies that these patients were at elevated mortality risk despite their relatively young age.

Overall, from the limited information available in this set of cases, no unexpected patterns or clusters were identified that would give reason to assume that aflibercept causally contributed to the death of these patients.

Summary and Conclusion

A total of 2,099 new PSUR qualifying cases reporting on death or fatal outcome were received in the current reporting period. As in previous reporting intervals, most cases were received from the US reimbursement program. The total number of fatal PSUR qualifying cases (2,099 cases), the number of cases received from the US reimbursement program (1,875 cases) and the number received from other sources (224 cases) were similar to the previous reporting interval (1,984 cases overall, 1,805 cases from the US reimbursement program and 179 cases from other sources, respectively; cf. Eylea PSUR No. 8). The overall reporting frequency of PSUR qualifying fatal cases was also similar during the current and previous reporting intervals (18.7 and 19.6 cases per 10,000 patient-years, respectively).

The vast majority of cases from solicited postmarketing sources describe little more than the patient's demise, with no explicit causality assessment provided by the reporter. Because case information is too limited for conclusive company assessment, such case are mostly considered "not assessable" and thus qualify as related for regulatory purposes.

Where the cause of death was specified, the relative distribution of death causes was consistent with the expected frequency distribution in this elderly population, with cardio- and

cerebrovascular disease, malignancies and (pulmonary) infections accounting for the majority of deaths. Cases with an identifiable cause of death and those with fatal events expressly considered to be causally related to aflibercept by the reporter, were reviewed in-depth. Patients were mostly of advanced age and pertinent risk factors additional to patient age were identifiable in the majority of cases. A dedicated review of reports with no additional reported predisposing factors revealed that these cases were less well-documented overall, suggesting that lack of pertinent information is more likely due to incomplete case information than evidence of true absence of these factors. Similarly, no signal arose from the review of reports of deaths of particularly young patients.

Overall, no patterns or clusters were noticed in regard to clinical characteristics, number of injections or the temporality of events that were considered indicative of a possible causal association between IVT treatment with aflibercept and patient death of any cause. None of the information gathered on fatalities changes the overall assessment of the positive benefit-risk profile of aflibercept. The company will continue to monitor fatal cases.

15.1.2 Macular Edema

Macular edema is a symptom of macular degeneration (AMD), blockage of the retinal vein (CRVO, BRVO) or associated with diabetes (DME diseases), amongst others, and some genetic disorders (such as retinitis pigmentosa or retinoschisis). Macular edema can also be caused by eye surgery (including cataract surgery), chronic or intermediate uveitis and some drugs (rosiglitazone, epinephrine, acetazolamide, betaxolol, timolol, latanoprost, thiazolidinediones, etc.).

The MAH was requested by EMA in the assessment report for PBRER 6 (2016) to further monitor the topic of macular oedema in the upcoming PBRERs/PSURs in order to assess long-term efficiency of aflibercept with the posology approved for CRVO indication.

Search Strategy

The pharmacovigilance database was searched for PBRER/PSUR-qualifying cases newly received during the reporting period with a reported event as defined by the MedDRA PT “macular oedema”.

Results

Only one case was identified in the Global Safety Database in the reporting period where retinal vein occlusion was reported as indication:

2019-074265: This spontaneous case report medically confirmed originating from France, refers to a 91-year-old female patient who received a first dose of Lucentis 2 weeks after diagnosis of Central retinal vein occlusion with Major macular edema, the second dose after two months and the third injection one month thereafter. About six weeks after the last Lucentis dose the patient had one single dose Eylea. Six days later she was diagnosed with “purulent endophthalmitis (left eye)” for which Eylea was withdrawn and 55 days from the

day of injection her "macular oedema worsened (left eye)". Accordingly, the visual acuity worsened from 1/10 to 2.5/10.

Summary and conclusion:

One case was received during the reporting interval of macula edema in a CRVO patient. Since Eylea was only given once no conclusion on the posology can be made. No safety signal arose from that individual case regarding the development of macular edema and the use of Eylea.

15.1.3 Macular hole

Based on a PRAC request, a cumulative investigation of macular hole was first presented in PSUR#5. This was followed by annual reviews in the forthcoming PBRERs. In the last Assessment Report of PBRER # 8, covering the period 01 DEC 2017 to 30 NOV 2018, the MAH was requested to comment on the over-representation of the Japanese cases, to discuss the possible mechanisms for Macular hole as outlined by Akira Hirata and al. (2018) (109) and eventually to consider adding this AE in the EU product information. A cumulative thorough and in-depth analysis of this topic (cut-off date of 16 SEP 2019) addressing the PRAC requests is appended to this PBRER in **Appendix 8**. Based on the currently available information, an SmPC update is not warranted.

Cases received since data cut off of the cumulative investigation until the DLP of this PBRER did not change the overall assessment of this topic.

PBRER qualifying cases received in the reporting interval:

The below section reflects the annual analysis of initial PSUR qualifying cases regarding macular hole received from 01 DEC 2018 to 30 NOV 2019.

Search strategy

For this evaluation all new PSUR/PBRER - qualifying cases from this reporting period (01 DEC 2018 to 30 NOV 2019) were searched for the MedDRA PT "Macular hole".

Results

The search for PT "Macular hole" resulted in 9 new PBRER/PSUR-qualifying case reports. Of these 9 cases, 3 case reports were spontaneous, 1 report was from an interventional study and 5 were received from literature (4 articles from Japan and 1 from USA)

In 3 of 9 cases, patients were male and in 5 cases female. In the remaining one case, the information on patient's gender was missing.

Age ranged from 51 to 78 years of age (mean, 67 years; median, 67 years), 4 patients were elderly with an age ≥65 years and 3 patients were between ≥18 to <65 years (age group was not reported in 2 patients).

The reported indication was in 4 cases diabetic retinal edema, in 3 cases age-related macular degeneration, in two cases the indication was not further specified.

The onset latency from last dose of aflibercept was reported only in one case (1 month). The onset latency relative to first dose was not reported in any of the cases.

Overall, the outcome of the cases was reported as recovered or recovering/resolving in 5 out of 9 received case reports (55.5%). For 4 case reports (44.4%) this information was missing.

The total number of IVT injections of aflibercept given before occurrence of the macular hole ranged from 1 to 10 (median 3.0; mean 4.1).

Regarding risk factors 4 out of 9 patients were elderly with associated risk factors such as diabetes, premacular membrane, vitreomacular adhesion, PCV with retinal detachment, drusen. Three additional patients had diabetes and one had CNV with REP atrophy and macular cystoid edema. The remaining case was of minimal information, not allowing a proper causal assessment.

Publications/presentations:

In a recent study presented by Lisa J. Faia at the Retina 2019 Meeting (110), which was held in Waikoloa, Hawaii, investigated whether surgical intervention in cases of macular hole in wet and dry AMD would make a difference in visual acuity and hole closure outcomes. The retrospective, single-center chart review involved 12,716 patients with neovascular AMD and 15,196 patients with non-neovascular AMD. Macular hole developed in 199 eyes (0.7%), a similar incidence to that reported in idiopathic cases in patients without AMD. Of the cases of macular hole, 39 (0.3%) were seen in eyes with wet AMD and 160 (1%) in eyes with dry AMD. The mean number of injections before diagnosis of macular hole in eyes with wet AMD was 2.4.

Among the eyes that developed macular hole, 104 (81.8%) underwent surgery and internal limiting membrane peel. This resulted in closure in 89.8% of cases, but outcomes were worse in wet AMD (closure rate 81%) than in for dry AMD (closure rate 91.5%). There was no difference in visual acuity in eyes with wet AMD that underwent surgery, but there was a statistical difference in eyes with dry AMD ($p< 0.001$). Even though closure rates were similar in both groups, visual outcomes were better in patients with non-neovascular AMD with macular hole who underwent surgery than they were in those with neovascular AMD. The number of anti-VEGF agents used did not appear to increase the rate of macular hole formation. It seems likely that macular hole may represent only a coexisting pathology in older patients with AMD rather than an adverse effect to anti-VEGF treatment. This study adds evidence that the benefits of anti-VEGF therapy greatly outweigh the risks.

Conclusion

Nine cases were retrieved for this reporting period, and except one case of minimal information, all patients presented with alternative explanations for the development of macular hole. Macular hole closed in most of the cases and in some cases the physicians decided to continue the anti-VEGF treatment. No new signal is derived from the cases received during the reporting interval.

Based on the cumulative investigation of macular hole (**Appendix 8**) and the cases received in the reporting interval the MAH proposes to close this topic analysis in future PSURs and to continue its review through routine pharmacovigilance activities.

15.1.4 Congestive heart failure

Background:

The MAH was requested by the CHMP to closely monitor congestive cardiac failure particularly in the DME population.

Cardiac failure congestive is not considered an ADR with Eylea therapy and is not listed as an ADR in the CCDS for Eylea.

Approximately 1–2% of the adult population in developed countries suffers from heart failure, with the prevalence rising to 10% among those older than 70 years. It is the most common cause of hospitalization in patients over the age of 65 (111). Risk factors for the development of congestive heart failure include amongst others diabetes mellitus, arterial hypertension, coronary artery disease, myocardial infarction, alcohol abuse, smoking and obesity.

Search Strategy

The Global Safety Database was searched for new all PSUR-relevant cases in the reporting period with the following criteria: SMQ Cardiac failure [Broad].

Case details

A total of 53 cases with at least one event belonging to the SMQ Cardiac failure were received. In 24 of the 53 cases at least one event was coded to the PT “Cardiac failure congestive”. The following analysis focuses on these 24 cases reporting 25 events of “Cardiac failure congestive”:

Twenty-three stemmed from interventional clinical trials and 1 from an US reimbursement program. All 24 cases were serious and medically confirmed.

Patient’s age ranged from 44 to 82 years (median, 62 years). Fifteen patients were male and 9 were female.

Outcome of the event cardiac failure congestive was reported as resolved in 7 cases and as not resolved also in 16 cases. Event outcome was fatal in one solicited case from an US reimbursement program (summarized below).

Interventional Clinical Trial Cases

Twenty three out of the 24 cases were received from interventional clinical trials. In all cases except one, patients received aflibercept. In one case, patient experienced event of cardiac failure congestive during the screening period. None of the clinical trial cases were assessed as causally related to aflibercept (neither by investigator nor by the company).

In 22 of 23 cases, patients were treated for diabetic retinopathy. In the remaining one case, patient was treated for cystoid macular oedema and central retinal vein occlusion.

Patient age ranged between 44 and 74 years (median, 60 years). 14 patients were male and 9 females.

Onset latency from the first dose was reported in 19 cases and ranged from 64 to 740 days (median, 372 days). Onset latency from the last dose was reported in 8 cases and ranged from 3 to 188 days (median, 49.5 days). No information on de-challenge or re-challenge were provided.

All patients presented alternative explanations for congestive heart failure taking into account their advanced age and underlying concomitant diseases / historical conditions (e.g. arterial hypertension, diabetes mellitus, coronary artery stenosis / disease, cardiomyopathy, myocardial infarction, sleep apnea syndrome, atrial fibrillation, pulmonary hypertension, valvular heart disease, renal impairment).

Spontaneous and solicited case reports

One solicited report with fatal outcome derived from a reimbursement program in the US sponsored by the license partner Regeneron. This solicited case referred to an 82-year-old male patient who initiated Eylea for the treatment of Wet AMD/Exudative age-related macular degeneration, right eye, with active choroidal neovascularization. Dosing and frequency were not specified. Patient received a total of 6 doses of Eylea. Patient's medical history and concomitant medications were not provided. Patient died from congestive heart failure approx. 1 year 10 months after the last dose of Eylea. The physician considered patient's death as not related to Eylea [redacted], MC). Based on the limited information provided regarding the patient medical history, cause of death, and Eylea treatment details, the company considers the causal relationship between the event of death and Eylea to be unrelated.

Summary and Conclusion

No new safety-relevant information was derived upon review of the cases newly received during the reporting interval referring to mostly elderly patients with plausible alternative explanations for the occurrence of congestive heart failure. The information as collected does not alter the overall assessment of the positive benefit-risk profile of Eylea. No causal relationship between congestive heart failure and Eylea treatment can be established from this and previous reviews. Since this topic has been monitored since PSUR 5.0 (reporting interval: 01 DEC 2014-30 NOV 2015) and a safety signal has not been identified, the MAH considers future monitoring through routine pharmacovigilance.

15.1.5 Wound healing complications

Based on a request received by HealthCanada, a cumulative review of wound healing complications and Eylea therapy was performed and presented in PSUR No. 6.

The request was triggered by a revision of the Canadian Lucentis® (ranibizumab) Product Monograph, which had been updated to indicate a more frequent occurrence of non-serious, non-ocular wound infection/inflammation in patients with diabetic macular edema (DME)

treated with ranibizumab (1.85/100 patient years) compared to patients in the control arm (0.27/100 patient years). It was stated in the monograph that the relationship to ranibizumab remains unknown.

Upon review of the cumulative Eylea data, it was concluded that there is no indication of a causal relationship for the development of non-ocular wound healing complications and aflibercept treatment in any of the approved patient populations.

This topic is subject for further monitoring in this PSUR according to the advice provided in the latest PRAC PSUR assessment report.

Search Criteria

PSUR/PBRER-qualifying cases received during this reporting period were searched for the following PTs:

Abdominal wound dehiscence, Anastomotic complication, Anastomotic fistula, Anastomotic leak, Debridement, Drain placement, Electrocoagulation, Eschar, Failure to anastomose, Gastrointestinal anastomotic complication, Gastrointestinal anastomotic leak, Impaired healing, Implant site dehiscence, Incarcerated incisional hernia, Incision site complication, Incision site erosion, Incision site inflammation, Incision site oedema, Incision site ulcer, Incisional hernia, Incisional hernia gangrenous, Incisional hernia repair, Incisional hernia, obstructive, Inflammation of wound, Intestinal anastomosis complication, Pharyngeal anastomotic leak, Post procedural fistula, Post procedural persistent drain fluid, Postoperative hernia, Postoperative wound complication, Procedural haemorrhage, Promotion of wound healing, Reproductive tract anastomotic leak, Stomal hernia, Suture related complication, Suture rupture, Urinary anastomotic leak, Wound, Wound closure, Wound complication, Wound contamination, Wound decomposition, Wound dehiscence, Wound drainage, Wound evisceration, Wound haematoma, Wound haemorrhage, Wound necrosis, Wound secretion, Wound treatment, Incision site dermatitis, Incision site erythema, Incision site rash, Incision site swelling, Incision site vesicles, Seroma, Incision site abscess, Incision site cellulitis, Incision site infection, Infected seroma, Postoperative wound infection, Wound abscess, Wound infection, Wound infection bacterial, Wound infection fungal, Wound infection helminthic, Wound infection pseudomonas, Wound infection staphylococcal, Wound infection viral, Wound sepsis.

The search for the current reporting period resulted in a total of 6 new PBRER/PSUR-qualifying cases, of which 2 cases were reported from interventional studies (investigator-sponsored studies; ISS) performed in the US, 1 case from an observational cohort study (OCS) performed in Japan, and 3 cases from spontaneous reporting (2 cases in the US, and 1 case in Japan).

These 6 cases, which were all medically confirmed, are outlined in the following table and further detailed in the subsequent individual case reports. The delay between the last Eylea injection prior to the surgical wound and the occurrence of the wound healing complication

could not be specified in 3 cases, since the dates of the last injection and/or the onset dates of the event were not provided.

Case No.	Lead preferred term (seriousness)	Onset latency [a]	Outcome	Relatedness (reporter)	Relatedness (company)
[redacted]	Wound infection (s) Necrotising fasciitis (s)	nc nc	not reported recovering / resolving	not reported related	unrelated related
[redacted]	Suture rupture (ns) Wound haemorrhage (ns)	nc Same day [b]	not reported recovered / resolved	not reported related	unrelated related
[redacted]	Wound dehiscence (s)	Same day	recovered / resolved	unrelated	unrelated
[redacted]	Post-OP wound infection (s)	104 days	not recovered / not resolved	unrelated	unrelated

nc=not calculable; ns=non-serious; s=serious
a: Time from last exposure (treatment) to onset of event.
b: This case described a spontaneous and intentionally forced bleeding following needlestick injury of the finger of an ophthalmologic technician who had prepared an Eylea infection for another person.

[redacted]

This patient (no demographic characteristics available) was involved in a Japanese, company-sponsored observational study titled "Drug Use Investigation of Eylea for CRVO" (Protocol: 16641). The patient received Eylea for the indication "central retinal vein occlusion". The case included the occurrence of **"wound infection"** (verbatim: wound infection) and "surgery" (verbatim: surgery). The patient's concurrent conditions included malignant tumor. On an unknown date, the patient started Eylea at an unspecified dose and frequency. On an unknown date, the patient underwent surgery and experienced wound infection (seriousness criterion medically significant). Treatment with Eylea was interrupted. The relationship of surgery and wound infection was not reported. Event outcomes were not reported. Further company follow-up with the investigator is not possible.

Company comment: Considering the patient's concurrent condition of malignant tumor as alternative explanation, and Eylea's very low potential for causing events distant from the eye due to very low and intermittent systemic exposure, the Sponsor assesses the event as unrelated to drug.

[redacted]

A spontaneous report from the US was received on 07 FEB 2019 from a patient's family member regarding a 52-year-old female patient (ethnicity not specified) who had flesh-eating bacteria (serious due to hospitalization and medical significance) and “was sick really bad, following administration of Eylea”. The reported events were **"necrotising fasciitis"** and "malaise". The patient's past medical history included diabetes, blood clots, and anemia. Concomitant medications included metformin, Xarelto, vitamin D, and iron. The patient started intravitreal treatment with Eylea in June 2017, every month or every 2 months for macular edema (probably DME, in view of the medical history). Dosing was not provided. The total number of doses was unknown. The patient was hospitalized due to flesh-eating bacteria on 10 NOV 2018 and needed 3 surgeries. The patient was "sick really bad" for about

a month before the surgery. After the surgery, the patient went to rehabilitation for 4 weeks. Part of the wound below the patient's abdomen was still open. The reporter stated the patient was doing a lot better at the time of the initial report. Outcome of the events was recovering/resolving. Action taken with Eylea was dose not changed (ongoing).

Follow-up information was received on 27 MAR 2019 from the initial physician via office staff. A new event of wound vac (i.e., wound vacuum-assisted closure) was added to the case (PT: "wound closure"). The patient was administered a dose of Eylea on 28 JAN 2019 and since then had had a total of 2 injections of Eylea in that same clinic. The physician reported that the previously reported event of flesh-eating bacteria happened before the patient came to the clinic, and that the patient received Eylea somewhere else prior to seeing them. The physician reported the patient came to the clinic with the medical history of the flesh-eating bacteria and had a wound vac. Outcome for the event of wound vac was unknown.

The causality assessment by reporter and Sponsor, respectively, was "related". No further information was provided at the time of this (most recent) report.

Company comment: Diabetic patient developed necrotizing fasciitis un unknown relationship to last Eylea injection. Necrotising fasciitis is a known complication in patient s with advanced DME, no causality to Eylea can be derived from this case

[redacted]

This spontaneous case from Japan was reported by a pharmacist and described the occurrence of "cardiac operation" (verbatim: cardiac operation) and **"suture rupture"** (verbatim: suture of surgical site ruptured and got brittle) in a male patient in his fifties who received Eylea solution for injection (no indication provided). On an unknown date, the patient started Eylea therapy. On an unknown date, the patient underwent cardiac operation (seriousness criterion medically significant) and experienced a ruptured suture. The reporter provided no causality assessment for these events with Eylea. Further company follow-up with the pharmacist was not possible.

Company comment: This elderly male patient underwent a cardiac surgery on an unspecified time after initiation of Eylea for an unspecified indication. Minimal information is provided for this case to allow for a meaningful assessment, the case lacks information on indication for the procedure, medical history, and temporal relationship.

[redacted]

A spontaneous report from the US was received on 19 MAR 2019 from a physician via an office staff member for the physician's office, regarding a female patient (office technician) who experienced "bleeding at the needle stick site" (coded to PT: **"wound hemorrhage"**), "technician poked herself in the finger with the Eylea filter needle" (coded to PT: "accidental exposure to product"), and "was sore at the needle stick site" (coded to PT: "limb injury"), while administering Eylea. Bleeding was encouraged to make sure that the technician did not absorb Eylea. The site was washed with soap and water and covered with a band-aid. Outcome of event "sore at the needle stick site" was "not resolved". Outcome of event

"technician poked herself in the finger with the Eylea filter needle" was "unknown". Outcome of event "bleeding at the needle stick site" was "recovered". The causality assessment by reporter and Sponsor, respectively, was "related".

Company comment: A bleeding needle stick while preparing the injection was reported which is not considered a wound healing complication.

[redacted]

This case was reported from study VGFTe-DR-1822 (Intravitreal Aflibercept as Indicated by Real-Time Objective Imaging to Achieve Diabetic Retinopathy Improvement - PRIME Trial). A 55-year-old male Caucasian patient with diabetic retinopathy experienced **"wound dehiscence"** which followed an event of gangrene one month earlier. The event was serious due to hospitalization; outcome was recovered/resolved. The patient's medical history included cataract, diabetic retinal edema, diabetic retinopathy, abdominal hernia, hernia repair, drug hypersensitivity, Type 2 diabetes mellitus, hypertension, and foot amputation. Concomitant medications reported included metoprolol succinate, lisinopril, and exenatide.

The patient received his first dose of IVT Eylea 2 mg/0.05 mL, PRN on 20 AUG 2018. The most recent dose of EYLEA prior to onset of event was administered on 29 APR 2019, and the patient received a total of 8 doses prior to the onset of the event. Study drug was continued without a change. On 29 APR 2019, the patient came to site for his regular scheduled visit. The patient had recently his foot and portion of his leg amputated due to gangrene. Upon leaving the exam room and taking a step with the amputated leg, the patient landed on the amputated leg, the stitches had just been removed. The wound began to bleed. The site staff had the patient elevate the amputated leg and pressure was applied to stop the bleeding. The patient's doctor was contacted, and the site was instructed to send the patient to the Emergency Room. The investigator assessed the event as not related to study drug. Rationale for causality assessment was noted as the event was not due to the study drug, but due to the fall. Underlying/concomitant disease was noted as other suspected cause for the event.

Company assessment: Unrelated causality, as the fall triggered the bleeding event.

[redacted]

This case was reported from study VGFTe-DR-1549 (Intravitreous Anti-VEGF Treatment for Prevention of Vision Threatening Diabetic Retinopathy in Eyes at High Risk [Protocol W]). A 52-year-old male Caucasian patient with diabetic retinopathy experienced **"post-operative wound infection"** (verbatim: infection (chronic) of amputation stump) on 04 DEC 2017 after receiving study drug. The event was serious due to hospitalization; outcome was not recovered / not resolved. The patient's relevant medical history included diabetes mellitus, neuropathy peripheral, and toe amputation. No relevant concomitant medications were reported.

The patient received his first dose of IVT Eylea 2.0 mg (right eye) on 24 APR 2017. The most recent dose of Eylea prior to onset of event was administered on 23 AUG 2017 (total of 4 dose). On 04 DEC 2017 (i.e., 104 days after the last injection performed on 23 AUG 2017),

the patient was hospitalized due to infection (chronic) of amputation stump. The patient experienced pain in amputated toe and had a severe infection in the area of the amputated toe. Treatment included antibiotics for seven days.

Company assessment: No causality is being assumed as diabetes and neuropathy pose strong alternative factors. In addition, the onset latency of more than 100 days after the last injection is not considered a suggestive temporal relationship for causality.

Conclusion:

In conclusion, the 6 cases received in the current reporting period do not support a causal link of aflibercept therapy and the development of systemic wound healing impairment.

Patients presented with plausible alternative risk factors such as malignancy, diabetes, neuropathy, fall, or. trauma (needle stick)

Overall, neither the reviews of the past PSURs nor the 6 cases received during the current reporting period support a causality between IVT Eylea treatment and the development of wound healing complications. Therefore, the MAH proposes to conduct routine PV surveillance for this topic.

15.1.6 Thrombotic microangiopathy

Thrombotic microangiopathies (TMAs) are a group of disorders characterized by thrombocytopenia, a microangiopathic hemolytic anemia evident by fragmented red blood cells and laboratory evidence of hemolysis, and microvascular thrombosis due to endothelial injury. They include thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS), as well as syndromes complicating bone marrow transplantation, certain medications and infections, pregnancy and vasculitis. TTP and HUS were previously considered overlap syndromes. However, in the past few years the pathophysiology of inherited and idiopathic TTP has become better understood and clearly differs from HUS.

The signal investigation on TMA has been presented in PSUR#7. The respective assessment report has requested to continue monitoring this topic in the next PSURs.

Search Strategy

The pharmacovigilance database was searched for the new PBRER/PSUR-qualifying cases received during the reporting period with a reported event as defined by the MedDRA SMQ “Haemolytic disorders” and in addition the MedDRA PTs: “Thrombotic microangiopathy”, “Microangiopathic haemolytic anaemia”, “Haemolytic uraemic syndrome”, “Thrombotic thrombocytopenic purpura”, “Coombs negative haemolytic anaemia”, “Coombs test negative”, and “von Willebrand factor multimers abnormal”.

Results

The search did not retrieve any results for the reporting period.

Summary and conclusion

The MAH performed a full signal investigation in November 2017 on TMA and assessed thoroughly the data from all sources reported; the signal was refuted. Since then no new PSUR qualifying case was received in the last two PBRER reporting periods Therefore, the MAH proposes to continue with routine post-marketing PV safety monitoring for this topic.

15.1.7 Artery dissection and aneurysms

In the context of a PRAC signal procedure on artery dissections and aneurysms (EPITT no. 19330) for all products included in the class of substances that inhibit VEGF signal transduction (sunitinib, sorafenib, pazopanib, lenvatinib, vadetanib, axitinib, bevacizumab, ramucirumab, aflibercept, pegaptanib, ranibizumab) PRAC has requested, from the MAHs of VEGF inhibitors for intravitreal administration, a cumulative review of all cases of artery dissections and aneurysms with their respective products.

All available information on the signal of artery dissection and aneurysm for IVT aflibercept from clinical trial, postmarketing surveillance and literature was reviewed and analyzed. The MAH concluded after the review of all available data (as of 21 MAY 2019) that a causal relationship between IVT administration of aflibercept and the development of aneurysms or aneurysms dissection/rupture is not supported by the current evidence from clinical trials, literature and post-marketing data. In the adoption of the fourth PRAC recommendation (intravitreal administration products EMA/PRAC/595787/2019), the PRAC has agreed that a causal association between the development or association of aneurysms and artery dissections following intravitreal administration of aflibercept cannot be established. The rapporteur concluded that due to the low systemic exposure following an intravitreal injection with a subsequent rather rapid elimination and with no evidence of any accumulation with repeated injections, the risk of development /aggravation of non-ocular aneurysms/dissection is considered near negligible. A change in product information and risk management plan was also not warranted. The MAH was asked to closely monitor these events in the coming PSURs.

Cases received after the cut off for the cumulative review (21 MAY 2019) until DLP of this PSUR did not change the overall assessment regarding the artery dissection/aneurysm and the use of Eylea

<u>Review of PSUR qualifying cases received during the reporting period:</u>

Search Strategy

For this evaluation all new PSUR/PBRER - qualifying cases from this reporting period (01 DEC 2018 to 30 NOV 2019) were searched for the MedDRA HLGT “Aneurysms and artery dissections”.

Results

The search for MedDRA HLGT "Aneurysms and artery dissections" resulted in 9 PBRER/PSUR-qualifying case reports. Of these 9 cases, 5 case reports were spontaneous, 1 report was a published report from interventional study and 3 from observational studies.

In 5 of 9 cases, patients were male and in 3 cases female (unknown gender in the remaining case).

Age ranged from 54 to 90 years of age (mean, 76.6 years; median, 81 years).

The reported indication was in 3 cases RVO, in 3 cases AMD, 1 case diabetic retinopathy, in one case unspecified neovascularization and in one case the indication was not reported.

Cases with systemic events (aneurysms, ruptures, dissections):

There were 8 new PSUR/PBRER qualifying cases from this reporting period (01 DEC 2018 to 30 NOV 2019) with systemic events of artery dissection/aneurysm. The cases are described below individually.

- Cases where aneurysms were reported:
    - [redacted]: observational study case non-medically confirmed reported from USA refers to an 86yo male patient with risk factors (elderly, male gender, with positive medical history for stent placement, cerebrovascular accident, myocardial infarction, dyslipidemia) who was diagnosed during a routine MRI for urologic purposes (benign prostatic hyperplasia) with aortic aneurysm (non-serious event, no causality reported). The patient was under Eylea treatment, the number of doses received and the time to onset relative to first and last doses were not reported.
    - [redacted]: PSP non-medically confirmed case from Australia, refers to an 84yo male patient for which no medical history or concomitant diseases were reported. After about five years of Eylea treatment, the patient was hospitalized for aortic aneurysms, which was treated with surgery (clipped). Temporal relationship not reported. No causal assessment was reported, Eylea continued.
    - [redacted]: spontaneous, medically confirmed case from Canada, referring to a male patient of approximately 90 years of age, who died due to a brain aneurysm after unspecified therapy duration with Eylea for CRVO indication. Medical history, concomitant medications or concurrent conditions were not reported. Temporal relationship to Eylea injection not reported. The fatal event was assessed as unrelated to Eylea.
    - [redacted]: this spontaneous, non-medically confirmed case report from USA, refers to a 60 yo female patient with history of diabetes and unspecified heart disease, who received one dose Eylea and the same month experienced an unspecified aneurysm (reported as verbatim "above

right feel like aneurysm"). Eylea was continued. Event was assessed as related to Eylea.

- Cases where ruptured or dissections were reported:
  - [redacted]: Spontaneous medically confirmed case reported from Japan with minimal information, referring to a patient of unspecified age and gender, with no medical history, concurrent disease or concomitant medication reported, who experienced the event unspecified "artery dissection" in an unclear temporal relationship with the Eylea administration. Causal assessment and the action taken with Eylea were not reported.
  - [redacted]: spontaneous medically confirmed case from Japan referring to a 75yo male patient who died two days after the ninth dose of Eylea (given for AMD indication) due to aortic aneurysm rupture. No causal assessment was reported but the alternative explanation was concurrent hypertension. No further follow up was possible for this case.
  - [redacted] literature medically confirmed case from Sweden referring to an 86yo male patient who died due to aortic aneurysm rupture about 1 year 3 months after starting aflibercept and 11 weeks after his 8th injection given for CRVO indication. Medical history was positive for cerebellar ischemic stroke, atrial fibrillation, myocardial infarction and congestive heart failure. No causal assessment reported.
  - [redacted]: spontaneous, medically confirmed case reported from Canada via regulatory authority refers to a 54yo male patient who died in an unclear temporal relationship with Eylea treatment due to vertebral artery dissection. Additional causes of death were given as: basilar artery thrombosis, cerebellar stroke, dizziness, endotracheal intubation, hydrocephalus, hypertension, lateral medullary syndrome, loss of consciousness, nausea, neck pain and vertigo. No causal assessment was provided, and no information was given on the medical history or concurrent conditions.

<u>Case with ocular, local events (retinal aneurysms):</u>

- One case was reported with retinal aneurysm in the reporting interval ([redacted]). The 78 yo female patient with underlying RVO had a long history of insulin dependent diabetes and positive medical history of Avastin therapy (colon cancer metastatic reported among other events), received 6 doses of Eylea for macular oedema and retinal vein occlusion (every 6 weeks, over a period of 9 months). On an unspecified date she experienced retinal aneurysms reported in a context of irregular retinal architecture with areas of retinal thinning, ischemia OD, significant paramacular and peripheral non-perfusion, vascular whitening OD, foveal avascular zone enlargement. According to the physician, "the patient had a high risk for

neovascularization and recurrence of oedema when treatment was withdrawn" and "vision loss without treatment".

- MAH Comment: The profound alterations of the retinal architecture including the vessels on a background of advanced age and diabetes (risk factors) in a context of retinal vein occlusion (confounding factors) are better alternative explanation.

Discussion

PSUR qualifying cases received during the reporting period with ocular and non-ocular events pertaining to artery dissection aneurysm were reviewed.

One report was received referring to a local retinal aneurysm in an elderly patient with underlying RVO, an ocular disease known to be accompanied with ocular aneurysm formation.

Patients with systemic complications were of advanced age (median 81 years) and most patients presented with risk factors considered predisposing for the development of artery dissection/aneurysm (increased cardiovascular risk profile with cerebrovascular accidents, myocardial infarctions, stent placement, unspecified heart disease, hypertension, diabetes mellitus, congestive heart failure, atrial fibrillation). In addition, all underlying indications AMD, RVO, and DR in these patients are considered related to an increase in the cardiovascular risk profile. Where known there was no suggestive pattern of a temporal relationship to Eylea therapy.

Overall, no new signal can be derived from these cases.

16. Signal and Risk Evaluation

16.1 Summary of Safety Concerns

Table 16-1 provides an overview on important identified risks, important potential risks and missing information as presented in the EU RMP for aflibercept that was valid at the beginning of the reporting period (Version 26.1).

New information received during the reporting period on the individual risks is presented in section 16.3.18.

Table 16-1: Summary of Safety Concerns Presented in RMPs for Aflibercept

• Endophthalmitis (likely infectious origin) [b, c] • Intraocular inflammation [a, c] • Transient intraocular pressure increase [a] • Retinal pigment epithelial tears [b] • Retinal tear / detachment [a] • Cataract (especially of traumatic origin) [a, d] • Hypersensitivity and immunogenicity [b]
• Arterial thromboembolic events including non-MI ATEs and cardiovascular ischemic events [a] • Venous thromboembolic events [b] • Hypertension [b] • Non-ocular hemorrhage [b] • Medication error [b] • Off-label use [b] • Embryo-fetotoxicity [a] • Retinal hemorrhage [b]
• Use of Eylea in patients with uncontrolled glaucoma [a] • Concomitant use of different anti-VEGF therapies and other therapies for wet AMD and CRVO [b] • Long term safety beyond 2 years [b] • Posology utilized in marketed use [b]

[a] Important risks/missing information in cRMP and EU RMP 26.1
[b] Important risks/missing information in EU RMP 26.1 only
[c] In cRMP Endophthalmitis and Intraocular Inflammation are summarized under Intraocular inflammation
[d] In cRMP “Traumatic cataract”

16.2 Signal Evaluation

16.2.1 Closed and Refuted Signals

The following signals were closed and refuted during the period of this PBRER/PSUR:

- Cluster of intraocular inflammations in United States of America
- Artery Dissection/Aneurysm

16.2.1.1 Cluster of intraocular inflammations in United States of America

A signal regarding an increase in intraocular inflammations (IOIs) in the USA was initially observed towards the end of the 2017 PSUR’s reporting period (see PSUR#7, reporting period 01 DEC 2016- 30 NOV 2017). Starting in August/September 2017 an increase in the number of reports of IOI in the US was observed. Most of the cases were non-infectious and many occurred in clusters at the same practice or by the same physician. In response, Regeneron Pharmaceuticals (MAH in US) conducted an extensive genealogical review of the manufacturing and distribution process for EYLEA® in the United States. No factors associated with the manufacturing of EYLEA® could be identified as related to the increased

IOI reporting rate. However, the analysis identified that specific batches of syringes which were co-packaged in certain lots of final EYLEA® kits distributed in the US were associated with higher rates of IOI as compared to other syringe batches (syringes are not co-packed with EYLEA® ex-US).

Regeneron informed the FDA and sent a voluntary communication to the healthcare community regarding an association with specific kit components packaged with certain lots of EYLEA® on 28 FEB 2018. No changes to the EYLEA® manufacturing process have been identified based on the current investigation. Upon cessation of the use of the identified syringe lots in MAR 2018, the rates of IOIs returned to historical levels by APR 2018 and remain at that level as of the DLP of this PSUR. An investigation in collaboration with the syringe manufacturer and the silicone oil manufacturer to identify any potential causative factors was completed during this reporting period. No clear root cause for the development of IOIs could be identified. Please refer to **Appendix 9** for the finalized signal investigation document for this signal.

Bayer as MAH outside the US informed health authorities outside the US about the voluntary Communication in the US. Ex-US no increase in IOI cases was observed.

The company is monitoring global IOI reports (see section for endophthalmitis and intraocular inflammations).

16.2.1.2 Artery Dissection/Aneurysm

In the context of a PRAC signal procedure on artery dissections and aneurysms (EPITT no. 19330) for all products included in the class of substances that inhibit VEGF signal transduction (sunitinib, sorafenib, pazopanib, lenvatinib, vadetanib, axitinib, bevacizumab, ramucirumab, aflibercept, pegaptanib, ranibizumab) PRAC has requested, from the MAHs of VEGF inhibitors for intravitreal administration, a cumulative review of all cases of artery dissections and aneurysms with their respective products.

All available information on the signal of artery dissection and aneurysm for IVT aflibercept from clinical trial, postmarketing surveillance and literature was reviewed and analyzed. The MAH concluded after the review of all available data (as of 21 MAY 2019) that a causal relationship between IVT administration of aflibercept and the development of aneurysms or aneurysms dissection/rupture is not supported by the current evidence from clinical trials, literature and post-marketing data. See full signal evaluation and response to PRAC in **Appendix 10.**

In the adoption of the fourth PRAC recommendation (intravitreal administration products EMA/PRAC/595787/2019), the PRAC has agreed that a causal association between the development or association of aneurysms and artery dissections following intravitreal administration of aflibercept cannot be established. The rapporteur concluded that due to the low systemic exposure following an intravitreal injection with a subsequent rather rapid elimination and with no evidence of any accumulation with repeated injections, the risk of development /aggravation of non-ocular aneurysms/dissection is considered near negligible.

A change in product information and risk management plan was also not warranted. The MAH was asked to closely monitor these events in the coming PSURs (see above section 15.1.7 for review of new PSUR qualifying cases received during the reporting period)

16.2.2 Ongoing Signal

No signal was ongoing at the end of the reporting period.

16.3 Evaluation of Risks and New Information

16.3.1 New Information on Important Potential Risks

On the following important potential risks new safety relevant information was received during the period of this PBRER/PSUR:

16.3.1.1 ATEs - Non-MI ATEs, Cardiovascular Ischemic Events and Ischemic Colitis

Following last year's PSUR#8, the MAH has received the following request:

The MAH is requested in the next PSUR to provide a cumulative review and analysis (including PK/PD and epidemiologic) of cases of systemic AE ***(ATE,*** *Ischaemic colitis, VTE, HTA and non-ocular haemorrhage):*

The MAH should provide a separate analysis:

- In patients under 50 years old; in cases with a time to onset from last dose <2 weeks; and in in cases without risk factors (as referenced in the publication Eur Heart J. 2017 Mar 14;38(11):785-791) (112).

The MAH has cumulatively investigated (as of 31 AUG 2019) all respective systemic safety topics including ATEs and ischemic colitis as requested by PRAC. Please refer to **Appendix 12** for the cumulative investigations.

Based on the review of all relevant data no causality of Eylea treatment to the development of ATEs could be established.

Cases received up to the DLP of this PSUR do not change the overall assessment.

The below analysis describes the PSUR qualifying cases received throughout this reporting period.

Background

Arterial thromboembolic events including non-myocardial infarction ATEs and cardiovascular ischemic events are considered an important potential risk in both the core RMP and EU RMP.

The AMD patient population can be considered particularly predisposed to develop ATEs. Cardiovascular risk factors including smoking, age, and nutrition have been associated with the development of neovascular AMD. Thus, AMD patients are at a higher risk of ATEs (113,

114). The incidence of stroke and MI in AMD patients has been estimated using the United States Medicare database (114). The incidence of MI in patients with neovascular AMD has been estimated to be 2.2% annually. The incidence of stroke in patients with neovascular AMD has been estimated to be 3.8% annually (113). Patients with previous ATEs were also at a higher risk of subsequent events, at 7.4% for inpatient MI and 35.1% for inpatient ischemic stroke (115). From two Medicare (US) studies it was concluded that, compared to patients without AMD, patients with AMD (especially with the neovascular form) were more likely to have ATEs, particularly stroke and MI.

Although studies show different incidence rates, the overall trend shows that there is a positive correlation between age and incidence. As the age group rises, the incidence rate for all types of ATE rose as well (116-124). When looking only at [ischemic] stroke, the incidence rate ranged up to 3,968/100,000/year. The highest incidence rate recorded was in Söderhamn, Sweden between 1983 and 1986 (117). For MI, the highest incidence for females was 1002.2/100,000 person years (121, 122). For men, the highest MI rate was 1,511.6/100,000 person years (121, 122). (116-124). When looking only at [ischemic] stroke, the incidence rate ranged up to 3,968/100,000/year. The highest incidence rate recorded was in Söderhamn, Sweden between 1983 and 1986 (117). For MI, the highest incidence for females was 1002.2/100,000 person years (121, 122). For men, the highest MI rate was 1,511.6/100,000 person years (121, 122).

MedDRA search

For this year´s evaluation PBRER /PSUR qualifying cases received during this reporting period were searched for the following SMQs:

- SMQ Ischaemic central nervous system vascular conditions,
- SMQ Ischaemic heart diseases,
- SMQ Ischaemic colitis.

Case details

During the reporting period of this PBRER/PSUR, 01 DEC 2018 – 30 NOV 2019, 237 new PSUR qualifying cases were retrieved applying the above search criteria:

- 151 case reports (including 159 events) for SMQ “Ischaemic central nervous system vascular conditions “,
- 95 case reports (including 101 events) for SMQ “Ischaemic heart disease “,
- 8 cases (including 9 events) for SMQ “Ischaemic colitis”.

Table 16-2 and Table 16-3 provide an overview of cases of ischaemic central nervous system vascular conditions and ischemic heart disease, separated by indication and source, both cumulatively and for the reporting period.

Table 16-2: Number of Cases for SMQ "Ischaemic Cerebrovascular Condition", Cumulatively/ Period by Indication

	AMD		DME		CRVO		BRVO[b]		mCNV		Unknown/ Unspecified/ other[c]		Total	
	cum[a]	per[a]	cum	per	cum	per	cum	per	cum	per	cum	per	cum	per
Spontaneous	**331**	**33**	**76**	**15**	**21**	**3**	**37**	**9**	**8**	**2**	**143**	**20**	**616**	**82**
Medically confirmed	317	30	69	14	21	3	37	9	8	2	119	17	571	75
Not medically confirmed	14	3	7	1	0	0	0	0	0	0	24	3	45	7
Interventional study	**127**	**5**	**114**	**17**	**7**	**0**	**3**	**0**	**0**	**0**	**11**	**2**	**262**	**24**
Related	27	1	27	0	2	0	3	0	0	0	3	1	62	2
Not related	100	4	87	17	5	0	0	0	0	0	8	1	200	22
Observational study	**92**	**20**	**27**	**11**	**3**	**1**	**6**	**2**	**0**	**0**	**20**	**11**	**148**	**45**
Related	92	20	27	11	3	1	6	2	0	0	20	11	148	45
Not related	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	**550**	**58**	**217**	**43**	**31**	**4**	**46**	**11**	**8**	**2**	**174**	**33**	**1,026**	**151**

AMD: Age-related macular degeneration; BRVO: Branch retinal vein occlusion; CRVO: Central retinal vein occlusion; DME: Diabetic macular edema; mCNV: Myopic choroidal neovascularization; SMQ: Standardized MedDRA Query

[a] Cumulative/period. Starting with PSUR#7 the case count of the reporting period as well as the cumulative case numbers are displaying PSUR/PBRER qualifying cases.

[b] Cases where indication was reported only as RVO where assigned to BRVO due to its higher prevalence compared to CRVO.

[c] Includes macular edema, macular degeneration, macular fibrosis, maculopathy, vitreous hemorrhage, dry age-related macular degeneration, retinal edema, retinal hemorrhage, and retinopathy of prematurity; also unknown or unspecified indication

Table 16-3: Number of Cases for SMQ Ischemic Heart disease, Cumulatively/Period by Indication

	AMD		DME		CRVO		BRVO[b]		mCNV		Unknown/ Unspecified/ other[c]		Total	
	cum[a]	per[a]	cum	per	cum	per	cum	per	cum	per	cum	per	cum	per
Spontaneous	**106**	**13**	**35**	**5**	**6**	**0**	**10**	**4**	**3**	**0**	**77**	**11**	**237**	**33**
Medically confirmed	103	13	32	5	6	0	8	4	3	0	62	10	214	32
Not medically confirmed	3	0	3	0	0	0	2	0	0	0	15	1	23	1
Interventional study	**170**	**4**	**229**	**25**	**11**	**1**	**3**	**0**	**0**	**0**	**19**	**10**	**432**	**40**
Related	19	1	21	0	5	1	1	0	0	0	2	0	48	2
Not related	151	3	208	25	6	0	2	0	0	0	17	10	384	38
Observational study	**39**	**11**	**30**	**8**	**4**	**0**	**2**	**1**	**1**	**0**	**10**	**2**	**86**	**22**
Related	39	11	30	8	4	0	2	1	1	0	10	2	86	22
Not related	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	**315**	**28**	**294**	**38**	**21**	**1**	**15**	**5**	**4**	**0**	**106**	**23**	**755**	**95**

AMD: Age-related macular degeneration; BRVO: branch retinal vein occlusion; CRVO: Central retinal vein occlusion; DME: Diabetic macular edema; mCNV: Myopic choroidal neovascularization; SMQ: Standardized MedDRA Query

[a] Cumulative/period. Starting with PSUR#7 the case count of the reporting period as well as the cumulative case numbers are displaying PSUR/PBRER qualifying cases.
[b] Cases where indication was reported only as RVO where assigned to BRVO due to its higher prevalence compared to CRVO.
[c] Includes macular degeneration, maculopathy, dry age-related macular degeneration, vitreous hemorrhage, retinal degeneration, retinal artery occlusion, cystoid macular edema, glaucoma, retinopathy, retinal telangiectasia, and detachment of macular retinal pigment epithelium; also unknown or unspecified indication

Considering the number of spontaneous and observational study case reports from above and the patient exposure as outlined in chapter 5. Table 16-4 displays the reporting rate by reporting period and cumulatively per 10,000 patient years for SMQ "Ischaemic heart disease "and SMQ "Ischaemic cerebrovascular condition". No meaningful difference can be observed when compared to last year's PSUR#8 reporting rates.

Due to the low incidence of ischemic colitis cases an overview tabulation is not shown for these cases.

Overall, compared to last year's reporting rate no relevant changes in the reporting rate for myocardial or cerebrovascular ATEs were noted, neither cumulatively nor for this reporting period. Reporting rates remained stable.

Table 16-4: Post-marketing Reporting Rate (cumulatively/period) per 10,000 Patient Years SMQ Ischaemic Heart Disease and SMQ Ischaemic Cerebrovascular Condition[b]

	SMQ			
	"Ischaemic heart disease"		"Ischaemic cerebrovascular condition"	
Indication	Cumulative	Period	Cumulative	Period
AMD	0.6	0.4	1.8	0.9
CRVO	0.4	0.0	0.9	0.6
DME	0.6	0.5	0.9	0.9
BRVO	0.8	0.3	0.7	0.8
mCNV	0.3	0.0	0.6	0.6
Across indications[a]	0.7	0.5	1.7	1.2

AMD: Age-related macular degeneration; BRVO: Branch retinal vein occlusion; CRVO: Central retinal vein occlusion; DME: Diabetic macular edema; mCNV: Myopic choroidal neovascularization; SMQ: Standardized MedDRA Query

[a] includes cases from the 5 indications + cases from unknown/unspecified/other indications

[b] Cumulative/period. case numbers are displaying PSUR/PBRER qualifying cases.

Analysis of Case Reports for SMQ "Ischaemic central nervous system vascular conditions" Received During This Reporting Period

A total of 151 PSUR qualifying case reports (including 159 events) meeting the search criteria were received during the reporting period.

All cases were reported as serious, 115 were medically confirmed, and 36 cases were non-medically confirmed.

Age ranged from 42 to 97 years with a median age of 74 years (age information was not reported in 24 cases).

Sixty-four patients were female and 73 were male, gender information was not reported in 14 cases.

The reported indication for aflibercept treatment was AMD in 58 cases, DME in 43 cases, CRVO in 4 cases, BRVO in 11 cases, and mCNV in 2 cases, in 33 case reports this information was missing/unknown/not reported.

The outcome of the event of interest was reported in 85 cases of which 47 were reported as recovered or recovering at time of report, 12 as not recovered, 18 as recovered with sequelae, and 8 with a fatal outcome.

The most frequent PTs (> 10) within the 159 events were: “cerebrovascular accident” (n=73), “cerebral infarction” (n=41), “transient ischaemic attack” (n=15), and “ischaemic stroke” (n=12).

The majority of cases are spontaneous reports (82), followed by solicited reports (45; classification: 19 patient support programs, 19 other reimbursement programs, 4 observational cohort studies, 3 market research) and interventional study case reports (24; study classification: 10 interventional clinical studies sponsored by Bayer or its license partner, 14 investigator sponsored studies).

The onset latency from *first* dose of aflibercept to the onset of the event was reported in 60 cases and ranged from 1 day to 1332 days (median 381 days, not available in 91 cases).

The onset latency from *last* dose of aflibercept to the onset of the event was reported in 53 cases and ranged from 1 day to 512 days (median 36 days, not available in 98 cases). Of the 53 cases, 22 cases were reported with a time to onset (TTO) <2 weeks; 15 cases with a TTO ≥2 and ≤4 weeks, and 16 cases with a TTO >4 weeks from last dose of aflibercept.

The number of aflibercept injections before the event was reported in 45 cases and ranged from 1 to 40 injections (median 7 injections, not available in 106 cases).

In 85 out of the 151 case reports a plausible alternative explanation was reported, i.e. relevant risk factors providing an alternative explanation for events related to “ischaemic cerebrovascular condition” were identified. These risk factors included hypercholesterolemia, diabetes mellitus, tobacco use, arrhythmia (including atrial fibrillation), cerebrovascular and cardiovascular diseases (including previous cerebrovascular infarctions, carotid artery stenosis and MI), hypertension and other conditions predisposing to a higher risk of ischemic cerebrovascular conditions. In the remaining 66 cases there was only limited information provided for a further medical assessment.

Reference to INR values (e.g. in the descriptive case narrative, or as laboratory parameter, or INR related PTs) was identified in only one case ([redacted]): a 93-year-old male patient experienced a cerebral infarction, cerebral hemorrhage and hemiparesis about 4 days after the last aflibercept injection. The patient had a normal INR value at time of event (1.0). Patients medical history/ concurrent condition included alcohol use and smoking. Outcome was reported as recovered with sequelae. No further information was reported on e.g. concomitant medication. Patients advanced age together with history of alcohol use and concurrent smoking provide a plausible alternative explanation for the reported event and together with

limited information provided on e.g. concomitant medication there is insufficient evidence for a causal association with aflibercept intravitreal use.

Previous treatment with ranibizumab and /or bevacizumab was reported in 26 out of 151 cases (16 cases with previous ranibizumab treatment, 7 cases with previous bevacizumab treatment, in 3 cases both drugs were previously used). For 5 cases ranibizumab and for 2 cases bevacizumab was reported as concomitant medication. Previous treatment with both drugs, ranibizumab and bevacizumab, was reported for 3 patients. In 85 out of 151 cases no information on historical or concomitant drugs was provided.

Relevant literature is described at the end of this section.

Analysis of Case Reports for SMQ "Ischaemic Heart Disease" Received During This Reporting Period

A total of 95 PSUR qualifying case reports (including 101 events) meeting the search criteria were received during the reporting period:

All 95 cases were reported as serious, 81 were medically confirmed and 14 non-medically confirmed.

Age ranged from 41 to 91 years with a median age of 69 years (not reported in 12 cases).

Thirty-two (32) patients were female and 54 were male, gender was not reported in 9 cases.

The reported indication for aflibercept treatment was AMD in 28 cases, DME in 38 cases, CRVO in 1 case, BRVO in 5 cases, and none cases in mCNV. In 23 case reports this information was missing/unknown/not reported.

Outcome was known in 74 cases of which 34 were recovered / recovering, 14 not recovered, 8 recovered with sequelae, and 18 with a fatal outcome.

The most frequent PTs (≥ 6) within the 101 events were: "myocardial infarction" (n=64), "acute myocardial infarction" (n=12), and "coronary artery disease" (n=6).

Forty cases were reported from interventional studies (study classification: 9 interventional company-sponsored clinical studies, 7 interventional other company sponsored studies, 124 investigator sponsored studies), 22 from observational studies (study classification: 3 observational cohort studies, 3 other reimbursement programs, 16 patient support programs) and 33 were received as spontaneous case reports.

The onset latency from *first* dose of aflibercept to the onset of the event was reported in 44 cases and ranged from 3 days to 1016 days (median 394 days, not available in 51 cases).

The onset latency from *last* dose of aflibercept to the onset of the event was reported in 33 cases and ranged from 1 day to 325 days (median 63 days, not available in 62 cases). Of the 33 cases, 8 cases were reported with a TTO <2 weeks; 8 cases with a TTO ≥2 and ≤4 weeks, and 17 cases with a TTO >4 weeks from last dose of aflibercept.

The number of aflibercept injections before the event was reported in 45 case reports and ranged from 1 to 28 injections (median 9 injections, information was not available in 50 cases).

There was no report representing positive de– or re-challenge.

In 67 out of the 95 case reports a plausible alternative explanation was reported, i.e. relevant risk factors providing an alternative explanation for events related to "ischaemic heart disease" were identified. These risk factors include hypercholesterolemia, diabetes mellitus, tobacco use, arrhythmia (including atrial fibrillation), cerebrovascular and cardiovascular diseases (including previous cerebrovascular infarctions, carotid artery stenosis and MI), hypertension and other conditions predisposing to a higher risk for ischemic heart disease. In the remaining 28 cases there was only limited information provided for a further medical assessment.

There was no reference to INR values (e.g. in the descriptive case narrative, or as laboratory parameter, or INR related PTs) identified in any of the cases.

Previous treatment with ranibizumab or bevacizumab was reported in 6 and 1 case, respectively. For one case ranibizumab was reported as concomitant medication. In 87 out of 95 cases no information on historical or concomitant drugs was provided.

Relevant literature is described at the end of this section.

Analysis of Case Reports for SMQ "Ischaemic Colitis"

Background

A cumulative signal investigation on ischemic colitis and the use of Eylea was presented in PSUR #5 (reporting period: 01 DEC 2014 to 30 NOV 2015). This was triggered by the submission of individual case safety reports and the fact that ischemic colitis has been described when aflibercept was administered, with a higher dose, by intravenous route in oncologic patients (as mentioned in the SmPC of Zaltrap®).

The MAH was requested to monitor the topic ischemic colitis in forthcoming PSURs.

Following last year's PSUR#8, the MAH has received the following request:

The MAH is requested in the next PSUR to provide a cumulative review and analysis (including PK/PD and epidemiologic) of cases of systemic AE (ATE, ***Ischaemic colitis,*** *VTE, HTA and non-ocular haemorrhage):*

The MAH should provide a separate analysis:

- In patients under 50 years old; in cases with a time to onset from last dose <2 weeks; and in in cases without risk factors (as referenced in the publication Eur Heart J. 2017 Mar 14;38(11):785-791) (112).

The MAH has cumulatively investigated (as of 31 AUG 2019) all respective systemic safety topics including ischemic colitis as requested by PRAC. Please refer to **Appendix 12** for the cumulative investigations.

Based on the review of all relevant data no causality of Eylea treatment to the development of ATEs could be established.

Cases received up to the DLP of this PSUR do not change the overall assessment.

The below analysis describes the PSUR qualifying cases received throughout this reporting period.

Review of new PSUR qualifying cases with ischemic colitis received during the reporting period:

MedDRA search

PBRER/PSUR qualifying case reports received throughout the reporting period within SMQ "Ischemic colitis" were retrieved from the safety database (01 DEC 2018 through 30 NOV 2019).

Results

The search for SMQ "ischemic colitis" resulted in 8 PBRER/PSUR-qualifying case reports. Of these 8 cases, 2 case reports were spontaneous, 3 cases derived from published literature and 3 from interventional studies.

In 2 of 8 cases, patients were female and in 6 cases male.

Age ranged from 57 to 91 years of age (mean, 77 years; median, 81.5 years; -in one case the patient age was provided as 8 decades, assumed in analysis as 80years old).

The reported indication was in 1 case RVO, in 1 case AMD, 2 cases diabetic retinopathy, in one case macular degeneration and in 3 cases the indication was not reported.

The reported PTs within the SMQ "ischemic colitis" were:

- Colitis ischaemic: 4 (all MC, 3 serious and 1 non-serious)
- Colitis microscopic: 1 (MC, serious)
- Gastrointestinal haemorrhage: 1 (MC, serious)
- Haematochezia: 1 (MC, non-serious)
- Intestinal perforation: 1 (MC, serious)
- Large intestine perforation: 1 (NMC, serious).

There was no case of positive de- or re-challenge.

In 3 out of the 8 case reports where information on medical history was reported (37.5%), relevant risk factors which could have been an alternative explanation for the reported events were identified. These risk factors include hypercholesterolemia, diabetes mellitus,

cerebrovascular and cardiovascular diseases (including previous stroke and MI), hypertension, colon and breast cancer, and other conditions predisposing to a higher risk for ischemic colitis conditions. In 5 out of 8 reported cases this information was not provided.

Outcome was known in 5 cases of which 1 recovered, 3 fatal, and 1 not recovered.

Previous treatment with bevacizumab was reported in 1 case.

In four out of eight cases in total "Ischaemic colitis" was specifically reported and in one of these 4 cases "Ischaemic Colitis" was reported as symptom for colon cancer.

In the remaining 4 out of eight cases other PTs pertaining to the SMQ "ischemic colitis" were reported (no explicit ischemic colitis events), none of these cases were suggestive for a drug-induced ischaemic colitis.

The cases will be described in more detail individually, with focus on number of injections and time to onset relative to first and last dose Eylea, where the information was provided:

Cases retrieved with above mentioned search strategy (SMQ ischemic colitis) with explicitly reported PT ischemic colits:

The case triggered by the Batteux et al. (125) publication was extensively discussed in the response to the RSI following last year's PSUR. The single case was reported to Bayer in 2016 (therefore not part of this PSUR period) but published during this reporting period. In the discussion part of that publication 3 further ischemic colitis cases under aflibercept therapy with minimal information were mentioned (retrieved by the author from the WHO Vigidatabase). These cases are listed below. In addition, one further new case with PT ischemic colitis was reported.

[redacted]**:** Literature MC case (Batteux et al. (125)), referring to a 68yo male Japanese patient who received Eylea for unreported indication (doses and dates were not reported) and after unspecified duration experienced ischaemic colitis. The action taken with the drug was not reported, the event was assessed as related to Eylea.

MAH Comment: the case lacks relevant information based on which a causal assessment can be performed. The case was mentioned without providing any details in the discussion section of the main article referring to a case report of an 80-year old female patient who experienced ischaemic colitis after Aflibercept administration (Batteux et al., (125)).

[redacted]**:** Literature MC case (Batteux et al. (125)), referring to an 83yo male Japanese patient who received Eylea for AMD (number of doses and administration dates not reported) and after unspecified duration experienced ischemic colitis and died. The event was assessed as related to Eylea.

MAH Comment: the case lacks relevant information based on which a causal assessment can be performed. The case was mentioned without providing any details in the discussion section of the main article referring to a case report of an 80-year old female patient who experienced ischaemic colitis after Aflibercept administration (Batteux et al., (125)).

[redacted]**:** Literature MC case (Batteux et al. (125)), referring to an 91yo male Australian patient who received Eylea for unreported indication (number of doses and administration dates not reported) and after unspecified duration experienced ischemic colitis. The event was assessed as related to Eylea. The event outcome, the treatment received, and the action taken with the drug were not reported.

MAH Comment: the case lacks relevant information based on which a causal assessment can be performed. The case was mentioned without providing any details in the discussion section of the main article referring to a case report of an 80-year old female patient who experienced ischaemic colitis after Aflibercept administration (125).

[redacted]**:** spontaneous MC case from Japan referring to a male patient in his seventies (reported 8 decades) who received Aflibercept for unreported indication and about 3. 5 months after the second and last dose, was diagnosed with colon cancer with hematochezia and ischemic colitis. The patient received the first dose Aflibercept about 5 months before the second dose. The patient was treated with surgery and Avastin for colon cancer. The event outcome and causal assessment were not reported.

MAH Comment: the event was reported in conjunction with colon cancer, in an incompatible temporal relationship with Eylea.

Other cases retrieved with the above search strategy (SMQ: ischemic colitis) without explicitly reported ischemic colitis:

[redacted]**:** Company-sponsored interventional clinical study case reported from Great Britain referring to an 87yo female with history of asthma, hypertension, angina, acute left ventricular failure, atrial fibrillation, CRVO, colon cancer and breast cancer with mastectomy. The patient received Eylea for CRVO and about one year from therapy start died due to intestinal perforation. The event was assessed as unrelated to Eylea.

MAH Comment: The intestinal perforation occurred in a context of concurrent colon cancer, which provides an alternative explanation.

[redacted]**:** spontaneous case NMC from Canada referring to an 84yo female patient who received Eylea for macular degeneration (number of doses and administration dates not reported). The patient has also received intraocular Avastin and intraocular Zaltrap (off label use of the systemic aflibercept formulation) for the same ocular indication on unspecified dates. In an unclear temporal relationship with all suspect drugs, the patient experienced the fatal events 'Abdominal pain upper', 'Cholecystitis infective', ‘Diarrhoea', 'Haemorrhage', 'Large intestine perforation', 'Organ failure', 'Sepsis', 'Surgery' and 'Vomiting'. The causality was not reported.

MAH Comment: the elderly patient experienced the fatal events in a context of infectious cholecystitis with surgery and further complication such as sepsis, organ failure and bowel perforation, all which may be considered as alternative explanations.

[redacted]**:** this Investigator-Sponsor Study case refers to a 66yo male patient with a history of diabetes, hypertension, myocardial infarction, chest pain, congestive heart failure, hepatitis C and stroke, who received 6 doses Eylea for diabetic retinopathy and about 6 months after the last dose (and approx. 18 months from first dose), experienced 'gastrointestinal bleed'. The patient was under concurrent treatment with Aspirin, Clopidogrel, Warfarin, Apixaban and NSAIDs (Naproxen, Bromfenac, Diclofenac). The event was assessed as unrelated to Eylea but related to Aspirin. Eylea was continued.

MAH Comment: the concurrent anticoagulant medication with additional risk factors such as advanced age, diabetes, Hepatitis C and NSAIDs provide a better alternative explanation for "gastrointestinal bleed', which was not associated to drug-induced ischaemic colitis.

[redacted]**:** this Investigator-Sponsor Study case from USA refers to a 57yo male patient with a history of diabetes, hypercholesterolemia and hypertension, received 2 doses Eylea about two months apart for DME indication and approximately 4 months after the last injection, the patient experienced 'Colitis collagenous'. The event resolved in 11 days and was assessed as unrelated to Eylea, which continued.

MAH Comment: this particular form of colitis is rather linked with genetic abnormalities, autoimmune conditions and age over 50. The temporal relationship is considered not suggestive for a causal association to Eylea therapy.

Literature published in the reporting interval on ischemic colitis:

The most relevant literature published was a case report discussed by *Batteux, Benjam in et al.* (126)., discussed extensively in the response document to RSI of last year's PSUR#8.

The original case mentioned in the Batteux publication was received by Bayer in 2016 (case ID 2016-048159) and was now published during this reporting period. The article triggered the creation of further 3 cases which were included in the discussion section of the Batteux article (case IDs [redacted]).

An external expert statement is complementing the company position on this article (see cumulative evaluation of ischemic colitis **Appendix 12**).

Scientific literature regarding ATEs

Following publications on ATEs were identified for inclusion in the current PSUR.

1. Starr MR et al (127) performed a retrospective review of all patients receiving intravitreal anti-VEGF injections in Olmsted County, Minnesota, from January 1, 2004, to December 31, 2013, for exudative age-related macular degeneration (AMD), diabetic macular edema (DME), proliferative diabetic retinopathy (PDR), or retinal vein occlusion (RVO). The purpose of this study was to identify the differences in the types of strokes seen in patients receiving intravitreal anti-vascular endothelial growth factor (VEGF) compared with normal control populations. There were 690 patients identified during the study period as receiving an intravitreal injection for AMD, DME, PDR, or RVO. Of these patients, 38 (5.8%) suffered a stroke after starting

intravitreal injection therapy. Of these strokes, 27 (71.1%) were ischemic, six (15.8%) were embolic, and five (13.2%) were hemorrhagic. There were no differences in the types of strokes identified among the patients receiving intravitreal injections between the case cohort and the control cohorts (P > .05 for all).
The authors concluded that there is no predilection to the development of ischemic infarcts or hemorrhagic strokes in those patients receiving intravitreal anti-VEGF compared with control populations.

2. Zhong P et al (128) conducted a meta-analysis to investigate the systemic safety of intravitreal anti-vascular endothelial growth factor for retinal vein occlusion patients. All randomized controlled trials published up to February 2019 of retinal vein occlusion patients who received intravitreal anti-vascular endothelial growth factor vs. control treatments were included. Fixed effect models were used and results were reported as odds ratios and 95% confidence intervals. Eight trials that evaluated 2,320 patients were retrieved. This analysis revealed that anti-vascular endothelial growth factor did not significantly increase the risks of cardiovascular events (odds ratio,1.54; 95% confidence interval, 0.66-3.57), hypertension (odds ratio, 0.92; 95% confidence interval, 0.63-1.33), or heart rate disorders (odds ratio,1.53; 95% confidence interval, 0.37-6.28) when compared with control treatment. Subgroup analyses did not show a significant increase of cardiovascular events in aflibercept (odds ratio,1.96; 95% confidence interval, 0.44-8.81) vs. ranibizumab trials (odds ratio, 1.47; 95% confidence interval, 0.54-4.02); 0.5mg ranibizumab trials (odds ratio, 1.73; 95% confidence interval, 0.61-4.96) vs. 0.3mg ranibizumab trials (odds ratio, 0.70; 95% confidence interval, 0.14-3.59); nor branch retinal vein occlusion (odds ratio, 1.32; 95% confidence interval, 0.40-4.33) vs. central retinal vein occlusion trials (odds ratio, 1.93; 95% confidence interval, 0.59-6.29).
The authors concluded that intravitreal administration of anti-vascular endothelial growth factor did not significantly increase the risks of cardiovascular events, hypertension or heart rate disorders in retinal vein occlusion patients.

3. Chatziralli I.P. et al (129) published a review article on anti-VEGF therapy and cardiovascular disease risks.
The authors concluded that current evidence from clinical trials demonstrated that anti-VEGF agents are safe for diabetic patients, with no increased risk of cardiovascular events. In addition, no definite differences in cardiovascular events between the 3 used anti-VEGF agents that is, aflibercept, bevacizumab and ranibizumab, have been identified.

4. Costagliola C. et al (130) published a review article on systemic thromboembolic adverse events in patients treated with intravitreal anti-VEGF drugs for neovascular age-related macular degeneration. The purpose of this review was to evaluate risk of thromboembolic events associated with intravitreal anti-VEGF.
The authors concluded that current data are insufficient to confirm the safety of these compounds, due to the paucity of specific studies. Thus, pharmacovigilance for all

anti-VEGF should be improved to verify the true role of anti-VEGF in the occurrence of systemic adverse events.

5. Dalvin LA et al (131) conducted a population-based, retrospective cohort study to assess the risk of stroke, myocardial infarction (MI), and death in patients undergoing intravitreal anti-vascular endothelial growth factor (VEGF) therapy.
   This study included 504 patients from Olmsted County, Minnesota, identified through the Rochester Epidemiology Project (REP) database as receiving at least 1 intravitreal anti-VEGF injection for exudative AMD from January 1, 2004, to December 31, 2013. Three age- and sex-matched control groups of individuals who did not receive anti-VEGF treatment and were derived from the REP database were also studied: control individuals with exudative AMD in the era before anti-VEGF (January 1, 1990, to December 31, 2003), controls with dry AMD, and controls without AMD. The five-year risk of stroke, MI, and death were assessed in patients compared with controls using Kaplan-Meier and multivariate analysis with Cox proportional hazards regression models.
   The study included 504 patients (321 female [63.7%]; mean [SD] age, 76.5 [10.0] years) who received at least 1 intravitreal anti-VEGF injection for exudative AMD during the study period. Kaplan-Meier analysis revealed a 5-year risk of 7.2% for stroke, 6.1% for MI, and 30.0% for death. Patients who received anti-VEGF had no increased risk of stroke or MI compared with controls with dry AMD (n = 504), controls with exudative AMD (n = 473), or controls without AMD (n = 504). There was an increased risk of mortality compared with controls with exudative AMD in the era prior to anti-VEGF therapy but not the other control groups on multivariate analysis (hazard ratio, 1.63; 95% CI, 1.30-2.04; P <.001).
   The authors concluded that intravitreal anti-VEGF therapy for exudative AMD was not associated with consistent increases in the risk of stroke, MI, or death compared with no therapy in patients with or without AMD.

Overall company comment on literature

Overall, there was no new and significant safety finding from the literature related to ATEs and intravitreal Eylea treatment during the period of this PBRER/PSUR.

The literature articles point to the conclusion that intravitreal administration of anti-vascular endothelial growth factor did not significantly increase the risks of cardiovascular events (Dalvin LA, 2019 (131)) including in diabetic (Chatziralli I.P, 2019 (129)) and RVO patients (Zhong P, 2019 (128)). There were also no differences in the types of strokes identified among the patients receiving intravitreal injections between patients receiving intravitreal anti-VEGF compared with control populations (Starr MR, 2019 (127)).

Summary and Overall Conclusion ATEs/Ischemic colitis

The AMD, DME, CRVO and BRVO patient population can be considered particularly predisposed to develop ATEs. Cardiovascular risk factors including smoking, age, and nutrition have been associated with the development of neovascular AMD. AMD patients are

therefore more likely than non-AMD patients to have risk factors for, and be at a higher risk of, ATEs (132-134).

The majority of the cases that were received within the PSUR period presented with relevant risk factors and/or other relevant medical history. Cardiovascular risk factors included hypercholesterolemia, diabetes mellitus, tobacco use, arrhythmia (including atrial fibrillation), cerebrovascular and cardiovascular diseases (including previous cerebrovascular infarctions, coronary artery disease and carotid artery stenosis), and hypertension.

There was also no trend of INR changes observed in context of Eylea treatment that would rise a safety concern for the development of ATEs.

In addition, regarding the review of ischemic colitis, most of these patients had underlying risk factors for the development of (ischemic) bowel syndromes.

In conclusion, the review of PSUR qualifying cases received during the reporting period provide no evidence for Eylea-associated occurrence of ATEs. No action is warranted based on the case reports received during this reporting period.

Please refer to **Appendix 12** for the cumulative review of ATEs including ischemic colitis.

16.3.2 Venous Thromboembolic Events

Following last year's PSUR#8, the MAH has received the following request:

The MAH is requested in the next PSUR to provide a cumulative review and analysis (including PK/PD and epidemiologic) of cases of systemic AE (ATE, Ischaemic colitis, ***VTE,*** *HTA and non-ocular haemorrhage):*

The MAH should provide a separate analysis:

- In patients under 50 years old; in cases with a time to onset from last dose <2 weeks; and in in cases without risk factors (as referenced in the publication Eur Heart J. 2017 Mar 14;38(11):785-791)(112).

The MAH has cumulatively investigated (as of 31 AUG 2019) all respective systemic safety topics including VTEs as requested by PRAC. Please refer to **Appendix 12** for the cumulative investigations.

Based on the review of all relevant data no causality of Eylea treatment to the development of VTEs s could be established.

Cases received up to the DLP of this PSUR do not change the overall assessment.

The below analysis describes the PSUR qualifying cases received throughout this reporting period.

Background

Venous thromboembolic events (VTEs) are included as an important potential risk in the EU RMP. To date, there is no clear evidence that anti-VEGF agents administered intravitreally are associated with the development of VTEs.

Search Strategy

For this evaluation, all new PBRER- / PSUR-qualifying cases during the reporting period were searched for the SMQ "Embolic and thrombotic events, venous".

Case details

During this reporting period, a total of 15 new PBRER- / PSUR-qualifying cases pertaining to the risk of venous thromboembolic events were received. All but one case was reported as serious. 11 were medically confirmed. They included 15 venous thromboembolic events: "Retinal vein occlusion" (4 events), "Pulmonary embolism" (3 events), "Deep vein thrombosis" (3 events), "Pulmonary thrombosis" (2 event), "thrombophlebitis" (2 event) and "Venous occlusion" (1 event).

Eight cases were spontaneously reported, 3 originated from interventional clinical trials, and the remaining 4 cases from observational studies (2 from a patient support program, one each from an observational study and published report of an observational study).

As far as reported (N=12), patient age ranged from 41 to 92 years (median 67 years). Twenty-one patients were elderly (≥ 65 years). Age was not reported in the remaining case. Three patients were male, 9 females. Gender was not reported for 3 patients.

The onset latency from first dose to onset of pertinent events was reported in 4 cases, ranging from 332 days to 480 days (median 405 days), and was not available in 11 cases. The onset latency from last dose to onset of events was reported in 2 cases, 27days and 95 days respectively, and was not available in 13 cases. No positive de-challenge or re-challenge information was provided.

Possible alternative explanations for the occurrence of the reported venous thromboembolic events were available for nearly half of the patients (remaining cases provided only very limited information for a further medical assessment):

- A relevant medical history and / or concomitant diseases known to be associated with a higher risk for VTEs were provided for 8 cases, such as malignant conditions, surgery, smoking, hypercholesterolemia / dyslipidemia, and arrhythmia (atrial fibrillation).
- Advanced age (≥ 65 years) as a risk factor for VTE was reported for 9 cases.
- "Retinal vein occlusion" (in 4 patients) reflect ocular conditions treated with Eylea or disease complications of other retinal conditions.

Outcome information for the 15 pertinent events was reported in 6 events: reported as recovered/ resolved (1 event), not recovered/not resolved (4 events) and fatal outcome was reported for 1 event (pulmonary embolism) relating to one patient:

A spontaneously reported medically confirmed case referred to an elderly patient who was treated with Eylea IVT for wet AMD and experienced a pulmonary embolism and died. Medical history included cardiac arrhythmia and diabetes mellitus. No causality assessment was provided by the reporter (2018-223215). Company assessment: This patient was at increased risk of cardiovascular events and venous thromboembolism due to reported risk factors (cardiac arrhythmia, diabetes mellitus). Causality to Eylea is deemed unlikely.

Summary and Conclusion

During the reporting period of this PBRER/PSUR, 15 cases of venous thromboembolism were received. Most patients presented with respective risk factors for venous thromboembolic events, such as advanced age, malignancy, surgery, smoking, dyslipidemia, a history of venous thromboembolism, cardiovascular disease. Overall, the safety information newly received on venous thromboembolic events during this reporting interval did not raise any new or additional safety-relevant concern for the intravitreal use of Eylea. Systemic pharmacodynamic effects including the development of venous thromboembolic events are deemed unlikely.

Overall, no new relevant safety data became available during this reporting period that would confirm a causal association between Eylea and the potential risk of non-ocular hemorrhage. Hence no further action is warranted based on these reports.

Please refer to **Appendix 12.** for the cumulative investigation of VTEs.

16.3.3 Hypertension

Following last year's PSUR#8, the MAH has received the following request:

The MAH is requested in the next PSUR to provide a cumulative review and analysis (including PK/PD and epidemiologic) of cases of systemic AE (ATE, Ischaemic colitis, VTE, ***Hypertension*** *and non-ocular haemorrhage):*

The MAH should provide a separate analysis:

- In patients under 50 years old; in cases with a time to onset from last dose <2 weeks; and in in cases without risk factors (as referenced in the publication Eur Heart J. 2017 Mar 14;38(11):785-791) (112).

The MAH has cumulatively investigated (as of 31 AUG 2019) all respective systemic safety topics including hypertension as requested by PRAC. Please refer to **Appendix 12** for the cumulative investigations.

Based on the review of all relevant data no causality of Eylea treatment to the development of hypertension could be established.

Cases received up to the DLP of this PSUR do not change the overall assessment.

The below analysis describes the PSUR qualifying cases received throughout this reporting period.

Background

Hypertension is included as an important potential risk in the EU-RMP.

MedDRA search

For this evaluation all cases for this reporting period were searched for the following MedDRA Preferred Terms:

"Accelerated hypertension", "Blood pressure ambulatory increased", "Blood pressure diastolic increased", "Blood pressure inadequately controlled", "Blood pressure increased", "Blood pressure systolic increased", "Diastolic hypertension", "Endocrine hypertension", "Essential hypertension", "Hypertension", "Hypertension neonatal", "Hypertensive angiopathy", "Hypertensive cardiomegaly", "Hypertensive cardiomyopathy", "Hypertensive crisis", "Hypertensive emergency", "Hypertensive encephalopathy", "Hypertensive heart disease", "Hypertensive nephropathy", "Labile hypertension", "Malignant hypertension", "Malignant hypertensive heart disease", "Malignant renal hypertension", "Maternal hypertension affecting foetus", "Mean arterial pressure increased", "Neurogenic hypertension", "Orthostatic hypertension", "Prehypertension", "Renal hypertension", "Renovascular hypertension", "Retinopathy hypertensive", and "Systolic hypertension".

Case Details

A total of 47 new PBRER/PSUR-qualifying cases (including 47 events of interest) were received during the current reporting period:

Thirty (30) cases were medically confirmed (23 serious cases and 7 non-serious cases). Seventeen (17) cases were not medically confirmed (16 serious case and 1 non-serious cases).

The reported events of interest (MedDRA PTs) were: "hypertension" (n=31), "blood pressure increased" (n=11), "hypertensive crisis" (n=3), "blood pressure systolic increased" (n=1), and "hypertensive urgency" (n=1).

Eleven (11) cases were reported from interventional studies (study classification: investigator sponsored studies), 12 from observational studies (study classification: 4 from a reimbursement program, 7 from patient support programs, 1 from an observational company sponsored study) and 24 were received as spontaneous case reports.

Age ranged from 41 to 92 years with a median age of 68 years (age information was not reported in 10 cases).

Twenty-nine (29) patients were female and 16 were male, gender was not reported in 2 cases.

The reported indication for aflibercept treatment was AMD in 15 cases, DME in 15 cases, BRVO in 3 cases, and the indication was unspecified in 13 cases. In one case the indication was reported as "colorectal cancer" and patient received intravenous aflibercept.

Outcome was known in 27 cases of which 16 recovered/recovering, 10 not recovered, and one was reported with a fatal outcome [redacted] – see further details summarized below in Table 16-5).

Previous treatment with ranibizumab and/or bevacizumab was reported in a total of 6 cases. Thereof previous treatment with bevacizumab was reported for 2 patients, treatment with ranibizumab and bevacizumab was reported in one patient and in 3 patients a previous treatment with ranibizumab was reported.

The onset latency from *first* dose of aflibercept to the onset of the event was reported in 12 cases and ranged from 8 days to 396 days (median 187 days, not available in 35 cases). There was no case reported with occurrence of hypertension on the same day as Eylea IVT injection.

The onset latency from *last* dose of aflibercept to the onset of the event was reported in 5 cases and ranged from 3 days to 29 days (median 10 days, not available in 42 cases).

The number of aflibercept injections before the event was reported in 16 case reports and ranged from 1 to 24 injections (median 6 injections, not available in 31 cases).

De- and re-challenge information was not reported.

In 26 out of the 47 cases information on medical history was reported, in which relevant risk factors provide a plausible alternative explanation for the event. These risk factors include hyperlipidemia, diabetes mellitus, obesity, tobacco use, and other conditions predisposing to a higher risk for hypertensive conditions and in one case [redacted]) the patient was not treated with Eylea IVT but with aflibercept i.v. for colorectal cancer. In 21 out of 47 reported cases there was only limited information provided for a further medical assessment.

There were 16 cases where the reporter assessed the event as related to Eylea, 4 cases an event of "hypertensive crisis" or "hypertensive urgency" and one case with a fatal outcome, these cases (21) are summarized below:

Table 16-5: Relevant PSUR qualifying hypertension cases

Bayer PV Case ID/ Country / Source / Age / Gender	**Event of interest as reported term / MedDRA PT** (s, serious; n, non-serious)	**Outcome**	**Onset from first dose (days)**	**Onset from last dose (days)**	**Case summary** ➢ ***Assessment comment***
[redacted] CHINA spontaneous 6 Decades male	Transient blood pressure increase / Blood pressure increased (n)	recovered	20	not reported	• Blood pressure increase 20 days after start of treatment with Eylea for polypoidal choroidal vasculopathy • Medical history of 'adrenal nodule' • No further information on medical history, concomitant medication,

Table 16-5: Relevant PSUR qualifying hypertension cases

Bayer PV Case ID/ Country / Source / Age / Gender	**Event of interest as reported term / MedDRA PT** (s, serious; n, non-serious)	**Outcome**	**Onset from first dose (days)**	**Onset from last dose (days)**	**Case summary** ➢ ***Assessment comment***
					event details and treatment as well as Eylea treatment dates has been reported ➢ *Available information provides insufficient basis to assume Eylea-induced hypertension, 'adrenal nodule' might provide an alternative explanation for the non-serious event*
[redacted] CHINA spontaneous 63 Years male	hypertension / Blood pressure increased (s)	recovering	68	29	• Hypertension 29 days after last Eylea IVT administration for AMD together with weakness, sweating, incontinence, palpitations • CT scan showed "little nodules of left adrenal gland, possible adenomas" • No further information on medical history, concomitant medication, event details and treatment as well as Eylea treatment dates has been reported ➢ *Available information provides insufficient basis to assume Eylea-induced hypertension, adrenal adenomas might provide an alternative explanation*
[redacted] UNITED STATES spontaneous 67 Years female	blood pressure was "sky high" like 200/110 / Hypertension (s)	recovered	not reported	not reported	• Blood pressure increase after start of treatment with Eylea for diabetic retinopathy • Medical history of diabetes mellitus and hypertension • No further information on medical history, concomitant medication, event details and treatment as well as Eylea treatment dates has been reported ➢ *Pre-existing hypertension provides a plausible alternative explanation*
[redacted]	blood pressure	recovering	not	not	• Hypertension after start of

Table 16-5: Relevant PSUR qualifying hypertension cases

Bayer PV Case ID/ Country / Source / Age / Gender	**Event of interest as reported term / MedDRA PT** (s, serious; n, non-serious)	**Outcome**	**Onset from first dose (days)**	**Onset from last dose (days)**	**Case summary** ➢ ***Assessment comment***
UNITED STATES observational study 53 Years female	was around 240/162 / Hypertension (s)		reported	reported	treatment with Eylea for diabetic retinopathy • Medical history included hypertension, type 2 diabetes, high cholesterol, anemia, restless leg • Patient's antihypertensive medication was changed, and patient was recovering ➢ *Pre-existing hypertension provides a plausible alternative explanation*
[redacted] AUSTRALIA interventional study Not reported female	hypertension / Hypertension (s)	recovered	not reported	not reported	• Patient was treated with Eylea IVT for DME in an Investigator initiated study and experienced hypertension • Medical history included diabetes mellitus • No further information on medical history, concomitant medication, event details and treatment as well as Eylea treatment dates has been reported ➢ *Available information provides insufficient basis to assume Eylea-induced hypertension*
[redacted] UNITED STATES spontaneous 80 Years female	blood pressure was sky high / Hypertension (s)	Not reported	not reported	not reported	• Patient was treated with Eylea IVT for macula degeneration and experienced hypertension • Concomitant medication included "blood pressure medication" • No further information on medical history, concomitant medication, event details and treatment as well as Eylea treatment dates has been reported ➢ *Available information provides insufficient basis to assume Eylea-induced hypertension, concomitant "blood pressure medication" point to a pre-existing hypertension*

Table 16-5: Relevant PSUR qualifying hypertension cases

Bayer PV Case ID/ Country / Source / Age / Gender	**Event of interest as reported term / MedDRA PT** (s, serious; n, non-serious)	**Outcome**	**Onset from first dose (days)**	**Onset from last dose (days)**	**Case summary** ➢ ***Assessment comment***
[redacted] UNITED STATES spontaneous 66 Years female	blood pressure went "sky high" with readings of 190/40 and up to 200/160 / Blood pressure increased (s)	not recovered	not reported	not reported	• Patient was treated with Eylea IVT for an unknown indication and experienced blood pressure increase together with “felt hoarse, felt unwell, felt confused, thought she had a virus and has "pain shooting" up and down her arms and neck” • Medical history of “fluid retention” • No further information on medical history, concomitant medication, event details and treatment as well as Eylea treatment dates has been reported ➢ *Available information provides insufficient basis to assume Eylea-induced hypertension*
[redacted] UNITED STATES spontaneous 76 Years female	blood pressure went up/ blood pressure sky rocketed / Hypertension (s)	Not reported	not reported	not reported	• Patient was treated with Eylea IVT for an unknown indication and experienced blood pressure increase in context of a hypersensitivity reaction to methylprednisolone for treatment of endophthalmitis • No further information on medical history, concomitant medication, underlying indication and Eylea treatment dates has been reported ➢ *Drug hypersensitivity provides an alternative explanation for the event*
[redacted] UNITED STATES spontaneous 75 Years female	Hypertension / Hypertension (n)	Not reported	not reported	not reported	• Patient was treated with Eylea IVT for exsudative macular degeneration and experienced hypertension in context of atrial fibrillation when patient was started to receive the 25th injection of Eylea IVT

Table 16-5: Relevant PSUR qualifying hypertension cases

Bayer PV Case ID/ Country / Source / Age / Gender	**Event of interest as reported term / MedDRA PT** (s, serious; n, non-serious)	**Outcome**	**Onset from first dose (days)**	**Onset from last dose (days)**	**Case summary** ➢ ***Assessment comment***
					• No further information on medical history, concomitant medication, event details and treatment has been reported ➢ *Available information provides insufficient basis to assume Eylea-induced hypertension*
[redacted] UNITED STATES spontaneous 84 Years female	very high BP / Hypertension (n)	Not reported	not reported	not reported	• Patient was treated with Eylea IVT for diabetic retinopathy and while the next planned dose for Eylea injection was drawn up into the syringe the patient got sick, was vomiting and had elevated blood pressure and the treatment with Eylea was not performed. • Medical history included diabetes, high blood pressure and breast cancer • No further information on medical history, concomitant medication, event details and treatment has been reported ➢ *Available information provides insufficient basis to assume Eylea-induced hypertension, patient had a pre-existing hypertension and event was reported in context of vomiting and feeling sick while waiting for the next injection, which provides a plausible alternative explanation*
[redacted] AUSTRALIA observational study not reported female	increased blood pressure post eye injection / blood pressure went up to two hundred / Blood pressure increased (s)	Not reported	not reported	not reported	• Patient was treated with Eylea IVT for wAMD and experienced increased blood pressure and malaise in context of an Eylea IVT injection • No further information on medical history, concomitant medication,

Table 16-5: Relevant PSUR qualifying hypertension cases

Bayer PV Case ID/ Country / Source / Age / Gender	**Event of interest as reported term / MedDRA PT** (s, serious; n, non-serious)	**Outcome**	**Onset from first dose (days)**	**Onset from last dose (days)**	**Case summary** ➢ ***Assessment comment***
					event details and treatment as well as Eylea treatment dates has been reported ➢ *Available information provides insufficient basis to assume Eylea-induced hypertension*
[redacted] UNITED STATES spontaneous 92 Years female	high blood pressure / Hypertension (n)	not recovered	not reported	not reported	• Patient was treated with Eylea IVT for AMD and experienced hypertension in context of iritis and panuveitis • Treatment with “new blood pressure medication” was reported • Medical history included heart disease and arthritis • No further information on medical history, concomitant medication, event details and treatment as well as Eylea treatment dates has been reported ➢ *Available information provides insufficient basis to assume Eylea-induced hypertension, i.e. non-serious hypertension in a patient with heart disease and (assumed) pre-exiting hypertension (patient was on concomitant Amlodipin and “new” blood pressure medication was started)*
[redacted] UNITED STATES spontaneous 78 Years male	high blood pressure / Hypertension (n)	Not reported	not reported	not reported	• Patient was treated with Eylea IVT for AMD and experienced hypertension • No further information on medical history, concomitant medication, event details and treatment as well as Eylea treatment dates has been reported ➢ *Available information provides*

Table 16-5: Relevant PSUR qualifying hypertension cases

Bayer PV Case ID/ Country / Source / Age / Gender	**Event of interest as reported term / MedDRA PT** (s, serious; n, non-serious)	**Outcome**	**Onset from first dose (days)**	**Onset from last dose (days)**	**Case summary** ➢ ***Assessment comment***
					insufficient basis to assume Eylea-induced hypertension
[redacted] UNITED STATES spontaneous not reported female	systolic pressure has gone up / Blood pressure systolic increased (n)	Not reported	not reported	not reported	• Patient was treated with Eylea IVT for RVO (total of 4 injections) and experienced systolic blood pressure increase and atrial fibrillation (unclear whether AF is a new event or medical history) • No further information on medical history, concomitant medication, event details and treatment as well as Eylea treatment dates has been reported ➢ *Available information provides insufficient basis to assume Eylea-induced hypertension*
[redacted] UNITED STATES spontaneous 85 Years female	blood pressure must be high / Hypertension (n)	Not reported	not reported	not reported	• Patient was treated with Eylea IVT for AMD and experienced hypertension • No further information on medical history, concomitant medication, event details and treatment as well as Eylea treatment dates has been reported ➢ *Available information provides insufficient basis to assume Eylea-induced hypertension*
[redacted] UNITED STATES spontaneous Not reported male	hypertension / Hypertension (s)	Not reported	not reported	not reported	• Patient was treated with Eylea IVT for AMD and experienced hypertension • No further information on medical history, concomitant medication, event details and treatment as well as Eylea treatment dates has been reported ➢ *Available information provides*

Table 16-5: Relevant PSUR qualifying hypertension cases

Bayer PV Case ID/ Country / Source / Age / Gender	**Event of interest as reported term / MedDRA PT** (s, serious; n, non-serious)	**Outcome**	**Onset from first dose (days)**	**Onset from last dose (days)**	**Case summary** ➢ ***Assessment comment***
					insufficient basis to assume Eylea-induced hypertension
[redacted] UNITED STATES interventional study 56 Years male	Hypertensive Urgency / Hypertensive urgency (s)	recovered	not reported	not reported	• Patient was treated with Eylea IVT for NPDR (total of 3 doses) in context of a clinical trial and experienced hypertensive urgency (200/120 mmHg) with shortness of breath • Chest X-ray revealed small bilateral pleural effusions with associated atelectasis • Echocardiogram revealed moderate LV hypertrophy, Mitral filling pattern suggestive of impaired left ventricle relaxation, trace mitral regurgitation • Treatment with Lasix, hydralazine and oxygen was started and patient recovered • Medical history included Type 2 diabetes mellitus, Hypertension, Hypercholesterolemia, Congestive heart failure. ➢ *Pre-exiting hypertension together with congestive heart failure provides a plausible alternative explanation for the event*
[redacted] FRANCE spontaneous 88 Years male	Hypertensive crisis / Hypertensive crisis (s)	recovering	not reported	not reported	• Patient was treated with Eylea IVT for AMD and experienced hypertensive crisis with malaise and headache • No further information on medical history, concomitant medication, event details and treatment as well as Eylea treatment dates has been reported ➢ *Available information provides insufficient basis to assume Eylea-*

Table 16-5: Relevant PSUR qualifying hypertension cases

Bayer PV Case ID/ Country / Source / Age / Gender	**Event of interest as reported term / MedDRA PT** (s, serious; n, non-serious)	**Outcome**	**Onset from first dose (days)**	**Onset from last dose (days)**	**Case summary** ➢ ***Assessment comment***
					induced hypertension
[redacted] FRANCE spontaneous 92 Years female	Hypertensive crisis / Hypertensive crisis (s)	recovered	not reported	not reported	• Patient was treated with Eylea IVT for AMD and experienced hypertensive crisis • Medical history of GERD and breast cancer, concurrent hypertension • No further information on medical history, concomitant medication, event details and treatment as well as Eylea treatment dates has been reported ➢ *Available information provides insufficient basis to assume Eylea-induced hypertension, i.e. pre-exiting hypertension provides a plausible alternative explanation for the event*
[redacted] UNITED STATES interventional study 67 Years female	Hypertensive crisis / Hypertensive crisis (s)	recovered	148	not reported	• Patient was treated with Eylea IVT for diabetic retinopathy (total of 4 doses) in context of a clinical trial and experienced hypertensive crisis (200/120 mmHg) in context of multiple other events including pneumonia, sepsis and septic shock, congestive heart failure, atelectasis and subsequent ARDS requiring intubation and BiPAP and recovered under treatment. • Patient further experienced a stroke with subsequent medically induced coma • Relevant medical history included diabetes mellitus, atrial fibrillation, hypertension, coronary angioplasty, obesity and hyperlipidaemia ➢ *Hypertensive crisis occurred in*

Table 16-5: Relevant PSUR qualifying hypertension cases

Bayer PV Case ID/ Country / Source / Age / Gender	**Event of interest as reported term / MedDRA PT** (s, serious; n, non-serious)	**Outcome**	**Onset from first dose (days)**	**Onset from last dose (days)**	**Case summary** ➢ ***Assessment comment***
					context of acute infection with septic shock and ARDSD and in a patient with pre-existing hypertension, which provide a plausible alternative explanation for the event.
[redacted] CANADA spontaneous 54 Years male	Hypertension / Hypertension (s)	fatal	Not reported	Not reported	• Patient experienced hypertension in context of basilar artery thrombosis, cerebellar stroke, dizziness, endotracheal intubation, hydrocephalus, lateral medullary syndrome, loss of consciousness, nausea, neck pain, vertebral artery dissection and vertigo and died. • No further information on medical history, concomitant medication, Eylea treatment dates and event details was reported. ➢ *Available information provides insufficient basis to assume Eylea-induced hypertension, overall very limited information for a further medical assessment.*

Summary and Conclusion

A search for cases occurring in the current reporting period resulted in 47 new PBRER/PSUR-qualifying cases (including 47 events). All cases either had strong confounders including pre-existing hypertension or provided only limited information for a further medical assessment. The Eylea treated population (i.e. AMD, CRVO and DME patients) can be considered particularly predisposed in experiencing events of hypertension.

The review of relevant ICSRs retrieved from the Bayer safety database did not provide sufficient evidence for Eylea-induced hypertension. Hence no further action is considered warranted.

16.3.4 Non-ocular Hemorrhage

*The MAH is requested in the next PSUR to provide a cumulative review and analysis (including PK/PD and epidemiologic) of cases of systemic AE (ATE, Ischaemic colitis, VTE, hypertension and **non-ocular haemorrhage**):*

The MAH should provide a separate analysis:

- In patients under 50 years old; in cases with a time to onset from last dose <2 weeks; and in in cases without risk factors (as referenced in the publication Eur Heart J. 2017 Mar 14;38(11):785-791) (112).

The MAH has cumulatively investigated (as of 31 AUG 2019) all respective systemic safety topics including non-ocular hemorrhage as requested by PRAC. Please refer to **Appendix 12** for the cumulative investigations.

Based on the review of all relevant data no causality of Eylea treatment to the development of non-ocular hemorrhages could be established.

Cases received up to the DLP of this PSUR do not change the overall assessment.

The below analysis describes the PSUR qualifying cases received throughout this reporting period.

Search Strategy

The pharmacovigilance database was searched for PBRER/PSUR-qualifying cases newly received during the reporting period with a reported event as defined by the SMQ “Haemorrhage terms” (excluding cases where the only reported hemorrhage was an ocular bleeding event: Scleral haemorrhage, Eye contusion, Hyphaema, Retinal aneurysm rupture, Optic disc haemorrhage, Retinopathy haemorrhagic, Vitreous haemorrhage, Eyelid contusion, Ocular retrobulbar haemorrhage, Injection site bruising, Eyelid bleeding, Vitreous haematoma, Eye haemorrhage, Optic nerve sheath haemorrhage, Subretinal haematoma, Conjunctival haemorrhage, Periorbital haemorrhage, Intraocular haematoma, Injection site haematoma, Injection site haemorrhage, Papillary muscle haemorrhage, Choroidal haematoma, Retinal haemorrhage, Corneal bleeding, Eyelid haematoma, Iris haemorrhage, Choroidal haemorrhage, Ciliary body haemorrhage, or Lacrimal haemorrhage).

Results

During this reporting period a total of 47 new PBRER/PSUR-qualifying cases pertaining to the important potential risk non-ocular hemorrhage were received. Of the 47 cases, 32 were spontaneously reported, 12 originated from interventional clinical trials (including one published report from an interventional study; 10 SAEs assessed by the investigator and/or the company as unrelated to Eylea), and 3 from solicited postmarketing sources (all from patient support programs). Forty-one cases were serious and 39 were medically confirmed.

Patient age ranged from 34 to 93 years (median 72 years; N=30). Twenty-five patients were male and 20 females, in 2 patients gender information was not reported.

The 47 cases reported 49 pertinent adverse events. As in previous reporting periods, intracerebral hemorrhage was the most frequently reported event. Table 16-6 provides an overview of all pertinent events, sorted by MedDRA SOC in decreasing order of frequency.

Table 16-6: PBRER/PSUR-qualifying cases of non-ocular hemorrhage newly received during the reporting interval: Number of pertinent adverse events

Adverse Event (MedDRA PT)	Number of Events
Blood and lymphatic system disorders	
Blood loss anaemia	1
Immune thrombocytopenic purpura	1
Gastrointestinal disorders	
Gastrointestinal haemorrhage	1
Haematochezia	1
General disorders and administration site conditions	
Puncture site haemorrhage	1
Hepatobiliary disorders	
Hepatic haemorrhage	1
Injury, poisoning and procedural complications	
Subdural haematoma	3
Contusion	2
Traumatic intracranial haemorrhage	2
Subdural haemorrhage	1
Traumatic haemorrhage	1
Wound haemorrhage	1
Musculoskeletal and connective tissue disorders	
Haemarthrosis	1
Nervous system disorders	
Cerebral haemorrhage	8
Haemorrhagic stroke	5
Intraventricular haemorrhage	2
Basal ganglia haemorrhage	1
Cerebral microhaemorrhage	1
Putamen haemorrhage	1
Renal and urinary disorders	
Haematuria	2
Reproductive system and breast disorders	
Menorrhagia	1
Vaginal haemorrhage	1
Respiratory, thoracic and mediastinal disorders	
Epistaxis	3

Table 16-6: PBRER/PSUR-qualifying cases of non-ocular hemorrhage newly received during the reporting interval: Number of pertinent adverse events

Adverse Event (MedDRA PT)	Number of Events
Vascular disorders	
Aortic aneurysm rupture	2
Haemorrhage	2
Haematoma	1
Internal haemorrhage	1
Subgaleal haematoma	1
Grand Total	**49**

Onset latency varied considerably between reports. Among the 24 cases where latency *from the first dose* of Eylea to onset of the (first) hemorrhage events was known, it ranged from 3 days to more than 1348 days (median 436 days). Onset latency *from the last dose* to event onset was known in 15 cases and in these cases ranged from one day to 106 days (median 30 days).

One or more risk factors or alternative explanations for the reported non-ocular hemorrhage were identifiable in 25 of the 47 cases:

- In 10 cases, reported concomitant or co-suspect medication included medicines with anticoagulant or antiplatelet properties, such as acetylsalicylic acid, clopidogrel, warfarin, non-vitamin K oral anticoagulants or non-steroidal anti-inflammatory drugs.
- In 8 cases, reported co-morbidity included established risk factors for the bleeding event, such as hypertension in patients experiencing intracerebral hemorrhage, or a malignancy.
- In 4 cases, a precipitating event such as a fall, injury or surgical procedure was reported that explains the non-ocular bleeding event.
- In 3 cases a bleeding event from a needle stick while preparing Eylea (Aflibercept) administration by the technician of the physician's office was reported.

The remaining 22 cases are poorly documented, and lack of reported risk factors or alternative explanations is more likely reflective of the limitations of data collection inherent to postmarketing reporting, rather than evidence of true absence of such confounders.

One case mentions that a coagulation test (INR) was normal on the day of the bleeding event (cerebral hemorrhage; case ID 2019-151379). No other coagulation test results were reported in retrieved cases.

The outcome of the bleeding event was reported in 31 of the 47 cases: the bleeding event had resolved or was resolving at the time of reporting in 17 cases (in 1 case with sequelae) and had not resolved in 9 cases. In 5 cases, the bleeding event was reported with a fatal outcome and these cases are summarized below:

- [redacted] **(spontaneous report, Japan)**: a 75-year-old male with concurrent hypertension experienced a fatal aortic aneurysm rupture approximately 3 days after the last Eylea injection. No further information in e.g. concomitant medication was reported.
    - *Company comment:* Hypertension provides a plausible alternative explanation for the reported event. Overall, there is only very limited information provided for a further medical assessment.
- [redacted] **(spontaneous report, Japan):** Patient was treated with Eylea IVT injection for DME and experienced 2 months later a cerebral haemorrhage with a fatal outcome. Patient's medical history included smoking, alcohol use, cataract, pyothorax, diabetes mellitus, hypertension and hyperlipidemia. No further information on e.g. event details, concurrent conditions, concomitant medication has been provided.
    - *Company comment*: Hypertension provide an alternative explanation for the reported event; overall limited information for a further medical assessment.
- [redacted] **(published report from interv. study, Sweden):** a 86 year-old male patient experienced a ruptured aortic aneurysm with fatal outcome 11 weeks after the 8th injection of Eylea IVT. No information on event details such as diameter and localization was provided.
    - *Company comment*: Patient's advanced age is a known risk factor for aortic aneurysm formation, and the medical history (ischemic stroke, myocardial infarction, atrial fibrillation, congestive heart failure and retinal vein occlusion) suggests an underlying predisposition to cardiovascular diseases. Temporal relationship not suggestive for drug causality.
- [redacted] **(spontaneous report, Canada):** a 84-year old female patient was treated with Eylea IVT and experienced infective cholecystitis, abdominal pain, vomiting, diarrhea, hemorrhage, large intestinal perforation, organ failure and underwent surgery. No further information was reported on e.g. event details, medical history, concomitant medication, Eylea treatment dates.
    - *Company comment*: Overall limited information for a further medical assessment.
- [redacted] **(interventional study report, US):** a 47-year old female patient was treated with Eylea IVT (total of 5 injections) for DME in context of a clinical trial and experienced intraventricular hemorrhage with altered mental status and was hospitalized. Treatment with external ventricular drain placement. The patient also had acute renal failure that progressively got worse during the hospital stay and family denied treatment with dialysis as per patients request. The patient died due to these

events. The medical history included hypertension, hypercholesterolemia, and diabetes mellitus.

- *Company comment*: Overall limited information on event details; history of hypertension may provide an alternative explanation for the bleeding event.

Scientific literature

The following publication on non-ocular bleeding events was identified for inclusion in the current PSUR:

Sultana J et al (135) published results (only abstract available) of a cohort study to compare the non□ocular hemorrhage risk of IVT aflibercept vs. ranibizumab (primary aim) and for single IVT anti□VEGFs vs. IVT dexamethasone (secondary aim). 4 Italian regional claims databases were used, covering 18 million inhabitants in a period ranging from 2011 to 2016. Incident aflibercept users were propensity score (PS)□matched 1:4 to incident ranibizumab users. Overall 21,766, 3,150 and 3,900 incident users of ranibizumab, aflibercept and dexamethasone were identified from 2009–2016 in 4 Italian regions. The incidence of non□ ocular hemorrhage with low, at 4 events per 1,000 PYs for each drug. Aflibercept was not associated with increased risk of hemorrhage vs. ranibizumab at 180 days (HR: 0.97 (95%CI: 0.37– 2.56)), which was confirmed at 365 days (HR: 1.01 (95%CI: 0.51– 1.99)). Results were consistent in the AT analysis: HR: 1.19 (95% CI: 0.52–2.75). No increased risk of hemorrhage was found for aflibercept and ranibizumab at 180 days compared to dexamethasone (HR: 0.70 (95% CI 0.30–2.60) and 0.67 (95% CI: 0.33–1.38), respectively).

The authors concluded, that no association was identified between aflibercept and non□ocular hemorrhage compared to ranibizumab. A comparable risk for these IVT anti□VEGFs and IVT dexamethasone was observed. Given the known benefits of IVT anti□VEGF in retinal diseases, hemorrhage does not appear to be a significant risk.

Summary and Conclusion

Non-ocular bleeding events are known side effects of intravenously administered anti-VEGF agents. To date, it is uncertain whether IVT administered anti-VEGF agents are related to systemic bleeding events.

During the reporting period of this PBRER/PSUR, 47 cases with various types of non-ocular bleeding events were reported. Intracerebral bleeding events were most frequently reported, however, most patients presented with risk factors for the development of the reported hemorrhage, such as anticoagulation/anti-platelet therapy, malignancy or hypertension, or the bleeding was reportedly precipitated by trauma or a fall. No abnormal coagulation test result was reported in any of these cases.

This was further supported by the cited publication (Sultana J, 2019 (135)) in which no association was identified in a cohort study for aflibercept IVT and non-ocular hemorrhage.

Overall, no new relevant safety data became available during this reporting period that would confirm a causal association between Eylea and the potential risk of non-ocular hemorrhage. Hence no further action is warranted based on these reports.

For the cumulative investigation on non-ocular hemorrhages, please refer to **Appendix 12**.

16.3.5 Medication Error and Misuse

Medication error can occur with the administration of any drug. For Eylea, medication error constitutes as important potential risk in the EU-RMP version.

Search

SMQ Medication error (Broad) was applied to identify pertinent PSUR/PBRER-qualifying cases.

Results

During the period covered by this report a total of 528 new PSUR/PBRER qualifying case reports including 595 events of potential medication error were received.

Most frequently reported medication errors were product use in unapproved indication (N = 179), Product dose omission (N = 115) and inappropriate schedule of drug administration (N = 71).

An overview of the PTs is provided in Table 16-7

Table 16-7: *Event count of PTs pertinent to Medication Error*

Event (MedDRA PT)	*Serious*	*Non-Serious*	*Grand total*
Product use in unapproved indication	6	173	179
Product dose omission	7	108	115
Inappropriate schedule of product administration	2	69	71
Multiple use of single-use product	1	39	40
Wrong technique in product usage process		35	35
Product storage error		26	26
Injury associated with device		21	21
Product use issue	5	9	14
Product prescribing issue		12	12
Incorrect dose administered	1	9	10
Needle issue	1	7	8
Inadequate aseptic technique in use of product		7	7
Product administered to patient of inappropriate age		6	6
Expired product administered		5	5
Incorrect product administration duration		5	5
Incorrect route of product administration		5	5
Treatment noncompliance	1	2	3

Table 16-7: ***Event count of PTs pertinent to Medication Error***

Event (MedDRA PT)	*Serious*	*Non-Serious*	*Grand total*
Drug administered in wrong device		3	3
Overdose		3	3
Poor quality product administered	1	2	3
Underdose		3	3
Wrong product administered		3	3
Accidental exposure to product		2	2
Product administration error		2	2
Wrong device used		2	2
Syringe issue		2	2
Incorrect dose administered by device		1	1
Labelled drug-drug interaction medication error		1	1
Medication error	1		1
Poor quality device used		1	1
Product administered at inappropriate site		1	1
Product dispensing issue		1	1
Product preparation issue		1	1
Wrong dose	1		1
Wrong patient received product		1	1
Device malfunction		1	1
Grand Total	27	568	595

Use in unapproved indication (N = 179)

Out of 528 new PSUR/PBRER a total of 179 cases with *PT use in unapproved indication* qualifying case reports were received during the reporting period. In 179 cases, there are 179 use in unapproved indication events reported. In 12 of the 179 events of product used in unapproved indication the indication is missing (N = 12). In at least 58 of the cases coded to the PT Product used in unapproved indication the reported indication can be considered approved, e.g. choroidal neovascularization, polypoidal choroidal vasculopathy, macular edema, macular degeneration. Diabetic retinopathy, approved in the US, was reported in additional 15 cases outside the US and therefore considered unapproved.

Table 16-8 provides an overview of the unapproved indications. In some cases, more than one indication was reported.

Table 16-8: Indications reported in cases with *PT use in unapproved indication*

Reported indication	Number of cases
Neovascularization (choroid, retinal)	20
Macular oedema, including cystoid	20
Chorioretinopathy	18
Age-related macular degeneration (wet)	16
Diabetic retinopathy and diabetic retinal oedema	15
Unknown indication	12
Dry age-related macular degeneration	10
Cataract including surgery	10
Retinopathy exudative, proliferative and congenital	6
Haemorrhage (vitreous retinal)	6
Telangiectasia	5
Haemorrhage (Conjunctival haemorrhage and eye)	4
Glaucoma	4
Retinopathy of prematurity	3
Maculopathy	3
Chorioretinal atrophy	3
Stargardt's disease	2
Retinoblastoma	2
Retinal detachment	2
Melanoma	2
Eye swelling	2
Eye disorder	2
Polypoidal choroidal vasculopathy	2
Vasodilatation	1
Thyroid disorder	1
Retinal vein thrombosis	1
Retinal vein occlusion	1
Retinal aneurysm	1
Eye Oedema	1
Eye inflammation	1
Trabeculectomy	1
Colon cancer	1
Choroiditis	1
Total	**179**

Product dose omission (N = 115)

There were a total 115 cases reported with *PT product dose omission* out of 528 initial PBRER qualifying cases. In 115 cases, 115 product dose omission events were reported. In 54 cases, no specific adverse events linked to the product dose omission were reported. In 41 cases, co-reported adverse events were cancer, malaise, aggression, cerebrovascular accident, back injury, hospitalization, myocardial infarction, fall, upper respiratory tract infection etc. In the remaining 20 cases, product storage issues, fear of injection, syringe/needle issues, product distribution issues, intentional omission were reported which might have been the reason for the product dose omission. Based on overall case analysis, adverse events are not linked with an omitted dose and are considered to rather reflect underlying medical conditions.

Inappropriate schedule of product administration (N = 71)

There were a total of 64 cases reported with *PT inappropriate schedule of product administration* out of 528 initial PBRER qualifying cases. There were a total of 71 *PT inappropriate schedule of product administration* events in those 64 cases. These cases mainly refer to a deviating treatment schedule/injection interval. In most of the cases more flexible treatments or treat and extend regimen were applied.

In 27 cases, an inappropriate schedule of product administration was reported alone or co-reported with off label use or prescribing issue or therapy cessation. In the remaining cases, the events are coincidental or related to progression of underlying disease. e.g. cataract, glaucoma, IOP increase, inflammatory eye reactions, visual impairment, retinal detachment, retinal hemorrhage, maculopathy. Based on overall case analysis, there are no relevant adverse events considered to be linked with an inappropriate schedule of product administration.

Other relevant medication error or misuse

Vial/dose fractioning

Vial/dose fractioning is a common practice in some countries (N = 40, coded to PT Multiple use of single-use drug). In 35 out of these 40 reports other adverse events were reported. Thirty-two cases were associated with intraocular inflammations and/or infections which is a labeled ADR following Eylea injection.

Overdose

Overdose of aflibercept was reported in 3 cases. Wrong technique in drug administration was reported in all 3 cases. One case was associated with an IOP increase and retinal artery occlusion and in two cases eye inflammation was reported along with the over dose. IOP increase is a known complication of intravitreal volume injection and be expected to occur following the injection of too much volume. IOP increase is an acknowledged and labeled ADR.

Conclusion

The review of cases pertaining to medication error did not identify a new safety concern with Eylea. (For Medication Error Report with Harm see **Appendix R6**).

16.3.6 Off-label Use

Background

Off-label use may occur with any drug. In the EU-RMP it is discussed as a potential risk.

Eylea is approved for the use in the indications wet AMD, CRVO, BRVO, DME and myopic CNV. In addition, in the U.S.A. Eylea is approved in the indication Diabetic Retinopathy (DR). Usually these indications occur in adults.

Based on PRAC's request the off-label use section in the PSUR focusses on treated patients below the age of 18.

Search strategy

For the following analysis all PBRER qualifying case reports from the respective reporting period (01 DEC 2018 – 30 NOV 2019) were searched for the PT Off label use and PT Product administered to patient of inappropriate age in patients below 18 years.

During this reporting period a total of 11 initial PBRER qualifying cases pertaining to the risk Off-label use in patients below 18 years were received. In 9 out of 11 cases the indications were specified: n=3 retinopathy of prematurity, n=2 retinoblastoma, n=1 each peripapillary choroidal neovascularization associated with optic disc drusen, Coats-like disease, Myopic choroidal neovascularization and exudative active familiarly vitreoretinopathy. In 2 cases the indication was not named.

The average age and median are 5 years and 3.4 respectively.

The cases are explained below;

[redacted] The literature case, *Gan W L et al (136)*describes the occurrence of product use issue ("Aflibercept injected in unapproved age") in a 6-year-old female patient who received Aflibercept solution for peripapillary choroidal neovascularization associated with optic disc drusen. On an unknown date, the patient started aflibercept at an unspecified dose and frequency**.** Peripapillary choroidal neovascularization (PPCNV) associated with optic disc drusen is a rare complication that can result in severe vision impairment in children. They reported the first case of pediatric PPCNV secondary to optic disc drusen successfully treated with intravitreal aflibercept. A 6-year-old girl presented with a one-week history of reduced vision in her right eye with best corrected visual acuity of 20/500. Fundus examination revealed bilateral elevated discs with a peripapillary pigmentary lesion in the right eye. Optical coherence tomography of the right eye showed marked sub foveal fluid. Both B-scan ultrasonography and fundus autofluorescence demonstrated findings consistent with optic disc drusen. Diagnosis of PPCNV was further confirmed on fluorescein fundus angiography. The child received three intravitreal aflibercept injections with complete resolution of the sub

foveal fluid. Her visual acuity improved to 20/25 with no recurrence at a 16-month follow-up. No adverse side effects were reported.

[redacted]**:** This literature case, *Gelzinis Arvydas, et al (137)* describes the occurrence of off label use in a 5-year-old boy who received aflibercept solution for abnormal retinal vasculature with telangiectasia and dilatations (*Coats-like disease)*.

Visual acuity was 0.02 in the right eye, and 1.0 in the left. The ophthalmologic examination of the right eye revealed retinal edema, macular exudates and telangiectasia in temporal and nasal retina. Initial left eye examination appeared normal, however, later performed fluorescent angiography (FAG) revealed abnormal retinal vasculature with telangiectasia and dilatations without retinal exudation. After 3 intravitreal injections of Aflibercept 2mg at every 4 weeks, cryo and laser photocoagulation was applied for the right eye. Retinal edema resolved after the first injection. Some telangiectasia remained active and the treatment was repeated after 6 months. After one year since initial treatment, visual acuity in the right eye improved to 0.15, central exudates almost resolved, however new telangiectasia and retinal edema started to appear. Further examination revealed multiple brain calcifications, without signs of leukodystrophy on later performed MRI scans. Coats plus syndrome was suspected, however neurologic investigation was normal. After the treatment (7 laser/cryo and 9 i/v injections during the first 19 months), FAG showed no vascular leakage in the right eye. However, macular edema reappeared, requiring additional anti-VEGF injections, which temporarily restored macular thickness and visual acuity**.** No adverse events are reported with Aflibercept.

[redacted]**:** This spontaneous case was reported by a physician reports about an 8 years age patient who received Aflibercept solution for injection for retinopathy congenital.

On 11 MAR 2019, the patient started Aflibercept 40 mg/ml (intraocular) at an unspecified dose once per month. The reporter documented a “good treatment” response since start of the treatment. No other information was provided. No safety concerns were reported.

[redacted] This spontaneous case was reported by a physician and describes the occurrence of intraocular pressure increased ('Elevated IOP') in a neonate patient who received Aflibercept solution for unknown indication. On an unknown date, the patient started Eylea 40 mg/ml (intraocular) at an unspecified dose and frequency. The patient was found to have intraocular pressure increased which resolved on same day. It was unknown, whether any action was taken with Aflibercept. The reporter provided no causality assessment for intraocular pressure increased with Aflibercept. No other information was provided. Further company follow-up with the physician is not possible.

[redacted]**:** The literature case, Shields R A et al (138) describes a 17-year-old male patient who received Aflibercept solution for Myopic choroidal neovascularization. On an unknown date, the patient started aflibercept 40 mg/ml (ophthalmic) at an unspecified dose and frequency.

17-year-old male was initially referred for sudden onset of a central scotoma in the left eye. His past ocular history was unremarkable other than severe myopia in both eyes (manifest refraction: –23.25 +2.75 × 113 in the right eye and –23.50 +3.75 × 068 in the left eye). Best-corrected visual acuity (BCVA) was 20/40 and 20/150 in the right and left eyes, respectively. The anterior segment exam was unremarkable, whereas fundus examination of the left eye was notable for subretinal pigmentary changes in the temporal fovea. Optical coherence tomography (OCT) demonstrated a staphylomatous contour and an outer retinal hyperreflective lesion with subtle subretinal fluid consistent with a Choroidal neovascular membrane (CNVM). The patient received monthly intravitreal bevacizumab for 3 months with only mild improvement in visual acuity due to loss of outer retinal integrity. One year later, he presented with sudden onset of vision loss in the right eye with a BCVA of 20/30 and 20/100 in the right and left eyes, respectively. Dilated fundus examination demonstrated a nasal and inferior subretinal hemorrhage in the parafoveal region. OCT revealed a mixed hyper- and hypo reflective subretinal lesion in the nasal/ inferior parafovea consistent with hemorrhage and a CNVM. He was treated with monthly intravitreal Aflibercept for 3 months in the right eye. Since, his disease was progressed and underwent vitrectomy. Postoperatively, he continued to receive the monthly injections of Aflibercept with complete resolution of subretinal hemorrhage and improvement in BCVA to 20/125 in the right eye. No adverse events were reported.

[redacted]**:** This spontaneous case describes an infant patient who received Aflibercept solution for Retinopathy of prematurity. On an unknown date, the patient started Aflibercept 40 mg/ml at an unspecified dose and frequency. No other details were reported.

[redacted]**:** This literature case, *Stathopolous et al (139)* describes a 16-month-old female patient, who received Aflibercept solution for Retinoblastoma.

16month-old girl with unilateral retinoblastoma was treated with Aflibercept on unknown date and dose. Three months after the third IAC (intraarterial chemotherapy), fundus showed persistent total retinal detachment causing massive ischemic retinopathy with rubeosis iridis, papillary neovascularization, and NVE (neovascularization elsewhere). Three months after treatment (consisting of one intravitreal ranibizumab followed by external scleral buckling without drainage and one intravitreal aflibercept on unknown date, dose), indirect ophthalmoscopy and Fluorescein angiography showed completely reattached and re-perfused retina and fully regressed neovascularization at both iris and posterior pole**.** The status remained stable with no further treatment at 3.7-year follow-up.

[redacted]**:** This literature case, Stathopolous et al (139) describes the occurrence of off label use ('Eylea used for treatment of retinoblastoma') and product use in unapproved indication ('Eylea used for treatment of retinoblastoma') in a 20-month-old male patient who received Aflibercept solution for Retinoblastoma.

On unknown date**,** 20-month old boy with bilateral retinoblastoma was treated with intravitreal injection of aflibercept 40 mg/ml. One month after the second salvage intraarterial chemotherapy with combined melphalan and topotecan, new subtotal retinal detachment with

peripheral temporal and inferotemporal retinal ischemia was seen on fundus examination and Fluorescein angiography, respectively. There was no neovascularization elsewhere but florid clinical iris rubeosis. Two months after, one intravitreal injection of aflibercept 40 mg/ml, given on unknown date and the third intraarterial chemotherapy, the retina was completely reattached and rubeosis iridis resolved. The status remained unchanged with no further treatments at 19-month follow up. No side effects reported with aflibercept.

[redacted]**:** This spontaneous case describes an adolescent patient, who received Aflibercept solution for an unknown indication. On an unknown date, the patient started Aflibercept 40 mg/ml (intraocular) at an unspecified dose and frequency. No other details were reported by the reporter.

[redacted]**:** This spontaneous case was reported by a healthcare professional and describes 24-week-old male patient who received Aflibercept solution for Retinopathy of prematurity. On an unknown date, the patient started Aflibercept 40 mg/ml at an unspecified dose and frequency. No other details were reported. No new follow-up information was received from the reporter.

[redacted]**:** This spontaneous case was reported by a physician and describes a patient who received Aflibercept solution for Retinopathy of prematurity. On an unknown date, the patient started Aflibercept 40 mg/ml 2 mg at an unspecified frequency. No other details were reported by the reporter.

Literature: Efficacy of intravitreal aflibercept monotherapy in retinopathy of prematurity evaluated by periodic fluorescence angiography and optical coherence tomography (Aslı Vural. Et al (140)

The authors evaluated the efficacy of intravitreal aflibercept (IVA) in vascular and macular maturation in neonates with type 1 retinopathy of prematurity (ROP) and aggressive posterior retinopathy of prematurity (APROP). Thirty-six eyes of18 patients with type 1 ROP or APROP in zone I or posterior zone II were enrolled in their study. At baseline, only fluorescein angiography (FA) was performed. After IVA injection, both FA and optical coherence tomography (OCT) were performed after 6.8 ± 0.8 (range6–8) and 19 ± 0.9 (range 18–20) weeks to follow vascular and macular changes.

Both diffuse flat neovascularization with leakage and abnormal vascular branching at the small arteriolar level were detected in all eyes (100%) at baseline FA. Regression of the disease was observed in 34 eyes (94.4%) in the first week with binocular indirect ophthalmoscopy. Early unresponsiveness in remaining two eyes of an infant required an IVA retreatment. Late reactivation was detected only in 19.4% of eyes, none of which required treatment during 12 months of follow-up. The most common feature after IVA injection was abnormal branching at capillary level, which was noted in 100% in the first post-injection FA and 50.0% of all eyes in the second FA. Meanwhile, the end limit of vascularization was observed in zone III in 83.3% of eyes. No vascular abnormality was also detected in 27.3% of eyes. The OCT examination at a mean postmenstrual age of 43.4 weeks revealed cystoid macular changes in four eyes of two infants (11.1%), normal foveal contour in 30 eyes of

15 infants (83.3%) and matured ellipsoid zone at the foveal center in 28 eyes of 14 infants (77.8%). Macular maturation was complete in all eyes in the last OCT analyses.

The authors concluded that Intravitreal aflibercept injection allows safe and effective treatment of ROP with appropriate vascular development, higher early response and lower late reactivation rates. Adequate vascular outgrowth that means reaching zone III could be achieved in most of the infants after IVA injection. The process of macular maturation was not significantly delayed because of IVA and/or disease itself as it had been confirmed with a periodical OCT analysis. Even if late reactivation develops very rarely, authors stated that, its re-treatment is not necessary if plus disease develops, which could easily be diagnosed with binocular indirect ophthalmoscopy.

Company comment: No safety signal was derived from this publication. The company currently conducts a study in patients with retinopathy of prematurity.

Conclusion:

The review of the case reports received during the period covered by this report and the literature did not reveal any relevant safety information about off-label use of Eylea in patients below the age of 18.

16.3.7 Embryo-fetotoxicity

Embryo-fetotoxicity is a potential risk in the Eylea RMP.

All initial PSUR-qualifying pregnancy cases were reviewed.

A total of 8 pregnancy cases have been reported during the current reporting period, one literature case from Japan, one case from an observational study (patient support program) in Australia, and 6 spontaneously reported cases (1 case each from Iraq, Switzerland, Germany, US, Russia, and Thailand). Except the case reported from the Australian patient support program, all remaining cases were medically confirmed. A brief description of all 8cases is provided in the following section.

[redacted]

This spontaneous case (from Iraq) was reported by a physician and described the occurrence of "exposure during pregnancy" (verbatim: drug exposure during pregnancy) in a female patient of unknown age who received Eylea for the indication "retinal vein occlusion". On an unknown date, the patient started Eylea 40 mg/mL at an unspecified dose and frequency. Further treatment at an unspecified dose and frequency occurred in December 2018. The exposure during pregnancy occurred on an unknown date. Last menstrual period and the estimated date of delivery were not provided. Despite follow-up attempts, no further information was received, and the case was closed.

[redacted]

This spontaneous case (from Switzerland) was reported by a physician and described the occurrence of "maternal exposure before pregnancy" (verbatim: patient became pregnant

4-5 weeks after last Eylea injection) in a female patient of unknown age who received Eylea for the indication "diabetic macula edema". From an unknown date until 22 NOV 2018, the patient received Eylea 40 mg/mL and experienced maternal exposure before pregnancy. Dose, frequency and total number of Eylea injections were not reported. The patient became pregnant in late December 2018. Last menstrual period and the estimated date of delivery were not provided; the potential fetal exposure to Eylea occurred during the first trimester. Despite the requested follow-up attempts, no further information was received, and the case was closed.

[redacted]

This case was reported from a patient support program in Australia (medically not confirmed) and described the occurrence of "abortion spontaneous" (verbatim: miscarriage) and "maternal exposure during pregnancy" (verbatim: the patient got pregnant during Eylea treatment) in a 32-year old female patient who received Eylea for the indication "diabetic macular edema". Other events included in the case report were serious "retinal detachment", non-serious "vision blurred", non-serious "diplopia", and non-serious "eye irritation". The patient's medical history included myopia and diabetes mellitus. Concomitant products included insulin aspart (Novorapid), insulin glargine (Lantus), and insulin since 2009 for diabetes mellitus. In JAN 2017, the patient started Eylea 40 mg/mL (intraocular) injections to both eyes. On an unknown date in 2017, patient got pregnant during Eylea treatment. Last menstrual period and the estimated date of delivery were not provided. On 11 DEC 2017, the patient experienced spontaneous abortion. Thus, the pregnancy outcome was reported as spontaneous abortion. The relationship of spontaneous abortion to the treatment with Eylea was not assessed by the reporter.

[redacted]

This spontaneous case (from Germany) was reported by a physician and described the occurrence of "maternal exposure during pregnancy" (verbatim: Eylea was administered to pregnant woman) in a female patient of unknown age who received Eylea for an unknown indication". On an unknown date, the patient started Eylea 40 mg/mL (intraocular) at an unspecified dose and frequency. The maternal exposure during pregnancy occurred on an unknown date. Last menstrual period and estimated date of delivery were not provided. No other information is currently available.

[redacted]

This spontaneous case (from the US) was reported by a physician and described the occurrence of "maternal exposure during pregnancy" (verbatim: patient became pregnant) in a 47-year old female patient who received Eylea for the indication "diabetic macula edema". The patient's past medical history included diabetes mellitus; concomitant medications were insulin, hormone patch. The patient started Eylea therapy on 07 DEC 2017 for the treatment of DME at a dose of 2mg/0.05mL. Frequency was every 4-6 weeks, intravitreally. Patient received an unknown total number of doses of Eylea. The last dose was administered on 24 APR 2019. The patient had been using a hormone patch and condoms for contraception

but found out she was pregnant while on treatment with Eylea. The event of pregnancy was reported with an onset date of 05 MAY 2019, and Eylea was subsequently discontinued (i.e., last dose was administered on 24 APR 2019). No other information is currently available.

[redacted]

This literature case from Japan1 describes the occurrence of "exposure during pregnancy" (verbatim: drug exposure during pregnancy) in a 27-year-old female patient who received Eylea for the indication "proliferative diabetic retinopathy and diabetic macular edema" (141). The patient's medical history included panretinal laser photocoagulation; concurrent conditions included Type 1 diabetes mellitus. On an unknown date, the patient started Eylea 40 mg/mL (intraocular) at an unspecified dose and frequency. The exposure during pregnancy occurred on an unknown date; Eylea was withdrawn. Last menstrual period and estimated date of delivery were not provided. Likewise, pregnancy outcome was not reported. Further company follow-up with the reporting health care professional was not possible, no further cooperation for the investigation was obtained from the reporter, and the case was thus closed.

[redacted]

This spontaneous case (from Russia) was reported by a physician and described the occurrence of "maternal exposure during pregnancy" (verbatim: pregnant under Eylea treatment) in a 42-year old female patient who received Eylea for the indication "central serous chorioretinopathy". On 05 AUG 2019, the patient started Eylea 40 mg/mL (intraocular) 2 mg at an unspecified frequency. The maternal exposure during pregnancy occurred in August 2019, and Eylea was withdrawn. Last menstrual period and estimated date of delivery were not provided. Potential fetal exposure to Eylea occurred during the first trimester. Further company follow-up with the physician was not possible.

[redacted]

This spontaneous case (from Thailand) was reported by a physician and described the occurrence of "exposure during pregnancy" (verbatim: pregnancy 3 months and not notify doctor before injection) in a female patient of unknown age who received Eylea for the indication "diabetic macular edema". In October 2019, the patient received Eylea 40 mg/mL (2 mg once). The exposure under pregnancy occurred on an unknown date. Last menstrual period and estimated date of delivery were not provided. Potential fetal exposure to Eylea occurred during the first trimester. The reporter commented that the patient had been pregnant for 3 months and did not notify the physician at the time when the first injection was administered in October 2019. According to the reporter, the patient is currently under observation. No other information is currently available.

Conclusion

The pregnancy outcome among the 8 reports on females who got pregnant after or during exposure to Eylea was documented in 1 case only (spontaneous abortion following maternal exposure during pregnancy; case No. [redacted]). No causality assessment was provided

by the reporter. The case concerned a 32-year-old pregnant female with insulin dependent diabetes mellitus.

Miscarriage is the most common complication of early pregnancy. Risk factors include maternal age, previous spontaneous abortion, smoking, low folate level, uterine abnormalities, fetal chromosomal abnormalities, maternal chronic disease (e.g., polycystic ovary syndrome and thyroid dysfunction, for example), and maternal infections. In addition, patients with diabetes have an increased risk for miscarriages. Main causes for miscarriage in diabetic females include congenital anomalies, neonatal complications of prematurity, stillbirth, birth asphyxia, and chorioamnionitis (142). The spontaneous abortion in this case may be well explained by the underlying risk factors of insulin dependent diabetes.

Overall, no safety concern was identified following the review of pregnancy cases received during this reporting period.

16.3.8 Retinal Hemorrhage

Background

Retinal hemorrhage can be a symptom of ischemic ocular disorders such CRVO, DME, and wet AMD. Retinal hemorrhage is a potential risk in the EU RMP and annually reviewed in the PSURs.

In the last Assessment Report of PBRER # 8, covering the period 01 DEC 2017 to 30 NOV 2018, the MAH was requested to provide in this PSUR #9 a cumulative review of retinal hemorrhage cases and a literature review. In this review, cases with no predisposing factors should be highlighted. Furthermore, the addition of this AE in the EU product information should be discussed. Please find the cumulative review on retinal hemorrhages and the use of Eylea (as of 01 OCT 2019) in **Appendix 7.** Based on the currently available information, an SmPC update is not warranted.

Cases received since data cut off of the cumulative investigation until the DLP of this PBRER did not change the overall assessment of this topic.

PBRER qualifying cases received in the reporting interval:

The below section reflects the annual analysis of initial PSUR qualifying cases regarding retinal hemorrhages received from 01 DEC 2018 to 30 NOV 2019.

MedDRA search

All newly received PBRER/PSUR qualifying case reports were searched for the PT: retinal haemorrhage.

Case details

A total of 32 PSUR qualifying case reports (including 32 events) meeting the search criterion were received during the reporting period:

Thirty-one events of retinal hemorrhage were serious, and 1 event was non-serious.

12 cases were reported from solicited sources such as patient support programs, market research, reimbursement programs. Five cases were received from literature including published study reports and 15 cases were spontaneous reports.

The onset latency from first dose of aflibercept to the onset of the retinal hemorrhage was reported in 5 cases and ranged from "1 day" to "2 years, 12 days" (i.e., range: 1 to 742 days; median: 4 days).

The onset latency from last dose of aflibercept to the onset of the event was reported in 5 cases and ranged from 1 day to 10 days (median: 4 days).

The number of aflibercept injections before the event was recorded/estimable in 5 case reports and ranged from 1 injection to 9 injections (median: 1 injection).

No positive de-challenge or re-challenge was reported.

In 16 out of the 32 case reports relevant risk factors were identified, which could have been an alternative explanation for "retinal haemorrhage". These risk factors, apart from the underlying eye disorders, included (patients could have had more than 1 one risk factor) diabetes mellitus (5 cases), pre-existing retinal hemorrhage (4 cases), concurrent ocular inflammation (1 case), concomitant/history of photodynamic therapy (4 cases), RPE tear/detachment (2 cases), and arterial hypertension (4 cases).

Age was reported in 27 cases and ranged from 49 to 85 years with a median age of 70 years.

Eleven patients were females and 17 patients were males (no gender was reported in 4 cases).

The reported indication for aflibercept treatment was predominantly AMD in 15 cases, DME/diabetic retinopathy in 7 cases, BRVO in 1 case, and "Other/unspecified" in 4 cases (“peripheral exudative hemorrhage chorioretinopathy; anti-VEGF; neovascularization; choroidal neovascularization”). No data on indication were provided for the remaining 5 cases.

Outcome of retinal hemorrhage was reported in 6 cases, of which 2 were recovered, 1 recovered with sequelae, 3 not recovered.

Reference to INR values was not reported during the reporting period.

Any concomitant drugs were reported in 7 cases.

Previous treatment with other VEGF inhibitors was reported in 5 cases:

- 2 cases with bevacizumab only
- 2 cases with ranibizumab only
- 1 case with unspecified VEGF inhibitors

There was no new relevant literature during the reporting period.

Summary and Conclusion

Retinal hemorrhage can be a symptom of all underlying Eylea indications.

During the review period 32 PBRER qualifying cases of retinal hemorrhage were received. The reported indication for aflibercept treatment was predominantly AMD in 15 cases, DME/diabetic retinopathy in 7 cases, BRVO in 1 case, and "Other/unspecified" in 4 cases. No data on indication were provided for the remaining 5 cases. Ischemic ocular diseases such as wet AMD, DME, and CRVO are associated with the development of retinal bleeds during the course of the disease. Some patients had underlying risk factors such as hypertension, diabetes mellitus or the concomitant use of photodynamic therapy. No causal association to aflibercept therapy can be derived from the cases received during the current reporting period.

PSUR qualifying cases received during the reporting period are in line with the single case review conducted for the cumulative investigation and do not alter the overall assessment of the cumulative evaluation (**Appendix 7**).

16.3.9 New Information on Important Identified Risks

On the following important identified risks new safety relevant information was received during the period of this PBRER/PSUR:

16.3.10 Endophthalmitis (Likely of Infectious Origin)

Background:

Endophthalmitis is an identified risk after intravitreal injections. In the core RMP endophthalmitis and intraocular inflammation (IOI) are discussed as one safety concern, while in the EU-RMP the concern is split in endophthalmitis (likely infectious origin) and IOI. In this chapter PBRER-qualifying cases of endophthalmitis (likely infectious origin) are analyzed and discussed which were received from 01 DEC 2018 to 30 NOV 2019. Endophthalmitis, culture-positive and culture-negative, is listed in the undesirable event section of the CCDS.

The intravitreal injection can introduce infection into the eye, if there is a break in sterile technique. Source of pathogenic agents is in most cases the patient’s conjunctival bacterial flora.

In a certain percentage the endophthalmitis is culture-negative even if an infectious origin is assumed.

Search strategy

Preferred terms: Candida endophthalmitis, endophthalmitis, eye infection, eye infection bacterial, eye infection chlamydial, eye infection fungal, eye infection intraocular, eye infection staphylococcal, infectious iridocyclitis, infective iritis, infective uveitis, mycotic endophthalmitis, and necrotising retinitis.

Results

During this reporting period a total of 365 new PSUR/PBRER qualifying cases pertaining to the risk endophthalmitis (likely infectious origin) were received. These cases include 368 events (one case may include more than one event/PT) coded to the following PTs: Table

16-9 endophthalmitis (N=334), eye infection (N = 24), eye infection staphylococcal (N = 4), eye infection bacterial (N=2), eye infection intraocular (N=2), mycotic endophthalmitis (N=1), necrotising retinitis (N=1).

Table 16-9: Preferred Terms in endophthalmitis cases

Event Count Body System / PT	Medically confirmed	Non-medically Confirmed	Total
Endophthalmitis	315	19	334
Eye infection	8	16	24
Eye infection bacterial	1	1	2
Eye infection intraocular	1	1	2
Eye infection staphylococcal	3	1	4
Mycotic endophthalmitis	1	0	1
Necrotising retinitis	1	0	1
Total	**330**	**38**	**368**

- 328 (89.9%) cases were medically confirmed.
- All of the 365 (100.0%) case reports were serious.
- Age was provided in 237 cases and ranged from 32 years to 118 years with an average age of 75.8 years.
- The onset latency from first dose to onset of events was ranging from 1 to 1810 days with a mean of 204 days (provided in 66 case reports), median 5 days.
- The onset latency from last dose to onset of events was ranging from 1 to 39 days with a mean of 5 days (provided in 91 case reports), median 4 days.
- Outcome was reported for 247 events. Reportedly 135 events were recovered/recovering/recovered with sequelae, 41 events were not recovered, for 71 events outcome was reported as unknown and for 121 events this information was missing.

Number of Eylea injections before event onset

The number of injections is not collected in a standardized manner in the safety database. To assess if the number of previous administrations could have an impact on intraocular inflammation occurrence, the onset latency from first dose has been analyzed. As Eylea is administered once every four weeks for at least 3 months at the beginning of treatment initiation in the indications wet AMD, CRVO, BRVO and DME, one injection is assumed if the event onset was on the same day or up to 31 days. Three injections are assumed if the event onset was within 93 days after treatment initiation.

The event onset latency from first dose was provided in 66 cases. In 45 cases (68.2%) of the 66 cases with information on onset latency from first dose provided, the event onset was

within 31 days assuming just one injection. In further 6 cases (9.1%) the events occurred within 93 days after treatment initiation assuming a maximum of 3 injections. In the remaining 15 cases (22.7%), there was no pattern in the onset latency between 125 and 1810 days.

As in 68.2% of the cases the reported event onset occurred after the first Eylea injection (within 31 days after the first Eylea administration), it is not assumed that the risk for infectious eye reactions rises with increasing numbers of Eylea injections.

Overall, the number of previous IVT administrations does not seem to have an impact on endophthalmitis occurrence.

Culture results

As per the structured field ("lab test") in the safety database, in 136 cases cultures were taken: of these in 84 cases, cultures showed positive results, e.g. mostly for Staphylococcus epidermidis, Staphylococci (unspecified) and Streptococci (unspecified), in 37 cases the cultures returned negative and in 15 cases the results are pending/unknown.

Handling issues

In 16 out of the 365 case reports the content of the vial was split to use the content for more than 1 patient. In 5 out of these 16 cases vitreous or anterior chamber cultures were positive.

Relevant literature received during reporting period:

There was no new relevant literature during this reporting period.

Relevant actions taken during the reporting interval for endophthalmitis/intraocular inflammations:

1. The quality investigations around the signal of intraocular inflammations in the US related to 2 specific batches of syringes co-distributed in the US market were finalized during this reporting period. No clear root cause could be identified. The signal was closed. See finalized signal management document in **Appendix 9.**
2. In JUL 2019 in Australia four adverse event reports of culture positive endophthalmitis (3 x Staph epidermidis, 1 Staph aureus) were reported to Bayer in association with a specific batch of Eylea. The review of the product complaints and adverse events databases did not identify a potential batch related issue. The cases were proactively communicated to HCPs to hold vials from that batch until quality investigation completed. Further, proactive communication to Australian HA (TGA) and wholesalers was done. TGA issued a Quarantine Notification. No quality defect was identified by Bayer for this batch and the Quarantine was closed out in AUG 2019 (see also section on regulatory actions for safety reasons).
3. DEC 2019 (late breaking information after DLP). Physicians in Israel reported intraocular inflammations following the injection of Eylea with 3 particular batches (KT03900, KT033KP, KT037VV). The Ministry of Health in Israel distributed a local

DHCPL asking HCPs to avoid using these 3 batches until all quality investigations are completed. Not more than 5 cases of intraocular inflammation were received per batch, cases were spread across the months coming from different sites, some cultures returned negative and some were positive for different microorganisms (Staph. epi, unspecified Streptococcus, Streptococcus viridans, Granulitacella adiacens). No further intraocular inflammation case was received from other batches coming from the same drug product batch. To date, no quality deficit of any of the 3 batches could be confirmed by Bayer. In the meantime, the Israeli Ministry of Health concluded their sterility investigations without any findings and communicated that the batches can continue to be used (January 2020). Overall, to date no product related safety concern could be identified that would have led to the development of intraocular inflammations (see also section 14 on late breaking information received after the DLP).

Summary and conclusion

Endophthalmitis is an established ADR of intravitreal injections including Eylea.

Overall, injection related endophthalmitis remains a risk with IVT aflibercept injection and is addressed as such in the CCDS and SmPC. Early diagnosis and treatment are critical to prevent long term complications and blindness. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay and should be managed appropriately. This warning has been included in the CCDS of aflibercept. In addition, in the CCDS a detailed description of the injection procedure is included.

The newly received safety information is in line with the known risk characterization for the identified risk endophthalmitis (likely infectious origin) and the use of Eylea.

No new product related safety concern/quality deficit was detected that was considered causally linked to the development of endophthalmitis cases.

16.3.11 Intraocular Inflammation

Background

In the EU-RMP, intraocular inflammation is discussed as an identified risk after intravitreal injections.

Non-infectious intraocular inflammatory reactions such as non-infectious endophthalmitis, vitritis, iritis and uveitis can occur after anti-VEGF IVT injections and are listed in the CCDS as expected events for aflibercept in the undesirable event section.

In the core RMP endophthalmitis and intraocular inflammation (IOI) are discussed as one safety concern, while in the EU-RMP the concern has been split in endophthalmitis (likely infectious origin) and IOI.

An evaluation of cases suspicious of non-infectious etiology which were received during the reporting period is presented below.

Search strategy

Preferred terms included in search: Anterior chamber cell, anterior chamber fibrin, anterior chamber flare, anterior chamber inflammation, aqueous fibrin, autoimmune uveitis, chorioretinitis, choroiditis, cyclitis, eye inflammation, hypopyon, iridocyclitis, iritis, non-infectious endophthalmitis, non-infective chorioretinitis, pseudoendophthalmitis, uveitis, vitreal cells, vitreous fibrin, and vitritis.

Results

During this reporting period a total of 257 new PSUR/PBRER qualifying cases pertaining to the RISK intraocular inflammation were received. These cases include 304 IOI events, one case may include more than one event (Table 16-10).

Table 16-10: Preferred Terms in intraocular inflammation cases

PT	Medically confirmed	Non-medically Confirmed	Total
Anterior chamber cell	10	0	10
Anterior chamber fibrin	1	0	1
Anterior chamber flare	2	0	2
Anterior chamber inflammation	7	0	7
Eye inflammation	100	10	110
Hypopyon	21	0	21
Iridocyclitis	10	0	10
Iritis	12	0	12
Non-infectious endophthalmitis	43	1	44
Pseudoendophthalmitis	2	0	2
Uveitis	24	3	27
Vitreal cells	12	0	12
Vitritis	46	0	46
Total	**290**	**14**	**304**

Thirty-eight cases out of the 257 IOI cases contain also events which belong to the risk endophthalmitis likely infectious origin. These 38 cases have also been included in the analysis of this topic. Therefore, the number of cases which contain only IOI events is 219.

- 243 (94.6 %) cases were medically confirmed.
- 224 cases (87.2%) out of the 257 case reports were serious.
- Age provided in 173 cases ranged 39 years to 96 years with an average age of 76 years.
- The onset latency from first dose to onset of events was ranging from 1 day to 1669 days with a mean of 453 days, median 150 days (available for 46 events in 38 cases).

- The onset latency from last dose to onset of events was ranging from the same day to 25 days with a mean of 6 days, median 3 days (available for 52 events in 48 cases).
- An outcome was reported for 208 out of 304 events: for 124 events outcome recovered/recovering was reported, for 19 events not recovered, for 65 events outcome was reported as unknown and for 96 this information was missing.

Number of Eylea injections before event onset

The entry of the number of injections is not collected in a standardized manner in the safety database. To assess if the number of previous administrations could have an impact on intraocular inflammation occurrence, the onset latency from first dose has been analyzed. As Eylea is administered once every four weeks for at least 3 months at the beginning of treatment initiation in the indications wet AMD, CRVO, BRVO and DME, one injection is assumed if the event onset was on the same day or up to 31 days. Three injections are assumed if the event onset was within 93 days after treatment initiation.

The event onset latency from first dose was provided in 38 cases (14.8% of the total number of cases) for 46 events. In 15 events in 14 cases (36.8%) the event onset was within 31 days assuming just one injection. Further 6 events in 4 cases (10.6%) occurred within 93 days after treatment initiation assuming a maximum of 3 injections. In the remaining 25 events in 20 cases (52.6%), there was no pattern in the onset latency between 134 and 1,669 days.

In 47.4% of the events with reported onset latency the onset occurred within three months after the first Eylea injection, whereas in 52.6% the event onset was after three months up to 4.6 years of start of Eylea treatment. Therefore, there is no evidence of an increasing risk for inflammatory eye reactions with increasing numbers of Eylea injections.

Handling issues

In 20 out of the 257 case reports the content of the vial was split to use the content for more than one eye.

Relevant literature received during the reporting period:

Barcat et al (143) compared rates of endophthalmitis following intravitreal injection of aflibercept and ranibizumab, vial versus pre-filled syringe in all patients receiving anti-VEGF treatment. Data was collected retrospectively between September 2012 and February 2018. The overall rate of endophthalmitis was 0.040% (9 out of 22,363 eyes). The rates of endophthalmitis following aflibercept and ranibizumab vial injection (0.069% [6 out of 8,639] and 0.039% [3 out of 7,787], respectively) were non-significantly higher than following pre-filled syringe, where no cases were observed in a total of 5937 injections (OR 6.87, P =0.184). Likewise, there was no significant difference between the aflibercept vial and ranibizumab vial injection group (OR 1.80, P = 0.405). The rate of endophthalmitis was higher following aflibercept vials than ranibizumab vials injections (Odds ratio 1.80, P = 0.405). The authors concluded, that although they could not demonstrate a significant increased risk of endophthalmitis after vial compared to pre-filled syringe injection, the absence of endophthalmitis in the pre-filled syringe group should be noted.

In a retrospective review of 78 patients (108 eyes) who underwent intravitreal injection of aflibercept from January 2017 to January 2019 Ben Yahia et al (144) reported data on visual loss following intravitreal injection of aflibercept. The indications for intravitreal injections included diabetic macular edema (72 eyes), choroidal neovascularization secondary to age related macular degeneration (21 eyes), and other conditions (15 eyes). Sudden decrease in visual acuity within the first three days from injection occurred in 11 eyes (10.2%). It was due to non-infectious vitritis in 8 eyes and to infectious endophthalmitis in one eye. In two eyes, the cause of visual loss was unclear. Vitritis was successfully managed with topical steroids in all cases. Visual acuity improved in 9 of 11 eyes. In 2 eyes visual loss was permanent. The authors concluded that transient or permanent visual loss following intravitreal injection of aflibercept, was mainly due to non-infectious vitritis and seemed to be more frequent than previously reported.

The following article by Greenberg et al describes part of the signal of intraocular inflammation in the US related to 2 syringe batches distributed in the USA. This signal was now closed during this reporting period as the quality investigations were completed without the detection of a root cause for the IOIs (**Appendix 9**). Greenberg et al (145) described the increase in sterile intraocular inflammation after Eylea injection that were reported to the American Society of Retina Specialists in 68 eyes (66 patients) reported from May 2017 through February 2018. Exclusion criteria were intravitreal antibiotic injection and follow-up of less than 7 days. Mean time to presentation was 2.6 days (median, 2.0 days; range, 0-15 days). Mean visual acuities before and after injection were 20/50 and 20/178, respectively. All patients showed intraocular inflammation: 24% with only vitritis, 16% with only anterior chamber reaction, and 60% with both. Two patients were affected bilaterally. Treatment included topical steroids (93%), with 1% supplemented by oral steroids. Inflammation resolved in 79% at study completion (mean, 34 days; range, 7-105 days; 51% resolved by 1 month). This group's mean final visual acuity was 20/55, and 15% lost 2 lines or more. Overall, 26 aflibercept lots were involved. Most patients presented early with decreased visual acuity and intraocular inflammation, but without injection, hypopyon, fibrin, or severe pain. Final visual acuity remained decreased in a significant minority of patients. The authors stated that the cause for these reported events, both clustered and sporadic, remains poorly understood. Hypothesized mechanisms included patient-specific, medication-specific, and delivery-specific factors.

In a case-control study, Melo et al (146) determined factors causing inflammation after intravitreal aflibercept injections. Inflammation developed in six eyes; three patients had anterior uveitis, and five had vitreous cells. Oil droplets were seen in all cases. Saldanha Rodrigues syringes were used in all cases. Among controls, Saldanha Rodrigues and Becton-Dickinson syringes were used in 10 and 17 eyes, respectively. Regression analysis showed an association between Saldanha Rodrigues syringes and inflammation (odds ratio = 21.66; 95% confidence interval, 1.10-425.06; P = 0.043). Biophysical analyses primarily showed aggregation possibly from free oil droplets or protein-oil droplet aggregation. The authors concluded that post-injection inflammation was associated with Saldanha Rodrigues syringes.

Silicone oil droplets, especially after syringe agitation, might play a role in the inflammatory reaction.

Baudin et al (147) determined the association of acute endophthalmitis with intravitreal injections of corticosteroids (triamcinolone acetonide and dexamethasone implant) or anti-VEGF (ranibizumab, bevacizumab, and aflibercept) agents in a nationwide study in 444 acute endophthalmitis cases. Associations were found for patients receiving corticosteroid intravitreal injections and those with non-prefilled anti-VEGF syringes. The risk of endophthalmitis was lower in male patients, higher for corticosteroids versus for anti-VEGF agents, and higher for non-prefilled syringes of anti-VEGF medications versus pre-filled syringes for ranibizumab and aflibercept.

In a retrospective cohort study using medical claims data from a large, national US insurer from 2005 to 2016 Bavinger et al (148) determined whether sterile pre-loading of anti-vascular endothelial growth factor agents reduces the risk of post-intravitreal injection endophthalmitis. A total of 706,725 bevacizumab, 210,849 ranibizumab, and 177,731 aflibercept injections were given to 130 327 patients. Here, the authors found that the odds of endophthalmitis with aflibercept and ranibizumab combined were higher compared with the sterilely pre-loaded bevacizumab (odds ratio: 1.29, 95%-confidence interval: 1.04-1.59, P=0.02), arguing for a safety advantage of sterile pre-loading of anti-vascular endothelial growth factor injections.

Company comment on literature pertaining to IOIs:

Publications show varying results when comparing IOI rates following the administration with a prefilled syringe (PFS) versus the vial presentation.

IOIs following the use of a local Saldanha Rodrigues syringes and now published by Gustavo Melo (149) led to a cumulative signal investigation in 2016 (presented in PSUR#6, reporting period: 01 DEC 2015 –30 NOV 2016) evaluating the link between silicone and the development of IOIs. The signal was refuted and no direct causality of IOI development due to silicone could be confirmed.

Relevant actions taken during the reporting interval for endophthalmitis/intraocular inflammations:

Please see previous section on endophthalmitis for related actions (closure of IOI signal in US upon completion of quality investigations, local occurrences of IOIs with regulatory actions in Australia and Israel).

Conclusion

Acute inflammatory eye reactions can occur after IVT injections of any anti VEGF agents including aflibercept.

It is assumed that in most cases these events are caused due to irritations by the injection procedure or improper injection technique.

The analysis of the event onset from first dose does not provide evidence that the risk for development of inflammatory eye reactions is dependent on the number of Eylea injections.

No new product related safety concern/quality deficit was detected that was considered causally linked to the development of IOI cases.

Reviewed literature did not raise a new safety concern.

The newly received safety information is in line with the known risk characterization for the identified risk inflammatory eye reactions and the use of Eylea

16.3.12 Transient Intraocular Pressure Increase

Background

Transient IOP increase is included as an important identified risk in the current EU RMP version 26.1 Intraocular pressure >21 mmHg is defined as ocular hypertension. A transient increase of IOP (IOP spike) is often observed after IVT injection of fluids. Transient IOP increase is usually a mild reaction which is compensated within 0.5 – 1 hour after injection so that IOP normalizes back to baseline values. Patients usually recover without sequelae.

In the phase III AMD studies, procedure-related IOP increases were usually mild and transient.

To date, there is no confirmed link between sustained IOP increase and the use of IVT anti-VEGFs.

Low rates of estimated yearly incidences of sustained IOP increase / ocular hypertension were identified in the clinical trials with aflibercept, which are consistent with the rates found in the fellow-eye and were even lower than expected from the rates reported in the literature for this elderly population.

MedDRA search

For this evaluation, all PBRER/PSUR-qualifying cases for this reporting period (01 DEC 2018 – 30 NOV 2019) were searched for the PTs “Intraocular pressure increase” and “Ocular hypertension”.

Case Details

A total of 39 new PSUR qualifying case reports (including 40 events) meeting the search criteria were received during the reporting period:

- Twenty-three events were medically confirmed of which 11 were serious and 12 non-serious. Seventeen events were not medically confirmed of which 12 were serious and 5 non-serious.
- Age ranged from 45 to 90 years with a median age of 72.5 years (not reported in 9 cases). Seventeen patients were female, and 17 patients were male, in 5 cases this information was not available.

- Outcome was known for 17 events of which 11 were recovered, 2 recovering, and 4 not recovered. Fourteen events were considered "related" (as assessed by the reporter), 2 events were unrelated, and for 24 events no relationship assessment was provided.
- All of the 4 unresolved events were serious.
- The onset latency from *first* dose of aflibercept to the onset of the event was reported for 9 out of 40 events and ranged from 1 day to 2022 days (median, 36 days, not available for 31 events).
- The onset latency from *last* dose of aflibercept to the onset of the event was reported for 4 out of 40 events and ranged from 1 day to 2 days (median, 1 day, not available for 36 events). In these 4 events, IOP increase occurred within 24 hours after the injection. For 1 out of these 4 events, the outcome was reported as recovered/resolved, for another one as not recovered and as unknown for the remaining 2 events.
- The number of aflibercept injections prior to the event was reported in 8 cases and ranged from 1 to 24 injections (median, 2 injections, not available in 31 cases).
- In 14 cases at least one confounding/risk factors for an IOP increase were identified (either within medical history/concomitant diseases, or concurrent intraocular inflammation, glaucoma or concomitant IOP-lowering drugs without glaucoma diagnosis). In 23 cases no confounding/risk factor for an IOP increase was identified:
    - <u>Confounding/risk factor within medical history/concomitant diseases (7 cases):</u>

      In 7 out of the 39 case reports, where information on medical history/concomitant disease was reported (17.9%), relevant confounding factors which could have been an alternative explanation for an increase in IOP were identified. These risk factors included cataract operation, glaucoma, macular rupture, and eye haemorrhage.
    - <u>Confounding/risk factor intraocular inflammation (4 cases):</u>
      Four out of 39 case reports of IOP increase were associated with intraocular inflammation (10.3%) including non-infectious endophthalmitis and endophthalmitis.
    - <u>Confounding/risk factor concomitant IOP-lowering drugs without glaucoma diagnosis (N=3 cases):</u>
      Furthermore, case narratives and concomitant medications were searched for the generic names of the most common drugs used to lower IOP (i.e., acetazolamide, apraclonidine, bimatoprost, brimonidine, brinzolamide, carbachol, clonidine, dorzolamide, latanoprost, levobunolol, pilocarpin, timolol). In 8 out of 39 cases patients were concomitantly treated with these medications.

      In 5 of these 8 cases glaucoma was explicitly reported as a historical condition/concomitant disease.

In the remaining 3 cases IOP-lowering drugs were documented as concomitant medication, but glaucoma was not explicitly mentioned as concomitant disease/historical condition, (see Table 16-11): Overall, the application of IOP-lowering concomitant medication in all of these cases suggests a pre-existing unreported increased IOP.

Table 16-11: Cases with increased IOP and the use of IOP-lowering medications where no history of glaucoma was reported

Case ID Country Source Age Gender Medical confirmation	Event as reported term / PT (seriousness)	Onset latency from last injection to IOP increase event	Outcome of IOP increase	Number of Eylea injections prior to event	Medical History / concomitant disease	Relevant concomitant medication	Description
[redacted] Australia observational study 77 years female non-MC	1) Intra-ocular pressure generally low but after a holiday pressure went up / Intraocular pressure increased (s); 2) Right cataract removed two years ago / Cataract operation (s);	unknown	unknown	20	Watery burning eyes, watery burning eyes, bilateral cataracts (diagnosed 3 years ago), Diabetes (16 years)	timolol maleate, travoprost (indication: glaucoma)	The patient started intravitreal aflibercept in September 2017 for the indication DME, the patient had 20 injections prior to the onset of IOP increase. On an unknown date, the patient was found to have an increased intraocular pressure and underwent cataract surgery. Eylea treatment was not changed. The reporter did not provide a causality assessment.
[redacted] United States spontaneous 90 years male MC	1) VA OS went from 20/50 to 20/200 / Blindness unilateral (s); 2) elevated pressure to 35 mmHg, left eye / Ocular hypertension (s); 3) patient refused the dose / Intentional dose omission (n);	unknown	recovered	unknown	not reported	timolol (no indication reported)	The patient started intravitreal aflibercept on 09 FEB 2012 for the indication AMD. Previous ocular therapy included an unknown number of doses of Lucentis. On 12 APR 2019 the patient had an increased IOP (35 mmHg) in the left eye which was treated with Lumigan (bimatoprost) eye drops (start date not reported). The patient refused his Eylea injection on 16 APR 2019 due

Table 16-11: Cases with increased IOP and the use of IOP-lowering medications where no history of glaucoma was reported

Case ID Country Source Age Gender Medical confirmation	Event as reported term / PT (seriousness)	Onset latency from last injection to IOP increase event	Outcome of IOP increase	Number of Eylea injections prior to event	Medical History / concomitant disease	Relevant concomitant medication	Description
							to the increased IOP. Outcome was reported as recovered on 30 APR 2019, on the same day the patient received an Eylea injection. The patient was referred to glaucoma specialist. The reporter assessed the event “ocular hypertension” as related to aflibercept.
[redacted] United States observational study 71 years female non-MC	1) pressure in eye went really high / Intraocular pressure increased (s);	unknown	not recovered	unknown	Type 2 diabetes mellitus, macular degeneration	dorzolamide hydrochloride/ timolol maleate (each with no indication reported)	Patient initiated intravitreal Eylea therapy on an unknown date for the treatment of Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema. The patient´s concomitant medication included: amiodarone hydrochloride, warfarin sodium, Xarelto (rivaroxaban), atorvastatin, dorzolamid/timolol, Humulin, Hydrochloroth, lisinopril, metformin and nifedipine (start dates were not reported).

Table 16-11: Cases with increased IOP and the use of IOP-lowering medications where no history of glaucoma was reported

Case ID Country Source Age Gender Medical confirmation	Event as reported term / PT (seriousness)	Onset latency from last injection to IOP increase event	Outcome of IOP increase	Number of Eylea injections prior to event	Medical History / concomitant disease	Relevant concomitant medication	Description
							On an unknown date the patient's IOP “went really high with the last injection and the patient had to stay in the office until they were able to get it down”. Intensity was reported as mild. Action taken with Eylea was unknown. The reporter assessed the event “IOP increased” as related to aflibercept.

AMD: Age-related macular degeneration; DME: Diabetic macular edema; IOP: Intraocular pressure; MC: Medically confirmed; n: Non-serious; s: Serious;

- Incorrect volume administration: In two cases it was reported that too much volume of the Eylea solution was injected leading to an IOP increase:

  C**ase no.** [redacted] was a spontaneous, medically confirmed report from Great Britain regarding a female patient approximately 70 years old. An Eylea injection was documented in February 2018. On an unknown date the patient started suffering from an increased IOP which was treated with a paracentesis. Outcome was reported as recovered and a causality assessment for this event with Eylea was not reported. The reported stated that while injecting Eylea she inadvertently injected more than the usual volume of Eylea into the eye. As a result, the patient had a pressure spike. The situation resolved after paracentesis and the patient´s vision returned to normal.

  C**ase no.** [redacted] was a spontaneous, medically confirmed report from Sweden regarding a male 50-year-old patient. On an unknown date Eylea was administered, also on an unknown date (as a reaction once after the injection), the patient started suffering from an increased IOP (over 60 mmHg), transient blindness, retinal artery occlusion and visual impairment. The patient was treated with pressure-lowering drops and after an hour the IOP was normal again. In the follow-up, the information "administer too large dose, up to 0.3 ml too much/too large volume injected into the eye" was additionally documented and recoded to the PT events "overdose", "wrong technique in product usage process", and "product packaging quantity issue".

- No confounding/risk factors (23 cases):

  In 23 cases no risk or preceding factors for the development of IOP increase were reported. In 2 of 23 cases an onset from the last dose of aflibercept was reported. Both had a temporal association (onset from last dose = 1 day) to the intraocular injection and thus were deemed to be related to aflibercept:

  - **Case no.** [redacted]: The patient´s medical history included otitis media serous, degenerative disc disease, hypertension and AMD. Lucentis was mentioned as historical drug. After the fifth Eylea injection the patient suffered from increased IOP ("slight eye hypertension") with blurred vision.
  - **Case no.** [redacted]: On the day of Eylea administration the patient suffered from increased IOP and was treated with surgery (left eye). Outcome was reported as recovered on the same day.

  For 21 out of 23 cases an onset from the last dose of aflibercept to the onset of IOP increase was not reported, thus one can neither exclude nor assume a causal relationship to aflibercept.

Fifteen out of 23 cases were poorly documented and did not allow an assessment regarding confounding/risk factors or alternative reasons for an IOP increase.

Literature:

Barash et al (150) designed a retrospective study to measure retinal perfusion density changes on optical coherence tomography (OCT) angiography and OCT thickness alterations associated with acutely increased IOP after intravitreal injections. Forty eyes (39 patients) with various retinopathies were recruited from October 2016 to June 2017 at a tertiary care retina clinic. Patients were older than 18 years, with vision >20/100, able to fixate and without media opacities precluding OCT angiography, receiving intravitreal bevacizumab or aflibercept for diabetic retinopathy, retinal vein occlusion, macular degeneration, retinal neovascularization, or radiation retinopathy. The authors found that intravitreal injections produce acute IOP changes that are associated with reduced macular and peripapillary perfusion density. The authors hypothesize that patients receiving regular intravitreal injections may be sustaining perfusion-related injury to ocular structures that may produce glaucomatous damage to the macula and optic nerve.

Gomez-Mariscal et al (151) evaluated acute and chronic changes in optic nerve head structures and IOP in patients receiving intravitreal injections of anti-VEGF. Twenty-nine eyes receiving intravitreal injections for the first time were studied. IOP, retinal nerve fiber layer thickness, and optic nerve head structures were evaluated by Spectralis optical coherence tomography with enhanced depth imaging technology. Structures were measured before and 5 min after each one of the three-monthly injections of a loading dose treatment. The authors concluded that repeated intravitreal injections could lead to irreversible changes in optic nerve head structures.

Ong et al (152) designed this study to assess the cumulative effect of chronic anti-VEGF therapy on retinal ganglion cell layer thickness. Post-hoc analysis was performed on data collected from a single-center prospective treatment-naive cohort. Patients who received continuous intravitreal aflibercept in one eye for nAMD over a minimum of 24 months were included. 103 patients (55 female, mean age 81.8 years) with an average of 32 ± 13 aflibercept injections over 45.3 ± 10.5 months were included. Retinal ganglion cell layer thickness decreased significantly in the study eye compared to the untreated fellow eye ($P < 0.05$), with a preference for the temporal sector (mean difference 5.68 µm, $P = 0.036$). Significant correlation was found between change in retinal ganglion cell layer thickness and number of injections ($r = 0.35$, $P < 0.025$). The authors concluded that progressive retinal ganglion cell layer thinning may be a sentinel marker for the onset of incipient glaucoma and should prompt the commencement of glaucoma surveillance in these patients.

From January 2013 to December 2016 Moon et al (153) retrospectively reviewed patients who were administered intravitreal ranibizumab or aflibercept injections for AMD. Their IOP was measured before injection, 1 week, 1 month, 2/3/4/5/6/9/

months and 1 year after injection. Sustained IOP elevation was defined when the final IOP increased 6 mmHg higher than the pre-injection IOP, and when there were two consecutively measured values >21 mmHg. It was found that sustained IOP elevation occurred in 9 out of 80 eyes (11.3%) in 1 year, and the mean survival time was 11.50 months after injection. Five eyes (12.8%) in the ranibizumab group and 4 eyes (9.8%) in the aflibercept group showed mean survival times of 11.39 and 11.61 months, respectively. There was no significant difference between the two groups. A significant risk factor in sustained IOP elevation was a history of primary open-angle glaucoma.

Summary and conclusion

Transient IOP increase is an acknowledged risk with aflibercept volume injection. From cases received during this reporting period or from literature, no clear causality could be established between Eylea therapy and *sustained* IOP increase

In only 1 serious and related case, the outcome was reported as not recovered. In this case, the patient probably suffered from glaucoma, since IOP-lowering "glaucoma" medication was reported as concomitant drug.

The number of aflibercept injections prior to the event was reported only in 8 cases. These data do not support the suspicion that patients with repeated injections are more prone to experience IOP increase.

No relationship between intravitreal aflibercept and the development of sustained IOP increase can be established upon data review.

It is of note that 2 studies were completed with Eylea treatment in patients with neovascular glaucoma (VEGA and VENERA study). The VENERA study was completed during this reporting period (see section 7 for completed clinical trials). Aflibercept reduced the IOP pressure effectively. No safety concern was identified in patients with uncontrolled treated with Eylea.

Transient intraocular pressure increase is a listed ADR in the CCDS of aflibercept and considered an important identified risk in the EU RMP. The cases on IOP increase received during the current reporting period do not suggest a change in the characteristics of the risk.

16.3.13 Retinal Pigment Epithelial Tears

Background

Retinal pigment epithelium (RPE) tear is included as an important identified risk in the EU RMP and is listed in the reference safety information as an undesirable effect. Patients with wet AMD (and particularly with concomitant RPE detachment) are considered to have a high risk for the development of RPE tears.

Search strategy

The pharmacovigilance database was searched for PBRER/PSUR-qualifying cases newly received during the PBRER/PSUR reporting interval for retinal pigment epithelial tear (MedDRA PT) as an adverse event.

Results

The search revealed a total of 8 new PBRER qualifying cases, of which 6 were spontaneously reported, 1 stemmed from an interventional clinical trial, and 1 from an observational study. All cases were serious and 6 were medically confirmed.

As far as reported (N=3), patient age ranged from 68 to 81 years (median, 71 years). One patient was male and 4 females; gender was not reported in the remaining 3 cases.

The indication(s) for administration of Eylea were reported in 6 cases and included neovascular AMD/ not further specified AMD. RPE detachment was the reported additional indication for Eylea in 1 case.

Onset latency from first and last dose was reported in one case and was 11 days (no information regarding onset latency provided in the remaining 7 cases).

Medical history was reported in 2 cases and included intraretinal cyst in one case and age-related macular degeneration in the other case.

In none of the cases an outcome was provided.

Relevant literature received during the reporting period:

Plyukhova et al (154) conducted a retrospective, 12-month study to assess the risk of RPE tear after anti-VEGF therapy and to identify possible prerequisites for the development of this complication. A total of 15 wet AMD patients (15 eyes) were included in the study with wet AMD and tears of the retinal pigment epithelium. Seven patients (7 eyes) received ranibizumab and 8 patients (8 eyes) received aflibercept from the end of 2016 and underwent a standard ophthalmologic examination and OCT/OCT-angiography/indocyanine-green angiography. There was a significant decrease in retinal thickness in the macular area and retinal pigment epithelium tear ($p = 0.007$), due to resorption of intraretinal fluid. The average number of injections, after which the RPE tear was registered, was 3.5 ± 1.35. The authors concluded that when treating patients with an exudative form of AMD and retinal detachment of the pigment epithelium, caution should be exercised due to the increased risk of rupture of RPE. Based on the data obtained in their study, they stated that the RPE detachment was associated with an increased risk of rupture of RPE. Furthermore, the authors were of the opinion that despite the RPE tear, the fact remains that the treatment should be continued.

Summary and Conclusion

The safety information newly received on this topic during the reporting interval is in line with the known risk characterization for the risk RPE tears and the use of Eylea. There is no change in the safety profile of this identified risk.

16.3.14 Retinal Tear / Detachment

Background

Development of retinal detachment after anti-VEGF intravitreal injection is discussed to be attributed to traction caused by the injection or due to the wrong injection site, accumulating fluid due to the underlying disease (inflammation or neovascularization) or by traction of fibrous or fibrovascular tissue, which occurs due to the underlying disease (inflammation or neovascularization) or the injection.

Retinal tear/detachment is included as an important identified risk in the core RMP and EU RMP, and both events are listed in the reference safety information as undesirable effects.

Search Strategy

The pharmacovigilance database was searched for PBRER/PSUR-qualifying cases newly received during the reporting interval with any of the following adverse events (MedDRA PTs): Retinal tear, Rhegmatogenous retinal detachment, Serous retinal detachment, Tractional retinal detachment, Retinal detachment or Macular detachment.

Results

The search revealed a total of 52 new PBRER/PSUR-qualifying cases (including 56 events), of which 19 were spontaneously reported, 13 were published reports from interventional studies, 12 came from observational studies, 5 from interventional studies, 2 from literature, and one case was a published report from an observational study. All cases were serious and 37 were medically confirmed. The pertinent adverse events were retinal detachment (N = 25), rhegmatogenous retinal detachment (N=16), serous retinal detachment (N=6), retinal tear (N=5), tractional retinal detachment (N=3), and macular detachment (N=1).

As far as reported (N=34), patient age ranged from 25 to 90 years (median, 66 years). Twenty patients were female and 18 were male; gender was not reported in the remaining 14 cases.

The exact temporal association between administration of Eylea and occurrence of retinal tear/detachment was reported in 11 cases (onset from first dose) and 9 cases (onset from last dose prior to the event). In these cases, the latency from the first dose of Eylea to onset of the retinal tear/detachment ranged from 34 days to more than 3.5 years (median, 5.9 months) and the latency from the last dose of Eylea to onset of the retinal tear/detachment ranged from 2 days to more than 3 years (median, 22.7 days).

One or more risk factors or alternative explanations for retinal tear/detachment (besides the underlying ocular disease) were identifiable in 27 out of the 52 cases. Seven cases included concurrent inflammatory processes, such as endophthalmitis, eye infection, iridocyclitis, anterior chamber inflammation, and anterior chamber uveitis. In 21 cases medical history/concomitant conditions included one or more risk factors such as cataract surgery, cancer surgery behind the eye, choroidal mass inflamed, detached retina repair, laser therapy, serous retinal detachment, (posterior) vitreous detachment, vitreous haemorrhage, von Hippel-Lindau disease, and retinal neoplasm.

Outcome of the retinal tear/detachment was reported as resolved or resolving for 13 events and as not resolved for 6 events (out of 56 events). Event outcome was missing/unknown in the remaining 37 events.

Summary and Conclusion

The safety information newly received on this topic during the reporting interval is in line with the known risk characterization for the risk retinal tear/detachment and the use of Eylea. There is no change in the safety profile of this identified risk.

16.3.15 Cataract (Especially of Traumatic Origin)

Cataract is listed in the undesirable event section of both the CCDS and the EU SmPC. In the Core RMP and the EU-RMP, traumatic cataract after IVT injections is discussed as an important identified risk. Traumatic cataract has been reported in patients receiving IVT injections, but limited information is available on cataract development or progression after IVT injection of VEGF inhibitors. Other risk factors for the development of cataract include increasing age, diabetes mellitus, alcohol abuse, family history of cataract, high blood pressure, obesity, previous eye injury or inflammation, prolonged use of corticosteroid medications and smoking. In the Eylea CCDS traumatic cataract is listed as a rare event, all the other forms of cataract are listed as common.

Search Strategy

The following MedDRA search strategy was applied to identify pertinent cases, MedDRA PTs:

“Atopic cataract”, “Cataract”, “Cataract cortical”, “Cataract diabetic”, “Cataract nuclear”, “Cataract operation”, “Cataract subcapsular”, “Cataract traumatic”, “Intraocular lens implant”, “Lens capsulotomy”, “Lens discoloration”, “Lens extraction”, “Lenticular injury”, “Lenticular opacities”, “Lenticular operation”, “Posterior lens capsulotomy”, “Radiation cataract”, “Toxic cataract”.

Results

A total of 215 new PBRER/PSUR-qualifying cases were received during the reporting period which included N=236 cataract or cataract-related events (1 case may include more than 1 event).

PT “Cataract”, N=129 (129 reported as serious events)

PT “Cataract operation”, N=93 (93 reported as serious events)

PT “Intraocular lens implant”, N=10 (7 serious)

PT “Cataract traumatic”, N=1 (1 serious)

PT “Lens extraction” N=1 (1 serious)

PT “Cataract nuclear”, N=1 (1 serious)

PT “Lenticular operation”, N=1 (1 serious)

A total number of 236 events were reported. Among these, 233 events were serious, out of which 43 were medically confirmed.

Sources: Out of 215 cases, 182 were from solicited sources, 1 case from a published report of an observational study, 27 cases from spontaneous sources, 1 case from the literature and 4 cases were reported from interventional studies.

Cataract was the most frequently reported MedDRA PT (129), followed by the MedDRA PT Cataract operation (93).

The gender distribution was 57.6% female patients (n=124), 39.5% male patients (n=85) and in 2,79% of cases the gender was not reported (n=6 cases).

Among the 215 cases, the following risk factors were reported as medical history/concomitant disease:

hypertension (19 cases)

Cataract/Cataract nuclear/Cataract operation (49 cases)

obesity (1 cases)

diabetes (47 cases)

elderly [65yo or above] (161 cases).

Patients’ age was provided in 201 cases and ranged from 49-91 years (median: 72 years, average: 71.79 years), as follows:

No patients in 31-40 years of age group

2 patients in 41-50 years of age group

25 patients in 51-60 years of age group

59 patients in 61-70 years of age group

72 patients in 71-80 years of age group

42 patients in 81-90 years of age group

1 patient over 90 years of age

The age was not specifically reported in 14 cases, but the patients were described as elderly in 1 case (65 y or above) and as adult (>=18y & <65y) were reported in one case. In the remaining 12 cases the patient age was not reported, and no age-group was provided either:

Only 1 case was reported in the context of traumatic cataract.

[redacted]: Spontaneous case was reported by a physician and describes the occurrence of cataract traumatic ('Post-traumatic cataract, left eye') in an 80-year-old patient, received Aflibercept solution. On 07 NOV 2019, the patient received Eylea 40 mg/ml. On an unknown date, the patient experienced a traumatic cataract. The reporter didn't provide the causality assessment for cataract traumatic with Aflibercept. The event's latency, outcome, action taken with the drug, patient's medical history and concomitant medications were not reported.

In 2 cases, the patient's age was 50 years of age or below.

[redacted]**:** A 49 years-old, female, African-American patient, with non-proliferative diabetic retinopathy experienced dense white cataract on 28 DEC 2018. The patient received first dose of Aflibercept (IAI) in right eye (OD) on 23 FEB 2017. The most recent dose of Aflibercept (IAI) prior to onset of event was administered on 01 NOV 2018, and the patient received a total of fourteen (14) doses prior to the onset of the event. Action taken with study drug was reported as drug withdrawn. Patient's relevant medical history included cataract nuclear, diabetic retinopathy, type 2 diabetes mellitus, hypertension, intraocular pressure increased. Cataract operation was done on 16 APR 2019. Event was not considered related to treatment by the reporter as it might have been caused by the injection procedure (traumatic) or due to underlying concurrent illness of posterior subcapsular cataract.

[redacted]**:** A 49 years-old patient who received aflibercept for diabetic macular edema developed cataract on unknown date. Start date of the drug was September 2018, the patient received only one Aflibercept 40 mg/ml injection. Patient's medical history and concomitant medications were unknown. Reporter (Physician) reported that the event was not related to the aflibercept and the outcome was unknown.

Both cases in patients below the age of 50 presented with risk factors (ie diabetes, history of cataract, hypertension). No signal can be derived from these cases.

Conclusion

The analysis of cases below the age of 50 years did not reveal a new safety signal

16.3.16 Hypersensitivity and Immunogenicity

Background

As a recombinant fusion protein, aflibercept is a potential antigen. Thus, within the range of drug hypersensitivity and allergic reactions, there is the potential for an immune reaction towards aflibercept. Hypersensitivity and immunogenicity are included as an important identified risk in the Eylea EU RMP, and hypersensitivity is labeled as adverse events in the Eylea CCDS.

The following section provides an overview of relevant new safety information on this topic received during this PSUR/PBRER reporting period.

Search Strategy

The following MedDRA search strategy was applied to the newly received cases during the reporting period:

- SMQ, "Severe cutaneous adverse reactions" (narrow search), "Anaphylactic reaction"(narrow search), and "Angioedema" (narrow search)
- Bayer MedDRA Labeling Group LG, "Allergic reaction" with PTs
  "Device allergy"
  "Documented hypersensitivity to administered drug"
  "Drug hypersensitivity"
  "Hypersensitivity"
  "Reaction to drug excipients"

Results

A total of 64 initial PBRER / PSUR qualifying cases pertaining to the important potential risk hypersensitivity / immunogenicity were received.

Fifty cases were spontaneously reported. One case was reported from interventional study (investigator-initiated research), and the remaining 13 cases from either PSPs (six cases) or reimbursement programs (seven cases).

Out of the 64 cases, 32 cases were medically confirmed, and 45 cases were serious (20 cases were serious and medically confirmed).

Patient / Event Details

As far as reported (N= 48), patient age ranged from 31 to 96 years (median age: 72 years). Thirty-three patients were 65 years or older, 15 patients were adults below 65 years of age.

Gender was female in 41 cases, male in 16 cases, and not reported in seven cases.

The 64 cases reported on 71 pertinent adverse events, with most frequently reported events stemming from the MedDRA SOC Eye disorders (37 events), followed by events from MedDRA SOC Immune system disorders (20 events), SOCs Skin and subcutaneous tissue disorders (7 events), General disorders and administration site conditions (6 events) and Vascular disorders (1 event). Table 16-12 below provides an overview of all pertinent events sorted by MedDRA SOC.

Table 16-12: Number of pertinent hypersensitivity events per MedDRA PT and MedDRA SOC

Event (MedDRA SOC)	Event (MedDRA PT)	No. of Events
Eye disorders	Conjunctival oedema	1
Eye disorders	Corneal oedema	8
Eye disorders	Eye oedema	6

Table 16-12: Number of pertinent hypersensitivity events per MedDRA PT and MedDRA SOC

Event (MedDRA SOC)	Event (MedDRA PT)	No. of Events
Eye disorders	Eye swelling	13
Eye disorders	Eyelid oedema	1
Eye disorders	Periorbital swelling	4
Eye disorders	Swelling of eyelid	4
Eye disorders	**Subtotal**	**37**
General disorders and administration site conditions	Face oedema	1
General disorders and administration site conditions	Swelling face	5
General disorders and administration site conditions	**Subtotal**	**6**
Immune system disorders	Anaphylactic reaction	2
Immune system disorders	Drug hypersensitivity	9
Immune system disorders	Hypersensitivity	9
Immune system disorders	**Subtotal**	**20**
Skin and subcutaneous tissue disorders	Angioedema	1
Skin and subcutaneous tissue disorders	Drug eruption	2
Skin and subcutaneous tissue disorders	Urticaria	4
Skin and subcutaneous tissue disorders	**Subtotal**	**7**
Vascular disorders	Circulatory collapse	1
Vascular disorders	**Subtotal**	**1**
	Grand total	**71**

The onset latency from first dose ranged from 1 day to 731 days with a mean of 191 days (median: 60 days). For 56 cases, onset latency from first dose was not available.

The onset latency from last dose ranged from 1 day to 5 days with a mean of 2.5 days (median: 2 days). For 57 cases, onset latency from last dose was not available.

Where outcome was known most patients recovered (N=14) or were recovering (N=4). None of the cases reported a fatal outcome.

For most of the cases, it is plausible to assume a potential causal association between reported symptoms and the use of Eylea based on e.g. positive temporal relationship, repeated drug exposure. For some patients, information on risk factors for hypersensitivity reactions was reported, such as a history of

angioedema (1 patient), allergy to shellfish and sulfonamide (1 patient), allergic reactions to analgesics and antibiotic (1 patient) and history of corneal abrasion (1 patient).

Events considered local reactions included e.g. conjunctival edema, corneal edema, eye edema, eyelid swelling, eye swelling, ocular hyperemia, eye pruritus, periorbital swelling. Of note, local irritations e.g. may also occur in the context of the injection procedure and peri-procedural maneuvers (e.g. use of eyelid specula and further topically administered drugs such as eye drops, povidone iodine).

Events considered systemic reactions included e.g., skin exfoliation and accompanying symptoms compatible with anaphylactic reactions ~~(in two patients, as detailed below),~~ symptoms compatible with a non-allergic circulatory collapse reported by a consumer (as detailed below), angioedema, as well as hypersensitivity, drug hypersensitivity, drug eruption, urticaria, pruritus, rash, erythema, swelling face, facial pain.

There were no reports of erythema multiforme or Steven-Johnson syndrome (SJS).

Potentially systemic events with reported anaphylaxis, skin exfoliation, angioedema in the context of a possible systemic hypersensitivity reaction were reported for 4 patients, as detailed below.

- A 64-year-old male patient who received Eylea for AMD experienced rash with pruritus 2 days after starting Eylea. One month later, the patient experienced drug eruption with pruritus and erythema within 2 days of receiving second dose of Eylea. The patient was treated with Adrenal Cortex Preparations, Hydrocortisone, Hydroxyzine Embonate, Loratadine and Prednisolone. Eylea was withdrawn. Two weeks later, the drug eruption and rash had resolved (positive temporal relationship, all symptoms resolved, [redacted]).
- A 79-year-old male patient-initiated treatment with Eylea for macular oedema and received clindamycin on the same day. The patient experienced drug eruption with erythema, pruritus and was hospitalized. The patient was treated with Calamine, Chlorphenamine Maleate, Ebastine, Methylprednisolone and loratadine and drug eruption was resolving (positive temporal relationship, co-suspect medication, [redacted]).
- A 36-year-old male patient was enrolled in Investigator sponsored study (ISS) for Vitreous Hemorrhage from Proliferative Diabetic Retinopathy ([redacted]). Approx. 1 year 3 months later, patient experienced anaphylactic reaction with patient receiving concomitant Rocephin. Patient was administered Benadryl, study drug was continued and event was resolved on the same day. No other clinical details were provided. Investigator considered the event to be unrelated to Eylea and related to Rocephin. In view of the long latency, resolution of the anaphylactic

reaction within same day while Eylea is being continued, lack of clinical details provided, the diagnosis of anaphylactic reaction is questionable.

- A report of angioedema ([redacted]) was reported in an 81-year old female patient who received Eylea for macular degeneration. It was unknown whether any action was taken with Eylea and outcome of angioedema outcome was unknown. In view of extremely limited information available, adequate medical assessment isn't possible.

One case with systemic symptoms was reported but is not considered to have occurred in the context of hypersensitivity A non-medically confirmed case ([redacted]) of non-allergic circulatory collapse, foot fracture, blindness transient, injection site pain, hypertension was reported in 74-year old female patient enrolled in a patient support program who received Eylea for wAMD for approx. 6 years. Patient's blood pressure was very high and blood pressure medication was initiated which was followed by a collapsed and fractured right foot and hospitalization for 2 months. The reported event of circulatory collapse could be explained by the initiation of antihypertensive drug therapy

No new relevant literature related to this topic of hypersensitivity/immunogenicity received during this reporting period was identified.

Summary and conclusion

Overall, the safety information newly received on this topic during the reporting interval is in line with the known risk characterization for this risk hypersensitivity / immunogenicity and the intravitreal use of Eylea. Hypersensitivity reactions including rash, pruritus and urticarial and severe anaphylactic reactions are ADRs known to be possibly associated with the use of Eylea and, as such, listed events as per Eylea CCDS. Hypersensitivity / immunogenicity is an important identified risk in the EU-RMP. There is no change in the safety profile of this important identified risk for Eylea.

16.3.17 New Information on Potential Risks (not categorized as important)

N/A

16.3.18 New Information on Identified Risks (not categorized as important)

N/A

16.3.19 Update on Missing Information

On the following topics (categorized as missing information in the RMP) new safety relevant information was received during the period of this PBRER/PSUR:

16.3.20 Use of Eylea in Patients with Uncontrolled Glaucoma

Background

Safety data in patients with uncontrolled glaucoma is considered missing as patients with this condition were excluded from the pivotal clinical trials. Therefore, in the EU-RMP use of Eylea in patients with uncontrolled glaucoma is listed as missing information.

Two studies have been conducted with Eylea treatment in patients with neovascular glaucoma (VEGA and VENERA study). The VENERA study was completed during this reporting period. No safety signal was derived from these studies.

Search strategy

All PBRER qualifying cases received during this period were reviewed for uncontrolled glaucoma by using the free text search “uncontrolled glaucoma” and “ocular hypertension” in the rubric “medical history (including ongoing conditions) as reported”.

Results

No case was received with “uncontrolled glaucoma” as concurrent condition or medical history.

11 case reports on ocular hypertension as medical history were received during this interval (Table 16-13).

Table 16-13: case reports on ocular hypertension

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Medical history as reported
[redacted] PORTUGAL study/interventional study 62 Years female	1) Fatigue (s);	1) depression 2) diabetes mellitus 3) psoriatic arthritis 4) dislipidemia 5) psychotic depression 6) worsening of depression 7) tendinitis 8) carpal tunnel syndrome 9) venous insufficiency of the lower limbs 10) menopause 11) posterior subcapsular cataract 12) phacosclerosis 13) ocular hypertension 14) post-injection ocular hypertension
[redacted] UNITED STATES	1) Chest pain (s);	1) Retinal exudates 2) Retinal haemorrhage

Table 16-13: case reports on ocular hypertension

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Medical history as reported
study/interventional study 60 Years male	2) Angina unstable (s);	3) Retinal aneurysm 4) Ocular hypertension 5) Angle closure glaucoma 6) Retinal neovascularisation 7) Retinal neovascularisation 8) Iris neovascularisation 9) Photophobia 10) Vision blurred 11) Vitreous floaters 12) Macular fibrosis 13) Retinopathy 14) Ischaemic cardiomyopathy 15) Generalised oedema 16) Oedema peripheral 17) Proteinuria 18) Dyspnoea 19) Nephrotic syndrome 20) Pulmonary oedema 21) Diabetic neuropathy 22) Dry eye 23) Type 2 diabetes mellitus 24) Chronic kidney disease 25) Plasma cell myeloma 26) Hypertension 27) Hyperlipidaemia 28) Oedema peripheral 29) Anaemia 30) Hypokalaemia 31) Glaucoma 32) Cataract nuclear 33) Diabetic retinal oedema 34) Diabetic retinopathy
[redacted] SLOVAKIA study/interventional study 58 Years male	1) Eye haemorrhage (s);	1) ocular hypertension 2) arterial hypertension 3) chronic kidney disease 4) hypoproteinemy 5) hypoalbuminemy 6) laserofotooagulation retinae 7) cataract 8) hemophtalmus in corporis vitrei 9) polyneuropathy diabetica
[redacted] UNITED STATES study/interventional study 45 Years male	1) Gastritis (s);	1) Type II diabetes mellitus 2) Hyperlipidemia 3) Hypertension 4) Senile nuclear sclerosis 5) Vitreous hemorrhage

Table 16-13: case reports on ocular hypertension

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Medical history as reported
		6) Retinal microaneurysms 7) Retinal exudates 8) Proliferative diabetic retinopathy 9) Hypertriglyceridemia 10) Tinea pedis 11) Microalbuminuria 12) Relative afferent pupillary defect 13) Ocular hypertension 14) Borderline glaucoma 15) Sepsis 16) Sepsis 17) Cellulitis 18) Kidney failure 19) Anemia
[redacted] UNITED STATES spontaneous/-- 87 Years male	1) Drug ineffective (n);	1) Atrial fibrillation 2) Hypertension 3) Hypercholesterolaemia 4) Polycythaemia vera 5) Skin cancer 6) Arthralgia 7) Cataract 8) Intraocular lens implant 9) Glaucoma 10) Ocular hypertension 11) Dry age-related macular degeneration
[redacted] UNITED STATES study/interventional study 60 Years male	1) Hypotension (s);	1) Type 2 diabetes mellitus 2) Chronic kidney disease 3) Multiple myeloma 4) Hypertension 5) Hyperlipidemia 6) Peripheral edema 7) Anemia 8) Potassium deficiency 9) Glaucoma 10) Senile nuclear sclerosis 11) Diabetic macular edema 12) Proliferative diabetic retinopathy 13) Vitreous hemorrhage 14) Retinal exudates 15) Eye hemorrhage 16) Retinal microaneurysms NOS 17) Ocular hypertension

Table 16-13: case reports on ocular hypertension

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Medical history as reported
		18) Anatomical narrow angle borderline glaucoma 19) Disc neovascularization 20) Retinal neovascularization NOS 21) Iris neovascularization 22) Photophobia 23) Blurry vision 24) Floaters 25) Preretinal fibrosis 26) Retinal arteriovenous nicking 27) Ischemic cardiomyopathy 28) Anasarca 29) Pedal edema 30) Proteinuria 31) Dyspnea 32) Nephrotic syndrome 33) Pulmonary edema 34) Diabetic nephropathy 35) Dry eye
[redacted] UNITED STATES study/interventional study 59 Years male	1) Myocardial infarction (s); 2) Renal failure (s); 3) Fluid retention (s); 4) Cardiac failure congestive (s); 5) Dyspnoea (s); 6) Hypotension (s); 7) Dyspnoea (s); 8) Cardiac failure congestive (s);	1) Retinal exudates 2) Eye hemorrhage 3) Retinal microaneurysms 4) Ocular hypertension 5) Anatomical narrow angle borderline glaucoma 6) Disc neovascularization 7) Coronary revascularization 8) Iris neovascularization 9) Light sensitivity to eye 10) Blurry vision 11) Floaters 12) Type 2 diabetes mellitus 13) Chronic kidney disease 14) Multiple myeloma 15) Hypertension 16) Hyperlipidemia 17) Peripheral edema 18) Anemia 19) Potassium deficiency 20) Glaucoma 21) Eye disorder 22) Proliferative diabetic retinopathy 23) Vitreous hemorrhage 24) Retinal fibrosis 25) Retinal arteriovenous nicking 26) Ischemic cardiomyopathy

Table 16-13: case reports on ocular hypertension

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Medical history as reported
		27) Anasarca 28) Pedal edema 29) Proteinuria 30) Dyspnea 31) Nephrotic syndrome 32) Pulmonary edema 33) Diabetic nephropathy 34) Diabetic macular edema
[redacted] UNITED STATES study/interventional study 60 Years male	1) Anxiety (s);	1) Type II diabetes mellitus 2) Chronic kidney disease 3) Multiple myeloma 4) Hypertension 5) Hyperlipidemia 6) Pedal edema 7) Anemia 8) Potassium deficiency 9) Glaucoma 10) Nuclear cataract 11) Diabetic macular edema 12) Proliferative diabetic retinopathy 13) Vitreous hemorrhage 14) Retinal exudates 15) Retinal dot hemorrhages 16) Retinal microaneurysms NOS 17) Ocular hypertension 18) Anatomical narrow angle borderline glaucoma 19) Retinal neovascularization NOS 20) Retinal neovascularization NOS 21) Iris neovascularization 22) Photophobia 23) Blurry vision 24) Floaters 25) Preretinal fibrosis 26) Retinal arteriovenous nicking 27) Ischemic cardiomyopathy 28) Anasarca 29) Pedal edema 30) Proteinuria 31) Dyspnea 32) Nephrotic syndrome 33) Pulmonary edema 34) Diabetic nephropathy 35) Dry eye

Table 16-13: case reports on ocular hypertension

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Medical history as reported
[redacted] UNITED STATES study/interventional study 73 Years male	1) Arrhythmia (s);	1) Ocular hypertension 2) Hypertension 3) Diabetes 4) Diabetic macular edema 5) Macular degeneration 6) Glaucoma 7) Glaucoma 8) Conjunctivitis 9) Conjunctivitis
[redacted] UNITED STATES study/interventional study 45 Years male	1) Pneumonia (s);	1) Type II diabetes mellitus 2) Hyperlipidemia 3) Hypertension 4) Ocular fundus arteriosclerosis 5) Vitreous hemorrhage 6) Retinal microaneurysms NOS 7) Retinal exudates 8) Proliferative diabetic retinopathy 9) Hypertriglyceridemia 10) Tinea pedis 11) Microalbuminuria 12) Relative afferent pupillary defect 13) Ocular hypertension 14) Borderline glaucoma
[redacted] UNITED STATES study/interventional study 44 Years male	1) Sepsis (s); 2) Cellulitis (s); 3) Sepsis (s);	1) Type II diabetes mellitus 2) Hyperlipidemia 3) Hypertension 4) Senile nuclear sclerosis 5) Vitreous hemorrhage 6) Retinal microaneurysms NOS 7) Retinal exudates 8) Proliferative diabetic retinopathy 9) Hypertriglyceridemia 10) Tinea pedis 11) Microalbuminuria 12) Relative afferent pupillary defect 13) Ocular hypertension 14) Borderline glaucoma

In one case with ocular hypertension as medical history an ocular event was reported: eye hemorrhage (2019-019692) in 58 old patient 1.9 years after start of

Eylea and 9 days after last injection. Alternative explanation was reported to be the underlying diabetes mellitus. In addition, this patient had hypertension and laser photocoagulation as medical history as possible alternative explanations for eye hemorrhages.

In the remaining cases systemic adverse events occurred typical for this elderly patient population with Eylea indications. Neither the ocular nor the systemic adverse events do raise any concern with Eylea treatment in patients with uncontrolled glaucoma.

Conclusion

No case with explicit uncontrolled glaucoma was received during the reporting period. Of note is the completion of the VEGA and VENERA study in Japanese patients with neovascular glaucoma. No safety concern arose from glaucoma patients treated with IVT aflibercept. No new safety concern arose from this review.

16.3.21 Concomitant Use of Different Anti-VEGF Therapies

Background

The concomitant use of other anti-VEGF agents has not been systematically investigated. It is included as missing information in the EU-Risk Management Plan.

Search strategy

The concomitant medication section of narratives of all PBRER-qualifying cases from the review period were searched for

1. Concomitant use of Lucentis (ranibizumab),
2. Concomitant use of Avastin (bevacizumab)
3. Concomitant use of Macugen (pegaptanib)

Results

As for bilateral aflibercept therapy the focus is on systemic events which might be caused by higher systemic anti VEGF availability the presentation of case details is focused on systemic events.

Concomitant use of Lucentis (ranibizumab)

In 26 cases (Table 16-14) concomitant use of Lucentis (ranibizumab) was reported and 12 were focused on systemic events.

Table 16-14: Overview of cases with concomitant use of Lucentis and systemic adverse events

Case No./ Country/ Source/ Age/ Gender	Case medically confirmed	Preferred term (Seriousness)	Comment
[redacted] UNITED STATES spontaneous/-- 75 Years female	Non MC	1) Disease progression (n); 2) Thrombophlebitis (n); 3) Drug ineffective (n);	77yo female with history of hypercholesterolemia and unspecified thyroid disorder experienced “inflamed veins in both lower legs/ultrasounds did not show any blood clots, may have been very small clots”, the same month when Eylea was re-started. The patient had Lucentis every month in the year before and Eylea for contralateral eye for several years, but it was stopped because the disease progressed. Upon Eylea restart, the non-serious event occurred. Non-medically confirmed case with limited information, where the advanced age with concurrent hypercholesterolemia and thyroid disorder may explain the thrombotic event, however no thrombi could be confirmed at US examination.

Table 16-14: Overview of cases with concomitant use of Lucentis and systemic adverse events

Case No./ Country/ Source/ Age/ Gender	Case medically confirmed	Preferred term (Seriousness)	Comment
[redacted] JAPAN spontaneous/-- 66 Years male	MC	1) Cerebral infarction (s); 2) Serous retinal detachment (s); 3) Detachment of retinal pigment epithelium (s); 4) Retinal tear (s); 5) Lens extraction (s); 6) Intraocular lens implant (s); 7) Vitrectomy (s); 8) Inappropriate schedule of product administration (n);	66yo male with history of smoking, alcohol abuse, hyperlipidemia, hypertension. The event “Cerebral infarction” occurred about 7 months after last Lucentis dose, but while the patient was still under Eylea (3 weeks from last dose administered bilaterally). The advanced age with significant risk factors explains better the development of cerebral infarction.
[redacted] JAPAN spontaneous/-- 70 Years male	MC	1) Parkinson's disease (s); 2) Speech disorder (n); 3) Memory impairment (n);	Medical examination led to a suspicion of Parkinson disease (with speech disorder and memory impairment as symptoms). MRI examination did not reveal any acute lesions, age-related changes were observed. The event occurred 26 months after last Lucentis dose and about 7 weeks after last Eylea dose.

Table 16-14: Overview of cases with concomitant use of Lucentis and systemic adverse events

Case No./ Country/ Source/ Age/ Gender	Case medically confirmed	Preferred term (Seriousness)	Comment
[redacted] JAPAN spontaneous/-- 68 Years male	MC	1) Cerebellar infarction (s); 2) Renal failure (s); 3) Chest discomfort (s); 4) Ocular ischaemic syndrome (s); 5) Chest pain (n); 6) Muscular weakness (n); 7) Renal function test abnormal (n);	Ex-smoker with diabetes, diabetic nephropathy, CRVO and hypertension, experienced renal failure and chest discomfort about 5 weeks after Eylea therapy. Four days later cerebellar infarction occurred. No Lucentis dates provided.
[redacted] PORTUGAL study/interventional study 62 Years female	MC	1) Fatigue (s);	
[redacted] SLOVAKIA study/interventional study 67 Years female	MC	1) Transient ischaemic attack (s); 2) Femoral neck fracture (s);	Elderly patient with diabetes and hypertension experienced TIA 2 years and 7 months after last Lucentis dose
[redacted] JAPAN spontaneous/-- 80 Years female	MC	1) Loss of consciousness (s);	Elderly patient with colon carcinoma, hypertension, atrioventricular block, cardiac pacemaker, paroxysmal atrial fibrillation and cardiac failure.

Table 16-14: Overview of cases with concomitant use of Lucentis and systemic adverse events

Case No./ Country/ Source/ Age/ Gender	Case medically confirmed	Preferred term (Seriousness)	Comment
[redacted] UNITED STATES study/observational study 80 Years female	MC	1) Death (s);	Elderly male with history of stroke, atrial fibrillation, unspecified heart disease, congestive heart failure, pulmonary edema, died about 12 weeks after the last Eylea dose.
[redacted] POLAND study/observational study 84 Years female	Non MC	1) Cerebrovascular accident (s);	PSP case with limited information reported, experienced the cerebrovascular accident in an unclear temporal relationship with Eylea and Lucentis.
[redacted] SWEDEN spontaneous/-- 76 Years male	MC	1) Myocardial infarction (s);	Elderly male with history of hypertension, experienced the fatal myocardial infarction in an unclear temporal relationship with Eylea and Lucentis administration.
[redacted] UNITED STATES study/observational study 88 Years	Non MC	1) Death (s);	88yo male with history of diabetes, unspecified heart disorder, hypercholesterolemia, hypertension, died about 2 years after the last dose

Table 16-14: Overview of cases with concomitant use of Lucentis and systemic adverse events

Case No./ Country/ Source/ Age/ Gender	Case medically confirmed	Preferred term (Seriousness)	Comment
male			Eylea and in an unclear temporal relationship with Lucentis administration.
[redacted] UNITED STATES spontaneous/-- -- female	MC	1) Cerebrovascular accident (s);	Case of minimal information reported, no assessment possible.

In remaining 14 cases, ocular events were reported, which are considered either known adverse reactions of Eylea treatment such as endophthalmitis, eye inflammation, eye pain, cataract, etc., or linked to progression of the underlying disease, like visual impairment, retinal edema and blindness.

Concomitant use of Avastin (bevacizumab)

In 22 cases (Table 16-15) concomitant use of Avastin (bevacizumab) was reported. In 11 cases were reported systemic events.

Table 16-15: Overview of cases with concomitant use of Avastin and systemic adverse events

Case No./Country/Source/Age /Gender	Case medically confirmed	Preferred term (Seriousness)	Comment
[redacted] UNITED STATES study/observational study 80 Years male	MC	1) Unevaluable event (s);	Elderly male with bilateral wet age-related macular degeneration and active choroidal neovascularization, under concomitant treatment with albuterol, amlodipine, aspirin, carvedilol, atorvastatin, levothyroxine, montelukast, symbicort, Ranexa, received Eylea IVT monthly in right eye. After unspecified number of doses and unknown timeframe relative to last injection, the patient missed the planned injection due to “Hospitalization/ Other health issues” (as reported, coded as “unevaluable event”).
[redacted] UNITED STATES study/interventional study 62 Years male	MC	1) Ischaemic stroke (s);	62yo male patient with diabetes, hypertension, stroke, heart failure and atrial fibrillation experienced the ischaemic stroke about 10 months from Eylea therapy start (which was also continued) and in an unclear temporal relationship with Avastin

Table 16-15: Overview of cases with concomitant use of Avastin and systemic adverse events

Case No./Country/Source/Age /Gender	Case medically confirmed	Preferred term (Seriousness)	Comment
			administration.
[redacted] HUNGARY study/interventional study 55 Years male	MC	1) Cardiac arrest (s); 2) Sepsis (s); 3) Diabetic ketoacidosis (s);	55yo male with diabetes, hypertension, chronic alcoholism experienced the cardiac arrest in a diabetic ketoacidosis context with sepsis, one month after the last Eylea dose and about 14 weeks after last Avastin dose. All events resolved and Eylea was continued.
[redacted] HUNGARY study/interventional study 53 Years male	MC	1) Transient ischaemic attack (s);	53yo male patient withy atherosclerosis, hyperlipidaemia, hypertension and diabetes, experienced the TIA after 17 months from the therapy start with Avastin in fellow eye and about 31 months from therapy start with Eylea in study eye. Both medications were continued, and the event resolved in two weeks.
[redacted] CANADA study/observational study 84 Years male	Non MC	1) Death (s);	PSP case with limited information reported; the patient died for unspecified cause in an unclear temporal relationship with both drugs, Eylea and Avastin.
[redacted] UNITED STATES study/observational study 91 Years	MC	1) Death (s);	Patient reimbursement program case referring to a 91yo female with history of B-cell lymphoma died of unknown cause in an unclear temporal relationship with both drugs,

Table 16-15: Overview of cases with concomitant use of Avastin and systemic adverse events

Case No./Country/Source/Age/Gender	Case medically confirmed	Preferred term (Seriousness)	Comment
female			Eylea and Avastin. However, the concurrent malignancy and advanced age provide a plausible alternative explanation.
[redacted] LITHUANIA spontaneous/-- 78 Years female	MC	1) Haemorrhagic stroke (s);	Case of minimal information, the 78yo female received 3 doses Avastin and then started Eylea. In an unclear temporal relationship with the drugs, the patient called to inform she would not come for dosing due to a haemorrhagic stroke she had.
[redacted] UNITED STATES study/observational study 99 Years female	MC	1) Death (s);	Patient reimbursement program case referring to a 99yo female with hypothyroidism, hypertension who received one single dose Eylea and about one year later died of unspecified date, in an unclear temporal relationship with Avastin.
[redacted] UNITED STATES study/interventional study 64 Years male	MC	1) Death (s);	64yo male with history of hypertension, diabetes, stroke, heart failure and atrial fibrillation, died of unspecified cause about 4 months after the 7th Eylea dose, in an unclear temporal relationship with Avastin administration.
[redacted] ESTONIA spontaneous/-- 76 Years female	MC	1) Vaginal haemorrhage (n);	76yo female with multiple sclerosis in remission, experienced the event vaginal haemorrhage in an unclear temporal relationship with both Eylea and Avastin. Case of minimal information, no assessment possible.

Table 16-15: Overview of cases with concomitant use of Avastin and systemic adverse events

Case No./Country/Source/Age /Gender	Case medically confirmed	Preferred term (Seriousness)	Comment
[redacted] UNITED STATES study/observational study 98 Years female	MC	1) Death (s);	Case of minimal information reported form a patient reimbursement program, referring to a 98yo female under concurrent treatment with lisinopril, Plavix, carvedilol, hydrochlorothiazide but with no medical history reported, who died of unreported cause about 7 months after one single dose Eylea and in an unclear temporal relationship with Avastin.

In remaining 11 cases were reported ocular events which are considered either known adverse reactions of Eylea treatment or linked to intravitreal procedure such as endophthalmitis, vitritis, uveitis, eye inflammation, cataract, retinal detachment, detachment of retinal pigment epithelium, eye pain or linked to progression of the underlying disease like visual impairment, vision blurred, therapeutic response decreased and blindness.

Concomitant use of Macugen (pegaptanib)

No cases were reported with concomitant use of Macugen (pegaptanib).

Summary and conclusion

The overall number of patients treated concomitantly with other anti VEGF drugs remains low. Almost all patients are of advanced age. The spectrum of systemic adverse events is in line with the conditions which are typical for this age group. Ocular events are either known adverse reactions of Eylea or symptoms of progression of the underlying disease/indication. No specific safety concern has been identified which would be attributable to the concomitant use of other anti VEGF treatments.

16.3.22 Concomitant Use of Other Therapies for Retinal Neovascularization

Background

The concomitant use of other therapies for retinal neovascularization has not been systematically investigated. It is included as missing information in the EU-Risk Management Plan.

Search strategy

The concomitant medication section of narratives of all PBRER-qualifying cases from the review period were searched for

1. Concomitant use of Visodyne (verteporfin) for photodynamic therapy
2. Concomitant use of triamcinolone

Concomitant use of Visodyne (verteporfin) for photodynamic therapy

No case with concomitant verteporfin use and systemic adverse events were received during the reporting period.

Literature:

The most relevant data available on the topic concomitant use of Eylea with other therapies was the PLANET study data published by *Paul Mitchell AO et al.(155)*. PLANET was a 96□ week, randomized, double□masked, sham□controlled, multicenter, Phase 3b/4 study. All patients received 3 monthly injections of IVT□AFL 2 mg; at Week 12 (W12), patients were randomized to IVT□AFL plus sham PDT (IVT□AFL monotherapy) or IVT□AFL plus active rescue PDT. Patients not requiring rescue received IVT□AFL every 8 weeks. Patients requiring rescue received IVT□AFL every 4 weeks plus active/sham PDT according to local label. From W52, patients not requiring rescue could have treatment intervals extended by

1□ to 2□week increments at investigator's discretion. Primary endpoint was mean BCVA change at W52. The W96 results were presented in the publication. Mean BCVA change with IVT□AFL monotherapy was non□inferior to IVT□AFL plus rescue PDT overall (+10.7 vs +9.1 letters [n = 318]) and in patients requiring rescue (+2.6 vs +0.0 letters [n = 54]). Mean CST change was –140.0 µm (overall) and –135.4 µm (rescue population). Proportions of patients with complete polyp regression and without active polyps were 33.1% and 82.1% (overall) and 29.1% and 85.6% (rescue population). Both groups received a mean of 8.1 (baseline to W52) and 4.6 (W52 to W96) injections. Most frequent ocular adverse events were conjunctival haemorrhage (6.4%; IVT□AFL monotherapy) and dry eye (6.8%; IVT□AFL plus rescue PDT groups). The publication concluded that after 2 years, IVT□AFL monotherapy was effective for most PCV patients; rescue PDT did not provide additional functional or anatomical benefits.

In another study, Weng HY (156) was able to demonstrate that combination therapy with intravitreal aflibercept and photodynamic therapy had significant visual and anatomical improvements for patients with polypoidal choroidal vasculopathy during one-year follow-up. Better baseline visual acuity and younger age were found to be associated with better visual outcome. The study was a retrospective case-series study, including 30 eyes from 30 patients with treatment-naïve PCV treated by combination therapy with IVA and PDT. Best-corrected visual acuity (BCVA), central retinal thickness (CRT), complete polyp regression rate, and dry macula rate were recorded every 3 months during 12-month follow-up. Clinical factors associated with final visual outcome and retreatment were investigated. The mean LogMAR BCVA was significantly improved from 0.73 ± 0.65 at baseline to 0.51 ± 0.60 ($p = 0.01$), and the mean CRT was also significantly improved from 339 ± 96 µm at baseline to 244 ± 43 µm at 12-month follow-up ($p < 0.001$). Complete regression of polypoidal lesions was 76.7%, and dry macula rate was 100% at 12 months. Better final BCVA was associated with younger age and better baseline BCVA ($p = 0.02$ and p < 0 001). The patients without complete polyp regression at 3-month follow-up were associated with retreatment ($p = 0.03$).

Rufino Silva (157) started a study Randomized, Double-masked, Sham-controlled Phase 4 Study, Efficacy, Safety, and Tolerability of Intravitreal Aflibercept Monotherapy Compared to Aflibercept With Adjunctive Photodynamic Therapy in Patients With Polypoidal Choroidal Vasculopathy (ATLANTIC) and published the results in 2019 during the Annual Meeting of the American Academy of Ophthalmology (AAO) held in San Francisco, USA. The study aimed to compare the efficacy and safety of intravitreal aflibercept treat-and-extend (IVA-TAE) plus sham photodynamic therapy (sPDT) versus IVA-TAE with verteporfin PDT (vPDT) in a white population with polypoidal choroidal vasculopathy (PCV). A 52-week randomized, double-masked, sham-controlled, Phase 4 investigator-driven clinical trial in 14 centers in Portugal and Spain. Patients were randomized to IVA 2 mg + sPDT or IVA 2 mg + vPDT. The primary outcomes were change in best corrected visual acuity (BCVA) from baseline and polyp regression at week 52. Results: Fifty patients, mean age 72.6 ± 9.2 and baseline BCVA of 62.8 ± 12.1 ETDRS letters, were included. At week 16, only 42% of eyes required PDT, and only one patient required PDT thereafter. At final visit no significant

difference in BCVA gains or polyps regression was observed. The authors concluded that PDT added no significant functional or anatomic benefit at 1 year.

Concomitant use of triamcinolone

Sixteen cases were received where patients were treated concomitantly with triamcinolone, in 12 cases systemic events were reported. In some cases triamcinolone may have been administered systemically (unspecified administration route).

Out of these 12 cases, the triamcinolone indication was ocular in one single case and in 5 additional cases the indication was not reported. All these cases are discussed in Table 16-16. No safety concerns emerged from this analysis. In six cases with systemic events the Triamcinolone was given for non-ocular indication. Upon data review, no safety concerns were identified.

Table 16-16: Overview of cases with concomitant use of triamcinolone and systemic adverse events

Case ID / Country / Source / Age / Gender	Event as reported term / PT (seriousness)	Case Medically Confirmed	Comment:
[redacted] JAPAN spontaneous/-- 69 Years female	1) Death nos / Death (s); 2) The whole body condition was pretty bad / General physical health deterioration (s); 3) Dysuria / Dysuria (s); 4) General edema exacerbation / Generalised oedema (s); 5) General edema exacerbation / Generalised oedema (s); 6) Central Retinal Vein Occlusion in left eye / Retinal vein occlusion (s);	MC	69yo female diabetic patient with nephro- and neuropathy, experienced dysuria and 2 episodes of general edema exacerbation in an unclear temporal relationship with Eylea. **Triamcinolone (Kenacort) was given once for diabetic retinal oedema**. One year after triamcinolone administration but while the patient was still under Eylea treatment, CRVO was noted on left eye (patient was treated for RVO in both eyes). The same month, her general health deteriorated and ultimately died about 2 weeks after last Eylea dose. The fatal event was considered unrelated to Eylea and for remaining events no causal assessment was reported.
[redacted] SLOVAKIA spontaneous/-- 69 Years female	1) reversible ischemic stroke / Ischaemic stroke (s); 2) off-label use / Off label use (n);	MC	69yo female with essential hypertension, untreated hypercholesterolemia, smoker, subclinical hypothyroidism, AV nodal reentrant tachycardia, acute respiratory distress syndrome, experienced the event reversible ischemic stroke the next day after having the 40th dose of Eylea. Cerebral media artery presented chronic occlusion on angiogram. No causal assessment reported but the event resolved in about 2

Table 16-16: Overview of cases with concomitant use of triamcinolone and systemic adverse events

Case ID / Country / Source / Age / Gender	Event as reported term / PT (seriousness)	Case Medically Confirmed	Comment:
			weeks. **Triamcinolone acetonide was started 3 months after the event for unreported indication.**
[redacted] CHINA spontaneous/-- 63 Years male	1) hypertension / Blood pressure increased (s);	MC	This 63yo male patient had a transient blood pressure increase about one month after the second dose Eylea. **Triamcinolone acetonide was given for unreported indication**. The CT scan showed a little nodule in the left adrenal gland, a possible adenoma.
[redacted] UNITED STATES study/observational study 95 Years male	1) passed away / Death (s);	Non MC	PSP case with minimal information reported referring to a 95yo male patient. **Triamcinolone was given for unreported indication**. Only concomitant medication was provided but without indication (Amoxiclav, Chlorhexidine Gluconate, Clobetasol (cream and solution), Clotrimazole, Fluticasone, Hydrochlorothiazide, Ipratropium, Losartan Potassium, Mupirocin, Nystatin, Omeprazole, Potassium Chloride, Spironolacton, Tamsulosin, Tramadol HCL). No causal assessment provided for death, unclear temporal relationship with both Eylea and Triamcinolone.
[redacted] UNITED STATES study/observational study 88 Years male	1) Death / Death (s);	Non MC	PSP case referring to an 88yo male with history of diabetes, heart disorder, hypercholesterolemia, hypertension who died 2 years from the last dose Eylea (which was administered for about 13 months). **Triamcinolone acetonide was given for unreported indication** in an unclear temporal relationship with the event.
[redacted] UNITED STATES spontaneous/-- 96 Years female	1) patient would not let the doctor proceed with the injection / Intentional dose omission (n); 2) the patient got nervous / Nervousness (n);	MC	96yo female patient with dementia and history of arthritis, chronic allergies, arrhythmia, sinus problems, got nervousness 2 and a half months after the last Eylea dose (non-serious, related), when the patient was scheduled to receive injection in both eyes. Eylea was withdrawn. **Triamcinolone acetonide was given for unreported indication.**

In the remaining four cases ocular events occurred in temporal relationship to the intravitreal injection of Eylea which are considered either known adverse reactions of Eylea or symptoms of progression of the underlying disease/indication, as presented in the Table 16-17 below:

Table 16-17: Overview of cases with concomitant use of triamcinolone and ocular adverse events

Case ID / Country / Source / Age / Gender	Event as reported term / PT (seriousness)	Case Medically Confirmed	Case Serious
[redacted] UNITED STATES spontaneous/-- -- male	1) inflammation (eye) / Eye inflammation (s); 2) vitrectomy membrane peeling / Vitrectomy (s); 3) (possible) missed doses / Product dose omission (n);	MC	Serious
[redacted] JAPAN spontaneous/-- 73 Years male	1) The capillary in the retina is broken and it bleeds / Retinal haemorrhage (s); 2) Choroidal neovascular hemorrhage / Choroidal neovascularisation (s); 3) My retina is weak and damaged / Retinal injury (s); 4) left eye of visual acuity reduced(from 0.7 to 0.5) / Visual acuity reduced (n); 5) Water is accumulated by bleeding from neovascular / Subretinal fluid (n); 6) Drug ineffective / Drug ineffective (n); 7) An ophthalmologist said that 9 months the dosing interval was too long / Inappropriate schedule of product administration (n); 8) Second dose in less than 1 month after first dose of Eylea / Inappropriate schedule of product administration (n);	Non MC	Serious
[redacted] UNITED STATES spontaneous/-- 84 Years female	1) right eye changed from dry AMD to wet AMD / Neovascular age-related macular degeneration (s); 2) wet AMD right eye / Neovascular age-related macular degeneration (s);	MC	Serious
[redacted] JAPAN spontaneous/-- -- --	1) Drug ineffective / Drug ineffective (n);	MC	Non Serious

Summary and conclusion

The overall number of reports in patients treated concomitantly with other therapies for retinal neovascularization is considered low. There is no evidence that the reported events are causally linked to the use of Eylea and either verteporfin or triamcinolone.

No new safety finding was observed from the review of these cases.

16.3.23 Bilateral Treatment with Aflibercept

Background

Bilateral therapy was added as missing information to the EU RMP of Eylea during the post marketing period. Starting with PSUR#4 data was reviewed from the reporting periods regarding bilateral use of Eylea. Here, bilateral therapy is defined as aflibercept treatment with a maximum delay between the injections of 28 days.

As in the PRAC PSUR evaluation report on the 6th PSUR it was stated that systemic AEs are more of concern than local AEs considering possible systemic exposure which can be increased in case of treatment in both eyes, the scope of the monitoring could be restricted to systemic AEs. Therefore, only cases with bilateral treatment and onset of systemic events were evaluated in this report.

Search strategy:

All case narratives were searched for the following free text: “both eyes” or “fellow eye treatment” or “bilateral treatment” excluding cases which only contain ocular adverse events.

During this reporting period this search revealed a total of 59 initial PBRER qualifying cases with systemic adverse reactions in which Eylea treatment was reportedly administered bilaterally (explained below). Due to missing information on exact injection dates, the interval between the injections in both eyes is unknown in most cases. 19 spontaneous reports, 39 observational study cases, one interventional study case were identified, see tabular overview below, Table 16-18:

Table 16-18: Cases with bilateral treatment and systemic events

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Outcome (Event)	Case Description	Comment
[redacted] CANADA spontaneous/-- 69 Years female	1) Death (s)	1) Death: fatal	Received Eylea for Diabetic macular edema. On 16 JUN 2017, the patient started Eylea 40 mg/ml, both eyes. Death occurred on an unknown date.	Latency, therapy frequency, cause of the death, medical history and concomitant medications were not reported
[redacted] UNITED STATES study/observational study 96 Years male	1) Death (s)	1) Death: fatal	Started Aflibercept therapy for the indication of Wet age-related macular degeneration in both eyes on 13 AUG 2014 with 1 mg, every four to eight weeks. Patient died on 13 NOV 2018. Cause of death was unknown. Patient's medical history included COPD (Chronic obstructive pulmonary disease) and pneumonia.	It was not reported, how many total doses of Eylea were received prior to event, nor when the last dose was administered. Medical history of COPD and old age are the confounders.
[redacted] AUSTRALIA study/observational study 43 Years female	1) Myocardial infarction (s); 2) Renal failure (s); 3) Anemia (s); 4) Vomiting (s); 5) Decreased appetite (s); 6) Exophthalmos (s); 7) Eye pain (n); 8) Stress (n);	1) Myocardial infarction: unknown; 2) Renal failure: --; 3) Anemia: --; 4) Vomiting: --; 5) Decreased appetite: recovered / resolved; 6) Exophthalmos: recovered / resolved; 7) Eye pain: recovered / resolved; 8) Stress: --;	Started Aflibercept for Diabetic macular edema on 02 MAR 2017, 40 mg/ml, both eyes, total of 9 Eylea doses, last dose prior the event was received on 21 MAR 2018. In MAY 2018, the patient experienced myocardial infarction, renal failure, anemia, vomiting and decreased appetite. On an unknown date, the patient experienced exophthalmos. Medical history included Myocardial infarction in 2017. Concurrent conditions included Diabetic since 2004, Smoker and Hypertension since 2018. In the past drug, the patient was treated with Lucentis. Eylea treatment was not changed.	Medical history of Myocardial infarction, concurrent conditions of diabetes, smoking, hypertension are the confounders for the systemic events.

Table 16-18: Cases with bilateral treatment and systemic events

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Outcome (Event)	Case Description	Comment
[redacted] UNITED STATES spontaneous/-- 54 Years male	1) Neuropathy peripheral (s); 2) Autoimmune disorder (s); 3) Hemiparesis (s);	1) Neuropathy peripheral: unknown; 2) Autoimmune disorder: unknown; 3) Hemiparesis: unknown;	Initiated Aflibercept for diabetic retinopathy and macular edema in both eyes on an unknown date in FEB 2018, with unknown dose, once a month frequency. Unknown total doses received prior to events. The last dose of Eylea was administered on 05 OCT 2018. Patient has experienced events on unknown day. It was reported that patient's doctor did not think the severe weakness was related to Eylea. Medical history included diabetes and high blood pressure.	Non medically confirmed. Medical history could be confounder for the events.
[redacted] AUSTRALIA study/observational study 89 Years female	1) Blood pressure increased (s);	1) Blood pressure increased: unknown;	Started Aflibercept for Neovascular age-related macular degeneration on 11 JUN 2018, 40 mg/ml (intraocular), both eyes, every 6 weeks, unknown total doses received. On an unknown date, the patient was found to have blood pressure increased. Eylea treatment was not changed. Medical history and concomitant medication were unknown.	Non medically confirmed.

Table 16-18: Cases with bilateral treatment and systemic events

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Outcome (Event)	Case Description	Comment
[redacted] UNITED STATES study/observational study 76 Years male	1) Death (s);	1) Death: fatal;	Initiated Aflibercept for type 2 diabetes, with severe non-proliferative retinopathy with macular edema on 20 JUL 2018, experienced death on unknown date with 2 mg dose, both eyes, monthly. Unknown total doses received. Last Eylea dose was administered on 01 NOV 2018. Cause of the death was unknown. Medical history included type 2 diabetes mellitus and concomitant medications of metoprolol denotes unknown heart disorders.	no latency details, unknown cause of death/no autopsy report. Old age, type 2 diabetes mellitus and concomitant medications of metoprolol denotes unknown heart disorders are the confounders.
[redacted] UNITED STATES study/observational study 90 Years female	1) Death (s);	1) Death: fatal;	Initiated Aflibercept therapy on 19 SEP 2017 for the treatment of wet age-related macular degeneration, with inactive choroidal neovascularization in both eyes. Received a total of 14 doses of Eylea. The patient received the last Eylea dose on 21 NOV 2018. On 08 DEC 2018, the patient died from an unknown cause. A death certificate /autopsy not provided. No info about medical history.	No information about medical history, concomitant medication and cause of death.
[redacted] UNITED STATES study/observational study 91 Years female	1) Metastatic gastric cancer (s); 2) Cerebrovascular accident (s); 3) Weight decreased (s);	1) Metastatic gastric cancer: unknown; 2) Cerebrovascular accident: unknown; 3) Weight decreased: unknown;	Started Aflibercept therapy into both eyes (OU) on unknown date for an indication of macular degeneration. Unknown total doses received. She experienced stomach cancer and tumors that have metastasized, stroke and lost much weight, down to 89 pounds, following the administration of Eylea. Action taken with Eylea was dose not changed (ongoing). The patient's medical history included drug allergies. Concomitant medications were not provided.	Therapy details, latency, concomitant medication was not provided. Eylea was ongoing. Non medically confirmed.
[redacted] AUSTRALIA study/observational study	1) Neovascular age-related macular degeneration (s); 2) Visual impairment (n);	1) Neovascular age-related macular degeneration: not recovered / not	Started Eylea for Neovascular age-related macular degeneration on 13 SEP 2018. Initially patient started with Eylea 40 mg/ml, left eye. In December 2018, the dose was changed to unknown, injection to right eye. From 13 SEP 2018, Eyela	Non medically confirmed. No information about latency, medical history

Table 16-18: Cases with bilateral treatment and systemic events

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Outcome (Event)	Case Description	Comment
80 Years female	3) Injection site discomfort (n); 4) Rhinorrhoea (n); 5) Lacrimation increased (n); 6) Gait disturbance (n);	resolved; 2) Visual impairment: unknown; 3) Injection site discomfort: recovered / resolved; 4) Rhinorrhoea: --; 5) Lacrimation increased: --; 6) Gait disturbance: --;	frequency was every 6 Weeks, into Both eyes. On an unknown date, the patient experienced rhinorrhea and gait disturbance. She also experienced ocular events of neovascular age-related macular degeneration, visual impairment, injection site discomfort and lacrimation. Eylea treatment was not changed. Patient's medical history and concomitant medications were unknown.	and concomitant medications.
[redacted] URUGUAY spontaneous/-- 80 Years male	1) Squamous cell carcinoma of skin (s); 2) Eyelid disorder (n); 3) Dermatitis atopic (n);	1) Squamous cell carcinoma of skin: --; 2) Eyelid disorder: --; 3) Dermatitis atopic: --;	Received Eylea from October 2018 until December 2018, with 40 mg/ml, unknown dose, both eyes for Age-related macular degeneration. On an unknown date, the patient was found to have squamous cell carcinoma of skin, experienced eyelid disorder and dermatitis atopic. Medical history included Skin lesion. The reporter considered dermatitis atopic, eyelid disorder and squamous cell carcinoma of skin were unrelated to Eylea.	Medical history of skin lesion, old age are confounders for squamous cell carcinoma.
[redacted] UNITED STATES study/observational study 79 Years male	1) Death (s);	1) Death: fatal;	Started Eylea therapy on an unknown date for Macular degeneration in both eyes. Dosing was 2 mg and frequency was reported as every 4 weeks for the first 3 injections followed by 2 mg every 8 weeks. Received an unknown total number of doses. The patient received the last dose on an unknown date. On 12 APR 2017, the patient was died from an unknown cause. A death certificate/autopsy report was not provided. The patient's past medical history and concomitant medications were not reported.	No information about latency, cause of death, medical history and concomitant medications.

Table 16-18: Cases with bilateral treatment and systemic events

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Outcome (Event)	Case Description	Comment
[redacted] UNITED STATES study/observational study 80 Years female	1) Hospitalization (s); 2) Blindness unilateral (s); 3) Eye infection (s); 4) Hallucination, visual (s); 5) Dyschromatopsia (s); 6) Visual impairment (s); 7) Vision blurred (s);	1) Hospitalization: unknown; 2) Blindness unilateral: recovered / resolved; 3) Eye infection: recovered / resolved; 4) Hallucination, visual: recovered / resolved; 5) Dyschromatopsia: recovered / resolved; 6) Visual impairment: recovering / resolving; 7) Vision blurred: recovering / resolving;	Initiated Eylea therapy on an unknown date for Macular degeneration in both eyes. Dosing was not specified, and frequency was reported as "every 8 weeks, then sometimes every 7 weeks or 5 weeks". Received an unknown total number of doses. Patient received the last Eylea dose on 24 JAN 2019. She experienced Visual hallucination, hospitalization for an unknown reason and ocular events of blind right eye, right eye infection, color vision disturbance, vision worsened, and Vision blurred. Except vision worsened and Vision blurred all other events were occurred in July/August 2018, vision worsened, and Vision blurred occurred on JAN 2019. Eylea treatment was not changed. Medical history included Congestive heart failure, Atrial fibrillation, cataract in both eyes, cataract in right eye removed, blind left eye	Non medically confirmed
[redacted] AUSTRALIA study/observational study 83 Years female	1) Dementia (s); 2) Cataract (s); 3) Headache (n);	1) Dementia: not recovered / not resolved; 2) Cataract: not recovered / not resolved; 3) Headache: recovered / resolved;	Started Eylea for Neovascular age-related macular degeneration in SEP 2018, 40 mg/ml, both eyes; dose, frequency and total number of injections were not reported. In September 2018, the patient experienced cataract, on an unknown date in 2018, experienced dementia and on unknown date, patient experienced headache. Eylea treatment was not changed. reporter considered dementia to be unrelated to Eylea. Medical history and concomitant medication were not reported.	Lack of clear therapy details. old age could be the confounder for dementia.
[redacted] UNITED STATES study/observational study 79 Years male	1) Blindness unilateral (s); 2) Cardiac operation (s); 3) Chest pain (s); 4) Retinal artery occlusion (s);	1) Blindness unilateral: not recovered / not resolved; 2) Cardiac operation: recovered / resolved; 3) Chest pain: unknown;	Started Eylea on 12 OCT 2016 with 2 mg, every 3 months in the left eye for macular degeneration. Subsequently, Eylea administered in Both eyes. Experienced visual loss right eye and Central retinal artery occlusion on unknown date, pains in chest and open-heart surgery were experienced on unknown date. Eylea was ongoing in the left eye. The patient's past medical history was not provided.	No information about latency, medical history and concomitant medications.

Table 16-18: Cases with bilateral treatment and systemic events

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Outcome (Event)	Case Description	Comment
		4) Retinal artery occlusion: not recovered / not resolved;		
[redacted] UNITED STATES study/observational study 66 Years female	1) Death (s);	1) Death: fatal;	Initiated Eylea therapy on 21 FEB 2018 for Diabetic retinopathy with macular edema in both eyes. Dosing and frequency were not specified. Last dose of Eylea was administered on 12 JUL 2018 and received total of 7 doses of Eylea prior to the adverse event. On an unknown date, the patient died from an unknown cause. A death certificate/autopsy report was not provided. Medical history included Diabetes.	No information about latency, cause of death. Medical history of Diabetes could be the confounder.
[redacted] UNITED STATES spontaneous/-- 52 Years female	1) Necrotising fasciitis (s); 2) Malaise (n); 3) Wound closure (n);	1) Necrotising fasciitis: recovering / resolving; 2) Malaise: recovering / resolving; 3) Wound closure: unknown;	Started Aflibercept in June 2017, every month or every 2 months for macular edema. Dosing was not provided. The last dose of Eylea was administered on 04 FEB 2019 in the left eye. The total number of doses were unknown. On 10 NOV 2018, patient experienced Necrotizing fasciitis and unknown date, malaise and wound closure (wound vac for open wound). Eylea was continued. Medical history included diabetes, blood clots and anemia. Concomitant medications included Metformin, Xarelto, Vitamin D, Iron.	medical history of diabetes could be the confounder.
[redacted] SLOVAKIA spontaneous/-- 69 Years female	1) Ischaemic stroke (s); 2) Off label use (n);	1) Ischaemic stroke: recovered / resolved; 2) Off label use: --;	Started Aflibercept for Wet age-related macular degeneration in both eyes, 40 mg/ml, both eyes, overall 40 doses from 10 NOV 2016 until 28 JAN 2019. On 29 JAN 2019, she experienced ischemic stroke. Medical history included Essential hypertension, Hypercholesterolemia, Nicotine poisoning, Subclinical hypothyroidism, Aspiration pneumonia, AV nodal reentrant tachycardia, Acute respiratory distress syndrome.	medical history of hypertension, hypercholesterolemia, AV nodal re-entry tachycardia and Nicotine poisoning could be the confounders.

Table 16-18: Cases with bilateral treatment and systemic events

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Outcome (Event)	Case Description	Comment
[redacted] UNITED STATES spontaneous/-- 87 Years male	1) Bradyphrenia (n); 2) Retinal oedema (n); 3) Drug ineffective (n);	1) Bradyphrenia: unknown; 2) Retinal oedema: unknown; 3) Drug ineffective: unknown;	Started Aflibercept therapy in 2017 in the right eye and in the summer of 2018 for the treatment of Macular degeneration both eyes. Dosing was not specified, frequency was reported as every 4 months initially, every 5 weeks at present. Received an unknown total number of doses. On unknown date, he developed Bradyphrenia and retinal fluid. Medical history and concomitant medications were not provided.	Non medically confirmed. Old age could be the confounder.
[redacted] UNITED STATES study/observational study 77 Years female	1) Death (s);	1) Death: fatal;	Started Eylea on 30 NOV 2015 for Diabetic Macular edema, both eyes. She received a total of 7 doses of Eylea in each eye (14 doses). The patient received the last Eylea dose on 17 OCT 2017. On an unknown date, the patient died from an unknown cause. A death certificate/autopsy report was not provided. According to the physician, the patient's death was not related to Eylea. Past medical history included Type 2 diabetes mellitus.	No information about latency, cause of death. Medical history of Diabetes could be a confounder.
[redacted] JAPAN spontaneous/-- 66 Years male	1) Cerebral infarction (s); 2) Serous retinal detachment (s); 3) Detachment of retinal pigment epithelium (s); 4) Retinal tear (s); 5) Lens extraction (s); 6) Intraocular lens implant (s); 7) Vitrectomy (s); 8) Inappropriate schedule of product administration (n);	1) Cerebral infarction: recovering / resolving; 2) Serous retinal detachment: unknown; 3) Detachment of retinal pigment epithelium: not recovered / not resolved; 4) Retinal tear: recovered / resolved; 5) Lens extraction: --; 6) Intraocular lens implant: --; 7) Vitrectomy: --;	Started Aflibercept solution for Age-related macular degeneration on 18 NOV 2014. Total 20 cycles were reported. In 3 cycles, Eylea was administered into both eyes (05 FEB 2019, 30 NOV 2018, and 26 SEP 2018). On 26 FEB 2019, the patient experienced cerebral infarction. Patient also experienced ocular events of detachment of retinal pigment epithelium, serous retinal detachment, retinal tear, lens extraction and underwent intraocular lens implant, vitrectomy. The patient's medical history included retinal laser photocoagulation (both eyes), bilateral cataracts and detached retina repair. Concurrent conditions included smoker (20 cigarette per day), alcohol use, liver disorder, hypertension and hyperlipidemia. The reporter stated about the causal relationship between the cerebral infarction and Eylea as unlikely, unknown and alternative explanation might be	Reporter (Ophthalmologist) assessed the causality as not related. Smoking, hypertension and hyperlipidemia are the confounders.

Table 16-18: Cases with bilateral treatment and systemic events

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Outcome (Event)	Case Description	Comment
		8) Inappropriate schedule of product administration: --;	underlying disease and concomitant condition.	
[redacted] UNITED STATES study/observational study 71 Years male	1) Death (s);	1) Death: fatal;	Started with Eylea on 03 AUG 2015 for Diabetic Macular Edema. Dosing and frequency were not specified. Patient received a total of 24 doses of Eylea - OU (both eyes). He received the last Eylea dose on 23 OCT 2018. On 17 NOV 2018 the patient died from an unknown cause. A death certificate/autopsy report was not provided. According to the physician the patient's death was not related to EYLEA. Medical history included diabetes mellitus, heart disease and hypercholesterolemia.	No information on cause of death. Medical history included diabetes mellitus, heart disease are possible confounders.
[redacted] AUSTRALIA study/observational study 74 Years male	1) Cataract operation (s); 2) Injection site pain (n); 3) Skin ulcer (n);	1) Cataract operation: unknown; 2) Injection site pain: recovered / resolved; 3) Skin ulcer: not recovered / not resolved;	Started with Eylea 40 mg/ml for Diabetic macular edema in 2017. Dose, frequency and total number of injections were not reported. In February 2019, the patient experienced skin ulcer, on 22 FEB 2019, the patient underwent cataract operation. on an unknown date, the patient experienced injection site pain. Eylea treatment was not changed. Medical history included Bilateral cataracts (Bilateral cataracts diagnosed before starting Eylea treatment) and Diabetes (Diabetes for ten years).	Diabetes could be the confounder for event skin ulcer.
[redacted] UNITED STATES study/observational study 90 Years female	1) Death (s);	1) Death: fatal;	Started Eylea therapy on 24 DEC 2016 with 2mg every 28 days in both eyes, for an indication of Exudative age-related macular degeneration, left eye, with active choroidal neovascularization. Unknown total number of doses received. Patient died from an unknown cause on 22 FEB 2019. A death certificate /autopsy report was not provided. Medical history was not provided.	Old age could be the confounder.
[redacted]	1) Breast cancer (s);	1) Breast cancer:	Initiated Eylea therapy on 30 JUL 2014 in the right eye for the	No information about

Table 16-18: Cases with bilateral treatment and systemic events

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Outcome (Event)	Case Description	Comment
UNITED STATES spontaneous/-- 74 Years female	2) Needle issue (s);	unknown; 2) Needle issue: unknown;	treatment of Age-related macular degeneration both eyes (Wet age-related macular degeneration). Dosing not specified and frequency was reported as every 5 to 6 weeks. Received an unknown total number of doses. The patient received the last Eylea dose on 27 FEB 2019, bilaterally. On an unknown date, the patient was diagnosed with breast cancer. Eylea was continued. Past medical history was not reported. The patient's concomitant medications included "several medications" (unspecified).	Medical history and specific concomitant medications.
[redacted] UNITED STATES spontaneous/-- -- female	1) Retinal disorder (n); 2) Unevaluable event (n); 3) Blood glucose increased (n);	1) Retinal disorder: unknown; 2) Unevaluable event: unknown; 3) Blood glucose increased: unknown;	Started Aflibercept in 2007 for an unspecified retinal eye disorder in the right eye. The patient initiated Eylea therapy in the left eye as well. Dosing was not reported, and frequency was every 5 weeks in both eyes. Total number of doses of Eylea were unknown. On unknown date, the patient experienced Blood glucose increased, retinal disorder and Ill-defined disorder and. Eylea treatment was ongoing. Medical history included Breast cancer, Thyroid problem, Diabetes.	Medical history of diabetes could be the confounder for event Blood glucose increased.
[redacted] AUSTRALIA study/observational study 32 Years female	1) Retinal detachment (s); 2) Vision blurred (n); 3) Diplopia (n); 4) Eye irritation (n); 5) Maternal exposure during pregnancy (n); 6) Abortion spontaneous (s);	1) Retinal detachment: recovering / resolving; 2) Vision blurred: --; 3) Diplopia: --; 4) Eye irritation: recovered / resolved; 5) Maternal exposure during pregnancy: --; 6) Abortion spontaneous: unknown;	Patient started Eylea 40 mg/ml injections to both eyes from January 2017 for Diabetic macular edema. Dosing and frequency details were not reported. On 11 DEC 2017, the patient experienced Abortion spontaneous, in 2018 the patient experienced retinal detachment with vision blurred and diplopia. On an unknown date, the patient experienced eye irritation. Medical history included Myopia and Diabetes. Concomitant products included Insulin Aspart (Novorapid), Insulin Glargine (Lantus) and Insulin since 2009 for Diabetes.	Medical history of diabetes could be the confounder for event Abortion spontaneous.
[redacted]	1) Death (s);	1) Death: fatal;	Started Eylea for Wet macular degeneration, both eyes. Dosing,	Medical history,

Table 16-18: Cases with bilateral treatment and systemic events

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Outcome (Event)	Case Description	Comment
UNITED STATES study/observational study 79 Years female			therapy dates and frequency were not specified. The total number of doses were not provided. On an unknown date, the patient died from an unknown cause. A death certificate/autopsy report was not provided. According to the physician, the patient's death was not related to Eylea. Medical history and concomitant medications were not provided.	concomitant medications and cause of death were not provided
[redacted] UNITED STATES study/observational study 91 Years female	1) Death (s);	1) Death: fatal;	Initiated Eylea therapy on 27 APR 2017 for Wet age-related macular degeneration, both eyes. Dosing and frequency were not specified. Patient received a total of 14 doses of Eylea. On 18 DEC 2018, the patient died from unknown cause. A death certificate/autopsy report was not provided. According to the physician, the patient's death was not related to Eylea. The patient's past medical history and concomitant medications were not provided.	Medical history, concomitant medications and cause of death were not provided
[redacted] UNITED STATES study/observational study 70 Years male	1) Death (s); 2) Off label use (n); 3) Product use in unapproved indication (n);	1) Death: fatal; 2) Off label use: --; 3) Product use in unapproved indication: --;	Started Eylea for Diabetic macular edema, both eyes on 26 OCT 2017. Dosing was 2 mg, intravitreally, every month. On 19 MAR 2019, the patient died from an unknown cause. The death certificate/autopsy report was not provided. The patient's medical history included Diabetic macular edema, Liver cell carcinoma and Type 2 diabetes mellitus. Concomitant medications included Lucentis	Medical history included liver cell carcinoma and diabetes mellitus could be possible confounders.
[redacted] UNITED STATES study/observational study 46 Years male	1) Photophobia (s); 2) Cerebrovascular accident (s);	1) Photophobia: unknown; 2) Cerebrovascular accident: unknown;	Initiated Eylea therapy on an unknown date for Type 2 Diabetes with non-proliferative retinopathy with macular edema, in both eyes. Dosing was 2 mg of Eylea, every 4 weeks. Received an unknown total number of doses. The last dose of Eylea was administrated on an unknown date. On an unknown date, the patient experienced 3 cerebrovascular accidents in the past (2006, 2007 and 2013) and photophobia. Eylea was continued.	Absence of therapy details, latency and Concomitant medications. Medical history of diabetes could be possible confounder.

Table 16-18: Cases with bilateral treatment and systemic events

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Outcome (Event)	Case Description	Comment
			Medical history included Type 2 diabetes mellitus. Concomitant medications were not provided.	
[redacted] UNITED STATES spontaneous/-- 55 Years male	1) Blindness unilateral (s); 2) Myocardial infarction (s); 3) Retinal scar (n); 4) Metamorphopsia (n); 5) Eye disorder (n); 6) Vision blurred (n); 7) Drug ineffective (n);	1) Blindness unilateral: unknown; 2) Myocardial infarction: unknown; 3) Retinal scar: unknown; 4) Metamorphopsia: unknown; 5) Eye disorder: unknown; 6) Vision blurred: not recovered / not resolved; 7) Drug ineffective: unknown;	Initiated Eylea on an unknown date (7 years ago) for the treatment of leaky blood vessels in eyes. Dosing was not specified, and frequency was every 6 months in both eyes, and started receiving Eylea every other month in the left eye. Received an unknown total number of doses of Eylea. On unknown date, patient experienced myocardial infarction along with other ocular events, Lost vision in the right eye except for peripheral, Retinal scar, Distorted vision, Eye disorder and Cloudy vision. Past medical history included high blood pressure and weak spots in left eye. Concomitant medications included unspecified blood pressure medicines.	Medical history of hypertension could be possible confounder for myocardial infarction.
[redacted] AUSTRALIA study/observational study -- female	1) Myocardial infarction (s); 2) Lower respiratory tract infection (s); 3) Pneumonia (s); 4) Intestinal obstruction (s); 5) Blood pressure abnormal (s); 6) Blindness transient (s); 7) Adverse drug reaction	1) Myocardial infarction: recovering / resolving; 2) Lower respiratory tract infection: recovering / resolving; 3) Pneumonia: recovering / resolving; 4) Intestinal obstruction: recovering / resolving; 5) Blood pressure abnormal: recovering / resolving;	Started Aflibercept with an unspecified dose, every 6 weeks in 2016 for Diabetic macular oedema. On an unknown date, she experienced myocardial infarction, lower respiratory tract infection, pneumonia, intestinal obstruction, adverse drug reaction ("reaction to betadine antiseptic"), accident ("recently slipped over"), ligament sprain and injection site erythema, was found to have blood pressure abnormal and experienced blindness lasting 2 hrs. Eylea treatment was not changed. The reporter considered lower respiratory tract infection, myocardial infarction, pneumonia, intestinal obstruction, accident, adverse drug reaction and ligament sprain to be unrelated to Eylea. Medical history included triple vessel bypass graft and stent	Non medically confirmed. Medical history of heart disease and diabetes could be possible confounder for myocardial infarction.

Table 16-18: Cases with bilateral treatment and systemic events

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Outcome (Event)	Case Description	Comment
	(n); 8) Accident (n); 9) Ligament sprain (n); 10) Injection site erythema (n);	6) Blindness transient: recovered / resolved; 7) Adverse drug reaction: recovered / resolved; 8) Accident: --; 9) Ligament sprain: recovering / resolving; 10) Injection site erythema: recovered / resolved;	placement. concurrent conditions included diabetes mellitus from 46 years	
[redacted] UNITED STATES study/observational study 80 Years male	1) Death (s);	1) Death: fatal;	Initiated Eylea therapy on 07 JUN 2017 for Wet age-related macular degeneration with 2mg into both eyes, every 4 weeks. The date of the last Eylea dose was unknown. On 22 APR 2019, the patient died from an unknown cause. A death certificate/autopsy report was not provided. Causality assessment was reported as not related to Eylea treatment. Medical history included Type 2 diabetes mellitus and concomitant medications were unknown.	Non medically confirmed.
[redacted] UNITED STATES study/observational study 59 Years male	1) Death (s); 2) Neovascular age-related macular degeneration (s); 3) Barrett's oesophagus (s); 4) Normal tension glaucoma (s); 5) Posterior capsule opacification (s);	1) Death: fatal; 2) Neovascular age-related macular degeneration: unknown; 3) Barrett's oesophagus: unknown; 4) Normal tension glaucoma: not recovered / not resolved;	started Aflibercept for proliferative diabetic retinopathy with macular edema on 29 JUN 2016, both eyes, every 6 weeks. He received the last Eylea dose on 22 MAR 2019. On an unknown date in MAY 2019, the patient passed away. A death certificate/autopsy report was not provided. According to the physician the patient's death was not related to Eylea. Additional systemic events are Barrett’s esophagus and knee operation along with the ocular events of Neovascular age-related macular degeneration, Normal tension glaucoma, Posterior capsule opacification, Eye hemorrhage, Visual acuity reduced, Foveal	Medically confirmed. physician assessed patient's death was not related to Eylea.

Table 16-18: Cases with bilateral treatment and systemic events

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Outcome (Event)	Case Description	Comment
	6) Eye haemorrhage (s); 7) Visual acuity reduced transiently (n); 8) Foveal reflex abnormal (n); 9) Anterior chamber pigmentation (n); 10) Knee operation (n); 11) Eye pain (n);	5) Posterior capsule opacification: recovered / resolved; 6) Eye haemorrhage: unknown; 7) Visual acuity reduced transiently: recovered / resolved; 8) Foveal reflex abnormal: unknown; 9) Anterior chamber pigmentation: unknown; 10) Knee operation: unknown; 11) Eye pain: recovered / resolved;	reflex abnormal and Anterior chamber pigmentation. Medical history included diabetes, open angle glaucoma both eyes and pseudophakia.	
[redacted] UNITED STATES spontaneous/-- 67 Years female	1) Nausea (n); 2) Headache (n); 3) Musculoskeletal stiffness (n);	1) Nausea: unknown; 2) Headache: unknown; 3) Musculoskeletal stiffness: unknown;	Initiated Eylea therapy into both eyes on an unknown date in 2018 for macular edema and diabetic retinopathy. The patient received an injection into the left eye every two months, and an injection into the right eye every month. Patient received an unknown total number of doses of Eylea. The patient received the last Eylea dose on 10 MAY 2019 in the right eye. On 11 MAY 2019 the patient experienced nausea, headache and a stiff neck. Past medical history included diabetes mellitus	Non-Medically confirmed
[redacted] UNITED STATES study/observational study 86 Years	1) Hernia (s); 2) Blindness unilateral (s); 3) Hypoacusis (s); 4) Cataract (s);	1) Hernia: unknown; 2) Blindness unilateral: not recovered / not resolved; 3) Hypoacusis: not	Patient initiated Eylea in October 2017 for unknown indication. Dosing was not specified. Frequency was every 4 weeks, then decreased to every 5 weeks and then to every 2 months, in both eyes. On 14 SEP 2018, patient experienced Hernia, Hearing impaired, Abdominal pain, Abdominal distension, Abdominal	Non-Medically confirmed.

Table 16-18: Cases with bilateral treatment and systemic events

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Outcome (Event)	Case Description	Comment
female	5) Abdominal pain (n); 6) Abdominal distension (n); 7) Hyperhidrosis (n); 8) Abdominal discomfort (n); 9) Blood pressure abnormal (n); 10) Eye injury (n); 11) Drug ineffective (n); 12) Palpitations (n);	recovered / not resolved; 4) Cataract: not recovered / not resolved; 5) Abdominal pain: unknown; 6) Abdominal distension: not recovered / not resolved; 7) Hyperhidrosis: recovered / resolved; 8) Abdominal discomfort: not recovered / not resolved; 9) Blood pressure abnormal: not recovered / not resolved; 10) Eye injury: not recovered / not resolved; 11) Drug ineffective: unknown; 12) Palpitations: unknown;	discomfort" and Hyperhydrosis, on unknown date palpitations and Blood pressure abnormal. Past medical history included Arthritis, Hypertension and Back problems.	
[redacted] UNITED STATES	1) Blood glucose increased (s);	1) Blood glucose increased: recovered /	Initiated Eylea on 15 AUG 2016 for Diabetic macular edema with severe non-proliferative diabetic retinopathy. Dosing was	Medical history of poorly-controller type 2

Table 16-18: Cases with bilateral treatment and systemic events

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Outcome (Event)	Case Description	Comment
spontaneous/-- 61 Years male	2) Malaise (s); 3) Mental status changes (n); 4) Product dose omission (n);	resolved; 2) Malaise: recovered / resolved; 3) Mental status changes: unknown; 4) Product dose omission: unknown;	2mg, every 4-6 weeks, in both eyes. On 18 JUN 2019, patient experienced Blood glucose increased, Malaise and on unknown date, he experienced Mental status changes. Eylea was continued. The patient's past medical history included poorly-controller type 2 diabetes, hypertension and hyperlipidemia	diabetes, hypertension and hyperlipidemia could be possible confounders for the events
[redacted] UNITED STATES spontaneous/-- 75 Years female	1) Headache (n); 2) Injection site pain (n); 3) Ocular hyperaemia (n); 4) Headache (n); 5) Injection site pain (n); 6) Ocular hyperaemia (n);	1) Headache: recovered / resolved; 2) Injection site pain: recovered / resolved; 3) Ocular hyperaemia: unknown; 4) Headache: recovered / resolved; 5) Injection site pain: recovered / resolved; 6) Ocular hyperaemia: recovered / resolved;	Initiated Eylea therapy on 28 MAY 2019 for the treatment of Macular degeneration in both eyes. Dosing was not specified. Eylea was scheduled for every 10 weeks, in both eyes, intravitreally. Patient received a total number of 2 doses of Eylea (1 in each eye). The last dose of Eylea was administered on 28 MAY 2019. On 28 MAY 2019 and 07 MAY 2019, she experienced headache. Other ocular events of ocular hyperemia and injection site pain were reported. Eylea was continued. Past medical history included Bleeding in retina in both eyes and occasional headaches from weather, hot or stress. Concomitant medications were not provided.	Non-Medically confirmed.
[redacted] UNITED STATES spontaneous/-- 63 Years male	1) Death (s);	1) Death: fatal;	Initiated Eylea therapy in December 2016 for the treatment of Diabetic macular edema, both eyes. Dosing was 2mg, every 3 weeks or as needed, in both eyes, intravitreally. Received an unknown total number of doses. The last dose of Eylea was administered on an unknown date. On 10 JUN 2019, the patient died from an unknown cause. The death certificate/autopsy report was not provided. According reporting physician, the event was not related to the Eylea. Past medical history included Diabetes. Concomitant medications were not provided.	Reporting physician, assessed the event was not related to the Eylea.

Table 16-18: Cases with bilateral treatment and systemic events

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Outcome (Event)	Case Description	Comment
[redacted] UNITED STATES study/observational study 96 Years female	1) Death (s);	1) Death: fatal;	Initiated Eylea therapy on 21 FEB 2017 for the treatment of Exudative age-related macular degeneration, both eyes, every 8 weeks with active choroidal neovascularization. Dosing and frequency were not specified. Patient received a total of 10 doses of Eylea. The patient received the last Eylea dose on 19 OCT 2017. On 17 MAR 2018, the patient died from an unknown cause. The death certificate/autopsy report was not provided. The patient's past medical history and concomitant medications were not provided.	Age (96 years) could be possible confounder.
[redacted] AUSTRALIA study/observational study 88 Years female	1) Cerebrovascular accident (s); 2) Mastectomy (s); 3) Vision blurred (n);	1) Cerebrovascular accident: unknown; 2) Mastectomy: unknown; 3) Vision blurred: unknown;	Started Eylea 40 mg/ml, both eyes on 16 JUN 2017 for Neovascular age-related macular degeneration with unknown dosing details. In MAY 2019, the patient experienced cerebrovascular accident, on an unknown date, the patient underwent mastectomy and experienced vision blurred. Action taken and outcome were unknown. Reporter assessed mastectomy to be unrelated to Eylea. Patient's medical history and concomitant medications were unknown.	Non-Medically confirmed.
[redacted] UNITED STATES study/observational study 92 Years male	1) Death (s);	1) Death: fatal;	Initiated Eylea therapy on 14 MAR 2017 for the treatment of Wet AMD/ Exudative age-related macular degeneration, bilateral, with active choroidal neovascularization, every 8 weeks (Q8W) in both eyes. Patient received a total of eighteen (18) doses of Eylea. The patient received the last Eylea dose on 21 JUN 2018. On 29 NOV 2018, the patient died from an unknown cause. The death certificate/autopsy report was not provided. Causality assessment was reported as not related to Eylea treatment. The patient's past medical history and concomitant medications were not provided.	Lack of information about cause of death, medical history and concomitant medications. Age (92 years) could be possible confounder.
[redacted]	1) Death (s);	1) Death: fatal;	Initiated Eylea therapy on 07 APR 2014 for the treatment of Age-	Lack of information

Table 16-18: Cases with bilateral treatment and systemic events

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Outcome (Event)	Case Description	Comment
UNITED STATES study/observational study 90 Years female			related Macular Degeneration. Dosing and frequency were not specified. Received a total of 42 doses of Eylea (11 OD (right eye), 27 OU (both eyes) and 4 OS (left eye)). The patient received the last Eylea dose on 12 OCT 2017. On an unknown date, the patient died from an unknown cause. The death certificate/autopsy report was not provided. Past medical history and concomitant medications were not provided.	about cause of death, medical history and concomitant medications.
[redacted] AUSTRALIA study/observational study 55 Years male	1) Diabetic complication (s); 2) Peripheral arterial occlusive disease (s);	1) Diabetic complication: fatal; 2) Peripheral arterial occlusive disease: unknown;	Started Eylea 40 mg/ml, both eyes from 22 MAR 2019 until 05 AUG 2019 for Diabetic macular edema. On 31 JUL 2019, the patient experienced thrombosis, 4 months 9 days after starting Eylea. On an unknown date, the patient experienced diabetic complication (seriousness criterion death). The patient died on 05 AUG 2019 and the reported cause of death was diabetes with unspecified complication. An autopsy was not performed. The reporter considered diabetic complication to be unrelated to Eylea. The patient's medical history included Diabetes.	Medical history of Diabetes could be possible reason for Diabetic complication.
[redacted] AUSTRALIA study/observational study 85 Years female	1) Cardiac disorder (s);	1) Cardiac disorder: unknown;	Patient started Eylea 40 mg/ml, both eyes on 03 SEP 2016 for Neovascular age-related macular degeneration. On an unknown date, the patient experienced cardiac disorder. Eylea treatment was not changed. medical history, event details and concomitant medications were not provided.	Non medically confirmed.

Table 16-18: Cases with bilateral treatment and systemic events

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Outcome (Event)	Case Description	Comment
[redacted] UNITED STATES study/observational study 67 Years male	1) Death (s); 2) Posterior capsule opacification (s); 3) Cataract (s); 4) Dry eye (n); 5) Presbyopia (n); 6) Myopia (n); 7) Cardiac disorder (n); 8) Hypertension (n); 9) Intraocular lens implant (n);	1) Death: fatal; 2) Posterior capsule opacification: not recovered / not resolved; 3) Cataract: not recovered / not resolved; 4) Dry eye: not recovered / not resolved; 5) Presbyopia: not recovered / not resolved; 6) Myopia: not recovered / not resolved; 7) Cardiac disorder: unknown; 8) Hypertension: unknown; 9) Intraocular lens implant: unknown;	Initiated Eylea therapy on 02 FEB 2018 for the treatment of Diabetes macula edema/Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, bilateral with 2 mg with frequency 6-8 weeks. Patient received a total of 8 doses of Eylea. The patient received the last Eylea dose on 06 MAR 2019. On 24 JUL 2019, the patient died from an unknown cause. A death certificate/autopsy report was not provided. On an unknown date, the patient experienced kidney failure, dialysis, heart problem (not specified) and high blood pressure. Patient also experienced other ocular events of posterior capsular opacification/ unspecified secondary cataract right eye, Keratoconjunctivitis sicca not specified as Sjorgrens (both eyes), Myopia (both eyes) and presbyopia. According to the physician, patient's death was not related to Eylea. Medical history included Kidney failure, Type 1 diabetes and Dialysis.	Physician assessed that death was not related to Eylea. Medical history included Kidney failure, Type 1 diabetes and Dialysis.
[redacted] UNITED STATES study/observational study 76 Years male	1) Death (s);	1) Death: fatal;	Initiated Eylea therapy on 20 SEP 2017 for the treatment of Exudative age-related macular degeneration, both eyes, with inactive choroidal neovascularization. Dosing and frequency were not specified. Patient received a total of 8 doses of Eylea. The patient received the last Eylea dose on 05 DEC 2018. On 05 MAR 2019, the patient died from an unknown cause. A death certificate/autopsy report was not provided. The patient's past	Cause of death, medical history and concomitant medications were not provided.

Table 16-18: Cases with bilateral treatment and systemic events

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Outcome (Event)	Case Description	Comment
			medical history and concomitant medications were not provided.	
[redacted] UNITED STATES study/observational study 80 Years male	1) Death (s);	1) Death: fatal;	Initiated Eylea therapy on 11 AUG 2014 for the treatment of Type 2 diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, both eyes. Dosing and frequency were not specified. Patient received a total number of 45 doses of Eylea. The patient received the last Eylea dose on 24 JAN 2019. On 15 MAR 2019, the patient died from an unknown cause. A death certificate/autopsy report was not provided. The patient's past medical history included Type 2 diabetes mellitus. Concomitant medications were not reported.	Cause of death and concomitant medications were not provided
[redacted] UNITED STATES study/observational study 88 Years female	1) Death (s);	1) Death: fatal;	Initiated Eylea therapy on 05 SEP 2014 for the treatment of Exudative age-related macular degeneration, both eyes, with active choroidal neovascularization. Dosing and frequency were not specified. Patient received total of thirty (30) doses of Eylea. The patient received the last Eylea dose on 07 DEC 2018. On an unknown date in April 2019, the patient died from an unknown cause. The death certificate/autopsy report was not provided. The patient's past medical history and concomitant medications were not provided.	Cause of death, medical history and concomitant medications were not provided
[redacted] UNITED STATES study/observational study 88 Years male	1) Death (s);	1) Death: fatal;	Initiated Eylea therapy on 03 APR 2012 for the treatment of Exudative macular degeneration with choroidal neovascularization, OU (both eyes). Dosing and frequency were not specified. Patient received 54 doses of Eylea in left eye (OS) and 4 doses in right eye (OD). The patient received the last Eylea dose on 02 JAN 2018. On an unknown date the patient died from an unknown cause. Death certificate/autopsy report was not provided. medical history and concomitant medications were not provided.	Cause of death, medical history and concomitant medications were not provided

Table 16-18: Cases with bilateral treatment and systemic events

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Outcome (Event)	Case Description	Comment
[redacted] UNITED STATES spontaneous/-- 77 Years female	1) Retinal vein occlusion (s); 2) Loss of consciousness (s); 3) Eye pain (s); 4) Endophthalmitis (s); 5) Intraocular pressure increased (s); 6) Visual impairment (n); 7) Vomiting (n); 8) Weight decreased (n); 9) Vitreoretinal traction syndrome (n);	1) Retinal vein occlusion: unknown; 2) Loss of consciousness: unknown; 3) Eye pain: recovered / resolved; 4) Endophthalmitis: unknown; 5) Intraocular pressure increased: unknown; 6) Visual impairment: not recovered / not resolved; 7) Vomiting: unknown; 8) Weight decreased: unknown; 9) Vitreoretinal traction syndrome: unknown;	Initiated Eylea therapy on June 2015 for the treatment of Wet Age-Related Macular Degeneration (AMD) in the right eye (OD), monthly. Patient initiated Eylea in the left eye (OS) on an unknown date in 2016 for Wet Age-Related Macular Degeneration (AMD). The patient was administered an injection in both eyes (OU) monthly until January 2018 and started using in the right eye from March 2019, monthly. Received an unknown total number of doses of Eylea. The patient received the last Eylea dose on an unknown date. On 18 JUL 2017, the day after the retinal detachment surgery, the patient began to experience vomiting, reported passing out and weight decreased. Ocular events of Retinal vein occlusion, Eye pain, Endophthalmitis, Intraocular pressure increased, Visual impairment and Vitreoretinal traction syndrome also reported. Action taken with Eylea was reported as dose not changed. The patient's past medical history and concomitant medications were not reported.	Non medically confirmed.
[redacted] UNITED STATES study/observational study 63 Years male	1) Cerebrovascular accident (s); 2) Myocardial infarction (s);	1) Cerebrovascular accident: recovered / resolved; 2) Myocardial infarction: --;	Started Eylea therapy on 12 OCT 2015 for the treatment of Exudative age-related macular degeneration with dose of 2 mg/ 5 ml, every 4 weeks. Received 27 doses of Eylea in both eyes prior the events. Last dose prior to the event was administered on 02 SEP 2017. On an unknown date in February 2018, the patient experienced stroke and in 2017, he experienced myocardial infarction. The patient's past medical history included Type 2 diabetes and smoking. Concomitant medications included Metformin, Valsartan/HCTZ (Hydrochlorothiazide), Plavix, Humalog, Amlodipine. Action taken with Eylea was dose	Medical history of Type 2 diabetes and smoking could be possible confounders for the events.

Table 16-18: Cases with bilateral treatment and systemic events

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Outcome (Event)	Case Description	Comment
			not changed.	
[redacted] UNITED STATES spontaneous/-- 86 Years female	1) Bladder cancer (s); 2) Periorbital swelling (n); 3) Erythema (n);	1) Bladder cancer: unknown; 2) Periorbital swelling: unknown; 3) Erythema: unknown;	Initiated Eylea therapy "maybe 5 years ago" for the treatment of Macular Degeneration in both eyes. Dosing was not specified. Frequency was reported as every 12 weeks in both eyes. Patient received an unknown total number of doses of Eylea. The last dose of Eylea was administered on an unknown date. On unknown date, patient experienced Bladder cancer. Ocular events of periorbital swelling and erythema. Eylea was continued. Medical history included High blood pressure, High cholesterol, Constipation and Dry eyes. Relevant tests/laboratory data were unknown. Concomitant medications were Hydralazine, Atenolol, Zetia, Refresh, MiraLax and Senokot.	Non medically confirmed.
[redacted] UNITED STATES spontaneous/-- 54 Years male	1) Toe amputation (s); 2) Osteomyelitis (s); 3) Cellulitis (s); 4) Off label use (n); 5) Product use in unapproved indication (n);	1) Toe amputation: unknown; 2) Osteomyelitis: unknown; 3) Cellulitis: unknown; 4) Off label use: unknown; 5) Product use in unapproved indication: unknown;	Initiated Eylea on an unknown date for the treatment of diabetes (pending clarification). Dosing was not specified. Frequency was reported as every 6 to 8 weeks in both eyes (OU). Patient received an unknown total number of doses of Eylea. The patient received the last Eylea dose on an unknown date. On an unknown date, the patient underwent surgery to amputate their right toe, because of osteomyelitis. Additionally, they developed cellulitis on their left toe. Eylea was not changed (ongoing). The patient's past medical history included Osteomyelitis and Diabetes.	Medical history of Osteomyelitis and Diabetes could be confounder for Osteomyelitis.

Table 16-18: Cases with bilateral treatment and systemic events

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Outcome (Event)	Case Description	Comment
[redacted] SOUTH AFRICA study/observational study 48 Years male	1) Cerebrovascular accident (s);	1) Cerebrovascular accident: --;	Patient started Eylea, 2 vials (both eyes) on 11 OCT 2019 for Age-related macular degeneration. On an unknown date, the patient experienced cerebrovascular accident. The reporter considered cerebrovascular accident to be unrelated to Eylea. The patient's past medical history, outcome and concomitant medications were not reported.	Reporter assessed cerebrovascular accident to be unrelated to Eylea
[redacted] UNITED STATES study/interventional study 66 Years female	1) Cerebrovascular accident (s);	1) Cerebrovascular accident: recovered / resolved with sequelae;	Received Aflibercept 2.0 mg, both eyes on 31 AUG 2017 for Diabetic macular edema. This was the only dose administered before the event onset. Study drug was continued. On 13 OCT 2017 patient was hospitalized due to stroke. The patient's relevant medical history included Type 2 diabetes mellitus, Cardiac failure congestive, Hypertension, Myocardial infarction.	Medical history included Type 2 diabetes mellitus, Cardiac failure congestive, Hypertension, Myocardial infarction are the possible confounders.
[redacted] UNITED STATES spontaneous/-- 71 Years female	1) Eye irritation (n); 2) Eye pruritus (n); 3) Eye pain (n); 4) Sensation of foreign body (n); 5) Visual impairment (n); 6) Vision blurred (n); 7) Rhinorrhoea (n); 8) Oesophageal disorder (n);	1) Eye irritation: unknown; 2) Eye pruritus: unknown; 3) Eye pain: unknown; 4) Sensation of foreign body: unknown; 5) Visual impairment: unknown; 6) Vision blurred: unknown; 7) Rhinorrhoea: unknown; 8) Oesophageal disorder: unknown;	Initiated Eylea therapy intravitreally (IVT) in both eyes, in MAY 2019 for the treatment of Wet macular degeneration. Dosing and frequency were not specified. Patient received an unknown total number of doses of Eylea. The patient received the last Eylea dose on an unknown date. On unknown date, she developed rhinorrhea and unspecified disorder of esophagus. Ocular events of Eye irritation, Eye pruritus, Sensation of foreign body, Visual impairment also reported. Eylea dose was not changed. Medical history included history of stroke, hyperlipidemia, Gastroesophageal reflux disease, thyroid disorder, anxiety, spinal stenosis, osteoarthritis. Concomitant medications included Plavix, Atorvastatin, Omeprazole, Levothyroxine, Fluoxetine, Alprazolam, Nitroglycerin, Centrum Silver, Caltrate, Ocuvite, and Meloxicam.	Gastroesophageal reflux disease could be confounder for the Esophageal disorder.

Table 16-18: Cases with bilateral treatment and systemic events

Case ID / Country / Source / Age / Gender	Preferred Term (Seriousness) (Event)	Outcome (Event)	Case Description	Comment
[redacted] AUSTRALIA study/observational study 72 Years male	1) Cataract operation (s); 2) Photophobia (n); 3) Blood glucose decreased (n); 4) Injection site discomfort (n); 5) Headache (n);	1) Cataract operation: recovered / resolved with sequelae; 2) Photophobia: not recovered / not resolved; 3) Blood glucose decreased: recovering / resolving; 4) Injection site discomfort: recovered / resolved; 5) Headache: --;	Started Eylea 40 mg/ml, both eyes for Diabetic macular edema in November 2018. Total of injections were unknown. On unknown date, the patient was found to have blood glucose decreased and headache. The reporter considered blood glucose decreased to be unrelated to Eylea. Patient also experienced ocular events of injection site discomfort, cataract operation, and photophobia. Medical history included Bilateral cataracts and Diabetes.	Diabetes could be confounder for the event Blood glucose decreased.
[redacted] THAILAND spontaneous/-- -- male	1) Cardiac failure (s); 2) Cardiac failure (s);	1) Cardiac failure: --; 2) Cardiac failure: --;	Started Eylea 40 mg/ml, 2 mg for Diabetic macular edema on 06 AUG 2019. Patient experienced one episode of heart failure in September 2019 and another on unknown date. Medical history/concurrent conditions, therapy details and concomitant medications were not reported.	Lack of information about Medical history/concurrent conditions, therapy details and concomitant medications.

Summary

A total of 59 cases were received during the reporting period with bilateral Eylea injections. Exact treatment dates for both eyes are missing in most of these cases. In 22 cases, there was no information about medical history and concomitant medication. The occurrence of systemic events reported in the remaining cases is mainly explained by the medical history, risk factors and/or patient`s age.

There were 23 cases with reported death (majority of cases from US reimbursement program N=21) out of 59 reports. No autopsy report/cause of death reported in all 59 cases. In 11 reports, there was no information about medical history/concomitant medication. In remaining cases, underlying relevant medical history was presented. Elderly age can be regarded to be a potential confounder for all the 23 death cases.

Overall, there is no pattern of certain adverse events which would be indicative for a concern of bilateral treatment with Eylea.

Conclusion

To date, bilateral therapy of aflibercept has not been associated with an increased risk of systemic safety findings. From the information on bilateral treatment received during this period no new concern with regards to a potential risk of systemic events can be observed.

16.3.24 Long-term Safety beyond 2 Years

No relevant information on long-term safety beyond 2 years was received during this reporting period.

16.4 Characterization of Risks

The information provided for this section is identical to the content of the Part II Module SVII, “Identified and potential risks” of the current EU-RMP version 26.1 which was valid at the beginning of the reporting period. The respective module is provided in **Appendix 11.**

16.5 Effectiveness of Risk Minimizations

The PASS (Measurement of Effectiveness Study) to assess Physician and Patient Knowledge of Safety and Safe Use Information for Aflibercept in Europe, # 16526, was completed during the reporting period of PSUR#7. The CSR was submitted to EMA for evaluation in 2017. Based on review the EMA requested an update and re-distribution of the Educational Materials according to the Type II variation assessment report (EMEA/H/C/002392/II/0039). The updated Educational Material for HCPs will include highlighted information regarding treatment of women of child-bearing potential, information on the injection procedure with respect to unnecessary dilation of the eye, with the need for vision and intraocular pressure evaluation after the injection as well as potential for medication misuse, particularly re-use of the vial. The effectiveness of the updated educational material will be evaluated for HCP

knowledge and understanding by a follow-up survey. The new study (cross-sectional survey) has started to measure the effectiveness of risk minimization activities, as committed towards EMA, after the distribution of revised educational material to ophthalmologists in Europe. The study is conducted in the same five countries as the first such study for Eylea and data collection started on 07 OCT 2019.

Table 16-19: Additional PV activity (Measurement of Effectiveness Study)

Study Status	Objectives	Safety concerns addressed	Milestones	Due dates
Follow-up survey to evaluate effectiveness of updated educational material (Study # 20285; PASS)	To evaluate: • The level of physicians' knowledge and understanding of key safety information contained in the prescriber guide especially on use during pregnancy, evaluation of vision and monitoring IOP post injection, and to identify potential misuse, including reuse of the vial	• Transient intraocular pressure increase (evaluation of vision and monitoring of IOP post injection) • Embryofetotoxicity (use during pregnancy) • Medication error and misuse (identify Potential misuse, including reuse of the vial)	**Study** 1. Protocol submission 2. Study start 3. Study report	As agreed with EMA, submission on 25 JUN 2018 Started in 4Q/2019 submission APR 2021 (estimated)

17. Benefit Evaluation

17.1 Important Baseline Efficacy / Effectiveness Information

Neovascular AMD:

AMD is the most common degenerative disease of the macula and is the most common cause of legal blindness in the developed world. AMD is a disease of the elderly, and evidence suggests that 10% of individuals aged 65 to 74 years, and 30% of those aged 75 to 85 years, show signs of AMD.

Primary and secondary efficacy results in phase 3 studies (VIEW 1 and VIEW 2) showed robust benefits. The results of these studies (both of the individual studies and the pooled analysis with consistent results over all parameters investigated) confirmed the non-inferiority

in improving VA not only of the aflibercept dosage schedules 0.5Q4 and 2Q4 but also of the treatment schedule 2Q8 (after three initial monthly doses) when compared to ranibizumab 0.5Q4. The clinical benefit of the treatment with aflibercept with respect to improving VA and its similarity to ranibizumab was also reflected in the analysis of secondary and additional efficacy endpoints used in these studies. The results in Year 2 of the pivotal studies showed that the improvements achieved by Week 52 (the time of the confirmatory primary efficacy analysis) were largely maintained on modified quarterly dosing up to the regular study end at Week 96. The ALTAIR Phase IV study showed that using a Treat and Extend algorithm treatment intervals in AMD can already be extended after 3 monthly followed by on treatment interval every two months up to 16 weeks using adjustments intervals of 2 and 4 weeks, respectively. Visual benefits were generally maintained in the ALTAIR study through the end of the study at Week 96.

As demonstrated in these two pivotal studies and in the Phase 4 ALTAIR study, the main benefit of less frequent dosing compared to the approved substance ranibizumab, is the reduction of the burden associated with the injection procedure itself and the reduction of monthly monitoring of subjects.

Furthermore, the subgroup analyses showed that there are no restrictions regarding efficacy of aflibercept in relation to organ function such as renal impairment, liver function or diabetes status.

The results from the primary and confirmatory secondary efficacy endpoints of the SIGHT study showed that aflibercept treatment was clinically and statistically superior to PDT treatment at Week 28. Visual improvements observed after 28 weeks of treatment with aflibercept were maintained, with a trend of further improvement, through 52 weeks of the study. Substantial visual and morphological improvements were observed in the PDT→ aflibercept group after initiating aflibercept treatment at Week 28. Visual and morphological improvements were greater in the aflibercept group than in the PDT→ aflibercept group at Week 52, suggesting early initiation of treatment with aflibercept may provide greater benefits than later initiation. Aflibercept was generally well tolerated over 52 weeks including by subjects who were switched from PDT treatment.

The safety profile of aflibercept observed in this study was consistent with other studies with aflibercept conducted outside of China.

In the VIEW1 extension study, visual acuity as measured by BCVA was largely maintained with repeated long-term treatment (beyond 2 years), and treatment with Eylea was generally safe and well-tolerated. No new safety signals were observed in this long-term extension study.

Retinal Venous Occlusive Disease:

Retinal venous occlusive disease is an important cause of vision loss particularly in patients with associated chronic macular edema. Depending on the site of the occlusion, the disease is subdivided into CRVO and BRVO.

CRVO: The results of the two-phase III studies in patients with macular edema due to CRVO, COPERNICUS and GALILEO, demonstrated the efficacy of monthly injections of 2 mg aflibercept. In the COPERNICUS study the proportion of patients gaining at least 15 letters of vision (primary endpoint at Week 24) was significantly higher in patients treated with aflibercept than in patients treated with sham injections (56.1% versus 12.3%; $p<0.001$). In the GALILEO study at Week 24, also more than half of subjects in the aflibercept 2Q4 group (60.2%) gained at least 15 letters of vision compared to 22.1% of subjects in the sham group ($p<0.001$). Benefits gained through the first 24 weeks were largely maintained during the PRN regimen in the Galileo and Copernicus study. The results of the individual studies (including sensitivity and subgroup analyses) and the integrated analysis were consistent over all investigated parameters and confirmed the superiority of aflibercept for improving visual acuity over sham treatment in subjects with macular edema secondary to CRVO.

BRVO: VIBRANT was a randomized, double-masked, sham-controlled, phase III study of the efficacy, safety of repeated IVT administration of aflibercept in subjects with macular edema secondary to BRVO. These results support that treatment with 2 mg aflibercept provides superior efficacy to macular grid laser treatment. Visual improvement in macular edema secondary to BRVO with aflibercept was rapid, being seen as early as after the first 4 weeks and was maintained through Week 24 with monthly injections and also on an extension of the treatment interval starting at Week 24 to bimonthly aflibercept administration until the end of the study. In addition to the observed vision gain, patients also showed improvements in morphology as assessed by OCT.

Diabetic Macular Edema

Diabetic macular edema is a serious, sight-threatening complication of diabetes mellitus, which itself is a common disease of industrialized societies with an increasing number of involved patients. The phase II study (DAVINCI) investigating therapeutic effect of aflibercept in patients with DME demonstrated statistically significant improvements in mean BCVA and CRT compared to laser. Based on the favorable results of DAVINCI, a phase III program, consisting of 3 randomized, controlled studies (VISTA DME, VIVID DME, and VIVID EAST) and compared 2 mg IVT injections of aflibercept given at 4- or 8-week intervals, to macular laser photocoagulation (laser) for up to 3 years.

At the primary endpoint at 52 weeks VIVID DME and VISTA DME demonstrated for the primary and the secondary efficacy results robust benefits of aflibercept for either dosing regimen. Notably, gains of ≥15 letters in BCVA from baseline were reported in 31.1% to 41.6% of subjects in the aflibercept groups across the 2 studies. An improvement of ≥15 letters in BCVA from baseline is clinically important because it is noticeable by and relevant to almost all patients and has been correlated with significant improvements in several functional activities. The superior effect of either aflibercept regimen over laser was maintained through Week 100 and week 148.

The study design of the VIVID EAST study was similar to VIVID DME. The primary endpoint was assessed at Week 52. The results of this study confirmed the results week 52 results from VIVID DME and VISTA.

These study results consistently indicated that aflibercept leads to clinically important treatment benefits in patients with DME and thus is likely to add to the currently available therapeutic armamentarium for DME management.

Myopic Choroidal Neovascularization

In adults younger than 75 years of age choroidal neovascularization (CNV) secondary to pathologic myopia is a frequent cause of vision loss. This condition is also referred to as mCNV.

The MYRROR (study 15170) was a randomized, double-masked, sham-controlled, phase III study of efficacy and safety of repeated IVT administration of aflibercept in Asian subjects with myopic CNV. All of the 122 randomized subjects received at least one study treatment; there were 91 randomized subjects in the aflibercept 2 mg group and 31 in the control group. After Week 24, patients of the control group were treated with aflibercept and all patients were followed until Week 48.

The primary efficacy analysis determined the difference in VA of either aflibercept 2 mg or sham injections after 24 weeks. At Week 24, the difference between treatment groups from baseline was 14.1 letters, 95% CI, 10.8, 17.4 ($p<0.0001$) in the full analysis set (FAS) (using the last observation carried forward principle, LOCF). The confirmatory secondary efficacy variable was the proportion of subjects who gained ≥15 letters in BCVA at Week 24, which was 38.9% in the aflibercept group and 9.7% in the control group ($p=0.0001$).

In conclusion, in the MYRROR study aflibercept 2 mg was shown to be effective in the treatment of visual impairment due to mCNV.

Neovascular Glaucoma

Neovascular glaucoma (NVG) is a secondary glaucoma triggered by the formation of new blood vessels (neovascularization) on the iris and the anterior chamber angle. Neovascular glaucoma is a serious condition that may lead to permanent loss of vision, a persistently painful eye and, especially in the advanced stages.

Bayer investigated Eylea treatment in NVG in the randomized, double-masked, sham-controlled phase 3 study in Japanese patients with NVG (VEGA Study, 17584).

A total of 54 subjects were randomized into the aflibercept group (N=27) and the sham group (N =27). The difference between the treatment groups in least square mean change of IOP from baseline to Week 1 (primary endpoint) was −4.9 mmHg, with a 95% CI of −10.2 to 0.3 mmHg with an upper limit of the CI above zero ($p = 0.0644$, analysis of covariance model, including treatment group and stage of NVG for randomization as fixed effect and baseline IOP as a covariate). Thus, the superiority of the aflibercept group over the sham group was not demonstrated statistically. However, the change in IOP in the aflibercept group was −9.9

mmHg (LS mean change), which was comparable to the expected clinically meaningful reduction used to design the study (assumption for the determination of sample size: mean ± SD of −10 ± 12 mmHg for the aflibercept group).

The proportion of subjects with improvement in the grade of neovascularization of the iris (NVI) at Week 1 was 70.4% in the aflibercept group and 11.5% in the sham group. In the aflibercept group, IOP (mean ± SD) decreased to 24.5 ± 12.0 mmHg pre-dose at Week 1 from baseline (33.0 ± 9.9 mmHg), and further decreased to 17.8 ± 9.0 mmHg by Week 9.). In the sham group, IOP pre-dose at Week 1 decreased slightly from baseline (36.7 ± 9.1 mmHg) to 31.8 ± 10.3 mmHg. The proportion of subjects in whom the IOP was controlled (≤21 mmHg) in the aflibercept group was 44.4% at Week 1. In the sham group, the proportion of subjects in whom the IOP was controlled was only 7.4% at Week 1. The proportion of subjects with improvement in NVA grade at Week 1 was 59.3% in the aflibercept group and 11.5% in the sham group. For all outcome measures mentioned there was a general trend for maintained benefit until the end of the VEGA study.

The second study in the indication NVG (VENERA study) was completed during this reporting period, see next section on newly identified information on efficacy.

17.2 Newly Identified Information on Efficacy / Effectiveness

An additional phase 3, single-arm, non-randomized and open-label study evaluating the efficacy, safety and tolerability of a single injection of 2 mg aflibercept IVT aflibercept at baseline in a total of 16 Japanese patients with neovascular glaucoma was completed (VENERA study). The primary endpoint (change in IOP from baseline to Week 1) showed a significant reduction in IOP of 8.3 ± 7.3 mmHg with a two-sided 95% CI of -12.2 to -4.4 mmHg (p = 0.0004). No new safety signal was derived from this study.

In the Regeneron sponsored PANORAMA study, patients with moderately severe to severe NPDR were randomized 1:1:1 to receive aflibercept every 8 weeks following 5 initially monthly doses (2q8), aflibercept every 16 weeks following 3 initial monthly doses and 1 q8 interval, and sham injections. The primary outcome measure of the study is the proportion of patients who have improved by ≥2 steps from baseline on the DRSS in the combined 2Q8 and 2Q16 groups at week 24, and in each group separately at week 52.

At week 24, a significant proportion of patients in the combined aflibercept dosing groups had a ≥2 step improvement from baseline on the DRSS compared to patients receiving sham injections (58% vs 6%). At week 52, 80% and 65% of patients in the 2Q8 and 2Q16 dosing groups, respectively, had a ≥2 step improvement, compared to patients receiving sham injections (15%). In addition, there was a 82-85% reduction in the number of patients developing a vision-threatening complication (VTC, defined as proliferative diabetic retinopathy/anterior segment neovascularization) and a 68-74% reduction in the number of patients developing center-involved diabetic macular edema (CI-DME) in the 2Q8 and 2Q16 aflibercept dosing groups compared to sham treatment. At week 100, the results seen at week 52 results were largely maintained with 50% and 62% of patients in the 2Q8→PRN and 2Q16

dosing groups, respectively having a ≥2 step improvement, compared to 12.8% patients receiving sham injections. There was a 77-83% reduction in the number of patients developing a VTC and a 68-76% reduction in the number of patients developing CI-DME over 100 weeks in the 2Q8→PRN and 2Q16 aflibercept dosing groups compared to sham treatment. No new safety signals were identified in this study. Aflibercept was shown to have a significant benefit for the treatment of diabetic retinopathy and reduction in the risk of VTCs and/or CI-DME. The final clinical study report (CSR) is currently being finalized.

17.3 Characterization of Benefits

Aflibercept 2 mg was shown to be effective in the treatment of visual impairment due to wet AMD, DME, RVO; mCNV, and NVG. The safety profile of aflibercept was similar across the indications. Overall, aflibercept was well tolerated and ADRs were mainly those known to be linked to the intravitreal injection procedure.

Overall, all newly received information in approved indications support efficacy results at the beginning of the reporting period.

18. Integrated Benefit-Risk Analysis for Approved Indications

18.1 Benefit-Risk Context – Medical Need and Important Alternatives

18.2 Neovascular AMD

The treatment paradigms for neovascular AMD have shifted tremendously since IVT anti-VEGF treatment have become standard-of-care in recent years. As a consequence, most previous therapy approaches are either obsolete or are applied in exceptional cases only.

Therapies before the Anti-VEGF Era

Therapies used before the introduction of IVT anti-VEGF therapies are currently either obsolete like surgical therapies and thermal laser photocoagulation. Generally, such therapies carry a high risk of immediate intervention-related deterioration of the visual function and at best stabilize visual acuity.

Photodynamic therapy using verteporfin offered some improvement over thermal laser photocoagulation. PDT combines the intravenous infusion of the light-sensitive dye verteporfin with a low-intensity laser treatment of the CNV. The trans-corneally applied laser energy activates the photodynamic dye to release free radicals, causing occlusion of the abnormal choroidal vessels. PDT has been shown to be beneficial in the treatment of certain types of CNV in advanced wet AMD. It is superior to conventional laser photocoagulation for lesions that involve the central macula because of its ability to selectively target pathological vascular tissue with sparing of the normal overlying tissue. Most patients treated with PDT require three to four treatments per year, depending on the presence of persistent leakage of the treated lesion on post-treatment angiography. On average, PDT leads to a stabilization of visual acuity only. Relevant improvements of visual acuity are seen only infrequently. PDT

treatment has been used until recently in a sizeable subset of patients with the PCV subtype of neovascular AMD. However, more recent clinical studies, especially ALTAIR (see Section X) have shown that IVT anti-VEGF therapy may lead to comparably better visual outcomes and comparable control of disease activity.

Anti-VEGF Therapy

Today, anti-VEGF therapy is the standard of care in the treatment of neovascular AMD. It results in improved vision in many subjects and provides vision stabilization to most subjects by directly blocking VEGF as a key player in pathophysiology of neovascular AMD. Unlike PDT, which temporally occludes the CNV, anti-angiogenic therapy prevents further neovascularization and reduces leakage from existing vessels.

At the time of the start of the pivotal phase 3 studies for aflibercept, the two anti-VEGF agents approved by the US Food and Drug Administration (also known as FDA) and the EMA, as well as other countries, for the treatment of neovascular AMD were pegaptanib and ranibizumab.

Pegaptanib (Macugen; Pfizer), an RNA aptamer, has been proven to reduce vision loss; it was approved by the FDA in 2004 and in Europe in 2006. It is injected into the vitreous every six weeks, where it binds to the VEGF-A165 isoform. In the phase III VEGF Inhibition Study in Ocular Neovascularization (VISION), IVT injection of pegaptanib slowed visual loss in neovascular AMD, and 6% of pegaptanib-treated subjects gained 15 letters or more compared with 2% in the control group. Pegaptanib is currently used in clinical practice only very infrequently.

Ranibizumab (Lucentis; Genentech-Roche/Novartis), an IVT injected antibody fragment that binds all VEGF-A isoforms, brought significant innovation to the treatment of neovascular AMD. Demonstrating thus far unparalleled efficacy, it was approved in the US, the EU, Switzerland, Australia, Japan, and other countries around the world for the treatment of neovascular AMD.

In the two pivotal clinical ranibizumab studies (MARINA and ANCHOR), ranibizumab was IVT injected at monthly dosing intervals. At 12 months, vision was maintained (defined as loss of <15 letters) in approximately 95% of the subjects in both studies, as compared to 62% (sham, MARINA) and 64% (PDT, ANCHOR) in the control arms. Importantly, unlike previously available therapies, ranibizumab not only stopped vision loss but improved vision in many subjects. Ranibizumab resulted in a gain of at least 15 letters in at least 1/3 of subjects in both pivotal studies. Mean visual acuity improved from baseline in the MARINA study by 6.9 to 7.2 letters and in ANCOR by 8.5 to 11.3 letters.

Ranibizumab is highly efficacious if applied every month, as was done in the MARINA and ANCHOR studies. Apart from the potential of serious risk associated with each procedure of IVT injection, it has turned out that monthly treatment, which may continue for a subject's lifetime, is very burdensome to subjects, their caregivers, ophthalmologists and the healthcare system. Although acknowledged as the most effective regimen for this agent, the monthly

treatment with ranibizumab is often altered to less frequent dosing intervals to reduce the associated treatment burden; this, however, may result in notably reduced efficacy with even loss of vision mid to long term despite formally continued treatment.

A need for improving the benefit risk balance by reducing the patient burden with less frequent injections and also injection related safety events has led to attempts to individualize therapy and thereby reduce injection frequency in an eligible subset of patients.

Before the approval of aflibercept, there was a compelling need for a treatment for neovascular AMD, which is efficacious and also reasonably convenient under real-life conditions. Aflibercept is able to address this medical need by allowing treatments with a fixed bi-monthly interval (after three initial monthly doses) without the need for in-between monitoring visits. During this report period for patients with neovascular AMD an alternative posology has been introduced. Using a Treat&Extend regimen after 3 monthly injections followed by one injection after 2 months, phsyicians can extend the treatment interval based on visual and/or anatomic outcome assessments at injections visits Still treating physicians can determine the schedule for monitoring, which may be more frequent than the schedule of injections. Such dosing regimens relevantly reduce the burden of treatment for neovascular AMD from a patient's and healthcare system's perspective.

18.3 Retinal Venous Occlusive Disease

Retinal venous occlusive disease (RVO) is an important cause of vision loss particularly in patients with associated chronic macular edema. Depending on the site of the occlusion, the disease is subdivided into CRVO, and BRVO.

At the time of the start of the aflibercept clinical development program for RVO in July 2009, the standard of care for macular edema secondary to RVO was observation until progression to anterior segment neovascularization, at which time patients were treated with panretinal photocoagulation (PRP). However, in the past 5 years, several major trials have investigated new therapeutic modalities for the treatment of macular edema secondary to RVO and the management of RVO has fundamentally changed.

Intravitreal Anti-VEGF Agents

Ranibizumab (Lucentis; Genentech-Roche/Novartis) was the first anti-VEGF therapy approved in the US and EU as a treatment for macular edema due to RVO. In the CRUISE study, monthly IVT ranibizumab injections of 0.3 mg or 0.5 mg lead to a mean change from baseline in BCVA of +12.7 letters and +14.9 letters, respectively, after 6 months (primary endpoint), the sham group gained +0.8 letters. At 12 months, when treatments were administered as needed (PRN) rather than monthly and sham patients were eligible to receive 0.5 mg ranibizumab, BCVA was generally maintained, but did not continue to improve, indicating that the best mode of treatment had not yet been determined. The mean change from baseline in BCVA score was +13.9 letters in both ranibizumab groups, and +7.3 letters in the sham/0.5 mg ranibizumab group.

Corticosteroids

Ozurdex is an IVT dexamethasone implant that was designed to deliver intraocular therapeutic levels of dexamethasone for the treatment of macular edema following BRVO or CRVO. The pivotal trial compared a single dexamethasone implant, at a dose of 0.7 mg or 0.35 mg, to a sham implant. The percentage of eyes with CRVO-ME achieving a 15 letter improvement in visual acuity was significantly higher in both Ozurdex groups than in the sham group, with the maximal effect seen at Day 60. However, by Day 90 and Day 180, there was no significant difference between groups. The incidence of ocular AEs was not reported separately for patients with macular edema due to CRVO, and overall did not differ significantly between the both dose groups. In both groups, there was a higher incidence of ocular hypertension at Day 60, and by Day 180, approximately 24% of patients with dexamethasone implants required IOP-lowering medication, while five patients required a surgical/laser procedure to reduce IOP. There was also a significant increase in anterior chamber neovascularization in both dose groups compared with sham, but no significant increase in the risk of incident cataract at 180 days.

Triamcinolone acetonide (Trivaris) is approved for IVT use in other diseases (e.g. uveitis) but not for macular edema secondary to RVO. In the Standard Care versus Corticosteroid for RVO (SCORE) trial, patients received either 1 mg or 4 mg IVT triamcinolone injections every 4 months, or observation alone. Both doses were associated with a 5-fold increase in the odds of achieving a 15 letter gain in visual acuity at 12 months. There also was a mean decrease in OCT-measured center point thickness across all study groups, but there was no statistically significant difference. Additionally, 35% of patients treated with 4 mg and 20% of patients treated with 1 mg required IOP lowering treatments by 12 months, compared with 8% of patients in the control group. Similarly, at 12 months, there was new lens opacity, or progression of existing lens opacity, in 33% of patients in the 4 mg group and 26% of patients in the 1 mg group, compared to 18% of patients in the control group.

Other Therapies and Interventions

Other experimental systemic therapies and interventions have been tried, but generally have not been successful or rigorously studied. These include hemodilution, streptokinase, anticoagulants, tissue plasminogen activator, oral pentoxifylline, and hyperbaric oxygen therapy.

The Central Vein Occlusion Study (CVOS) Group demonstrated that macular grid laser photocoagulation is not beneficial for eyes with macular edema associated with CRVO. Patients showed no significant improvement in vision after 3 years of treatment with grid laser therapy, although fluorescein angiographic leakage was reduced. In the same study, scatter laser photocoagulation decreased the risk of NVG among patients with iris neovascularization.

Panretinal laser photocoagulation (PRP) is useful for the treatment of neovascular complications associated with RVO and in particular CRVO. However, the CVOS Group demonstrated that prophylactic PRP is not indicated, and instead, PRP should be administered

only after the onset of iris or retinal NV to prevent development of NVG and other retina ischemic sequelae such as vitreous hemorrhage or retinal traction.

A variety of surgical interventions for the treatment of CRVO have been tried, including chorioretinal venous anastomosis formation, radial optic neurotomy, and pars plana vitrectomy. These approaches have had variable success, have not been rigorously studied, and do not currently have a prominent role in the management of CRVO.

Recent studies and approvals have provided new options for the management of RVO, but medical need still exists. The options are not mutually exclusive, but choices should be made based upon relative benefit risk ratios as to which option becomes first-line treatment and which take on adjunctive roles.

Ranibizumab is highly efficacious if applied every month, as studied in CRUISE. However, there still is a high medical need for a drug with longer durability that would allow an extension of the dosing intervals, thereby reducing the burden of treatment for patients, ophthalmologists and the healthcare system.

While Orzudex is offering such longer treatment intervals, the benefit-risk ratio of this IVT dexamethasone implant is probably inferior to anti-VEGF drugs, with efficacy at best similar to ranibizumab or aflibercept and additional safety issues that are not present (or much less frequent) with anti-VEGF drugs, like IOP increase and cataract development.

Therefore, prior to the approval of aflibercept, there was a compelling need for a longer-lasting treatment of macular edema due to RVO, which is similar in efficacy and safety to ranibizumab, but offers the opportunity to prolong dosing and monitoring intervals beyond monthly.

18.4 Diabetic Macular Edema

Standard treatment of DME has been focal/grid laser photocoagulation, as well as vitrectomy for advanced stages of DR and some selected cases of DME. The disadvantage of macular laser photocoagulation treatment and surgical therapy is the limited number of patients showing significant gain in visual acuity. Many patients still lose visual acuity despite these procedures, and in some cases, vision is further compromised as a result of the intervention. Therefore, and due to the significant unmet need for a less invasive and more effective pharmacological therapy for DME, ophthalmologists had turned to off-label usage of pharmacological compounds to improve visual outcomes and to avoid the disadvantages of laser and surgical treatments.

Anti-VEGF compounds have become the standard of care for the treatment of DME. This approach is highly attractive, as it directly targets VEGF, one of the main mediators of DR and DME. The first results reported for anti-VEGF agents in case reports suggesting effectiveness were later supported by large, randomized, laser-controlled trials by the Diabetic Retinopathy Clinical Research Network (DRCRnet), using ranibizumab. These data were later confirmed by the Phase II study RESOLVE and the phase III studies RISE, RIDE and

RESTORE which led to the approval of ranibizumab for the treatment of DME. However, prior to the approval of aflibercept, there was still was a need for a drug with longer durability that would allow an extension of the dosing intervals, thereby reducing the burden of treatment for patients, ophthalmologists and the healthcare system.

Ozurdex® is an erodible intravitreal dexamethasone implant that was designed to deliver intraocular therapeutic levels of dexamethasone for the treatment of adult patients with visual impairment due to diabetic macular edema who are pseudophakic or considered insufficiently responsive to or unsuitable for non-corticosteroid therapy. While Ozurdex® is offering longer treatment intervals, the benefit-risk ratio of this intravitreal dexamethasone implant is probably inferior to anti-VEGF drugs, with efficacy at best similar to ranibizumab or aflibercept and additional safety issues that are not present (or much less frequent) with anti-VEGF drugs, like IOP increase and cataract development.

ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg is a non-erodible implant injected into the eye (vitreous) and is approved by the FDA for the treatment of DME in patients who have been previously treated with a course of corticosteroids and did not have a significant increase in eye pressure. A single implant delivers fluocinolone acetonide, a steroid, for 36 months. A UK real world effectiveness study of ILUVIEN was a retrospective study from data collected from patient medical records in DME subjects. After administration of the implant, visual acuity improved in 18% of subjects by 15 or more letter and anatomic improvements were robust. However, was a small and significant increase in the median IOP observed at 12 months, requiring IOP lowering therapy in 15% of subjects (Holden et al. 2017 (158)). The risk of subsequent cataract development and IOP rise may further increase over time due to the long-term delivery of steroid to the back of the eye of up to 3 years. Myopic Choroidal Neovascularization

In pathologic myopia, mechanical strain caused by the abnormal elongation of the eyeball, among other things, leads to stretching and thinning of the Retinal Pigment Epithelial Layer and Bruch’s membrane, resulting at times in Bruch's Membrane rupture(s) and VEGF release as part of subsequent wound-healing process. This results in the development of mCNV, which represents the most vision-threatening complication of pathologic myopia. The long-term prognosis for natural progression of mCNV without treatment is extremely poor. Yoshida and coworkers found that approximately 90% of their patients had a VA of 20/200 or less after 5 years, and almost all (96.3%) had a VA of 20/200 after 10 years.

Over the last decade two main treatment options for myopic CNV have been developed:

Photodynamic Therapy

Verteporfin for photodynamic therapy (vPDT) is approved for the treatment of visual impairment caused by choroidal neovascularization secondary to pathologic myopia in Europe, USA, Hong Kong, Singapore, Taiwan and South Korea, but not in Japan.

A large-scale study on vPDT for myopic CNV was conducted by the VIP study group as a randomized double-blind controlled study in Europe and North America. The proportion of

patients who lost less than 8 letters of VA was 72% (58/81 patients) in the PDT group at 12 months after initiation of treatment. In the sham injection group of this study 44% (17/39 patients) lost less than 8 letters of VA, suggesting that PDT was useful to maintain VA in myopic CNV ($p<0.01$) (159). However, after 24 months, 36% (29/81 patients) had lost at least 8 letters of VA in the vPDT group compared with 51% (20/39 patients) in the sham injection group ($p=0.11$) (160). Thus, vPDT in myopic CNV may only slow disease progression but does not persistently improve VA in the majority of patients.

Anti-VEGF drugs

In recent years, IVT administration of anti-VEGF drugs has been tested for the treatment of visual impairment caused by choroidal neovascularization secondary to pathologic myopia. No anti-VEGF drugs were approved for this indication at the start of the MYRROR study in late 2010. Meanwhile, ranibizumab has been approved by the EMA for the indication "Treatment of visual impairment due to choroidal neovascularization secondary to pathologic myopia" in July 2013 based on the results of the RADIANCE study (NCT01217944). The Novartis application was also supported by results of an open-label study on ranibizumab for the same indication (REPAIR study, NCT01037348).

Since the epidemiological literature and interaction with ophthalmologists from academia suggested that the incidence and prevalence and, consequently, the medical need for myopic CNV treatment was the highest in the Asian population, the MYRROR study was conducted to evaluate therapeutic benefits of aflibercept 2 mg in this geographic region. Following the study's results demonstrating robust efficacy and safety in the treatment of visual impairment caused by choroidal neovascularization secondary to pathologic myopia, the MAH has submitted applications to make this treatment option also available for patients in other parts of the world. A positive opinion was adopted by the CHMP in September 2015.

18.5 Neovascular Glaucoma

Neovascular glaucoma (NVG) is a secondary glaucoma triggered by the formation of new blood vessels (neovascularization) on the iris and the anterior chamber angle. Neovascular glaucoma is a serious condition that may lead to permanent loss of vision, a persistently painful eye and, especially in the advanced stages, is unlikely to respond to treatment.

Alternative approved treatments include IOP lowering drugs, laser therapy of the retina (PRP), filtration surgery, surgical cryotherapy of the retina (if PRP is not possible) and/or ciliary body, surgical removal of the eye (refractory cases with chronic pain). Despite the significant burden of these alternative treatments the outcome is poor, with a high percentage of patients completely losing visual function and developing chronic refractory pain sometimes requiring surgical removal of the eye. Thus, there is a significant unmet need for a new treatment that allows faster control of the disease in the acute stage. The anti-angiogenic properties of Aflibercept, together with its established safety profile make it a potentially effective treatment option to promote quick regression of neovessels in patients with NVG

and stopping the disease process early on, avoiding persistently elevated IOP and risk of permanent vision loss.

Bayer did investigate Eylea treatment in NVG in a randomized, double-masked, sham-controlled phase 3 study in Japanese patients with NVG (VEGA Study, 17584). VEGA showed clinically meaningful improvement of NVG but did formally not reach statistical significance of the primary endpoint. In addition, Bayer has completed an open-label single arm study in 16 Japanese patients treated with 2 mg aflibercept at baseline to increase the pivotal trial experience for NVG (VENERA study. 19652) The primary endpoint (change in IOP from baseline to Week 1) showed a statistically significant reduction in IOP of 8.3 ± 7.3 mmHg with a two-sided 95% CI of -12.2 to -4.4 mmHg (p = 0.0004). The safety profile was similar to the one observed for other indications.

18.6 Benefit-Risk Analysis Evaluation

18.7 Neovascular AMD

Aflibercept was added as an additional treatment option for neovascular AMD in 2011 in the US and starting in 2012 in other countries worldwide, aimed to address an important medical need: Reducing the burden of treatment while still maintaining optimal vision gains during continuous treatment. The phase 3 studies in neovascular AMD proved that with every other month IVT injection of aflibercept (after three initial monthly doses), vision gains and maintenance of such gains are comparable to monthly ranibizumab injections, which can be considered the prior gold standard of neovascular AMD treatment. By reducing the number of injections and/or the visit frequency, treatment with aflibercept reduces the burden of treatment to the patient, the caregiver, the ophthalmologist, and the health care system. At the same time, aflibercept was shown to possess a similar safety profile as ranibizumab, with mainly injection-related ocular side effects and no clear evidence for systemic side effects. In addition, the PLANET study has now provided in the PCV subset of neovascular AMD robust evidence over a 96-week study period for clinically meaningful visual gains and control of disease activity.

Review of the safety data from the clinical program conducted with aflibercept in AMD subjects concluded that it was generally well tolerated with an acceptable safety profile. This conclusion was based on a broad and robust safety data base for aflibercept as established during the clinical development program. The safety profile observed in the preceding phase 1/2 studies was consistent with that seen in the phase 3 studies including the more recent Ph3b/4 studies PLANET in patients with the PCV subtype of neovascular AMD and in ALTAIR.

18.8 Retinal Venous Occlusive Disease

Aflibercept was added as an additional treatment option for macular edema due to RVO in the USA in September 2012 (for CRVO) and in June 2014 (for BRVO); in August 2013 (for CRVO), and in February 2015 (for RVO combining CRVO and BRVO) in the EU and also in

many other countries worldwide, aimed to address an important medical need: Intravitreal treatment with EYLEA offer the therapeutic option to extend the time between injection/monitoring visits and thereby reducing the burden of treatment while still maintaining optimal vision gains. The phase III studies in macular edema due to RVO proved that aflibercept treatment is highly efficacious with a favorable safety profile, with mainly injection-related ocular side effects and no evidence for drug-related systemic side effects. Generally, the safety profile was consistent with that seen for EYLEA in the neovascular AMD phase III studies.

Retinal venous occlusive disease, particularly in subjects with associated chronic macular edema, is an important cause of vision loss, and thus requires medical treatment. Primary efficacy data from pivotal studies on monthly administered 2 mg aflibercept over 24 months demonstrated sustainable and durable efficacy, superior to the standard of care (i.e. observation and PRP treatment as needed for management of complications). Given the superiority of aflibercept for improving visual and associated outcomes in RVO over pure observation and its favorable safety profile as demonstrated in the pivotal studies, it is reasonable to conclude that the benefits of aflibercept outweigh the risks.

18.9 Diabetic Macular Edema

Aflibercept was added as an additional treatment option for DME in the USA in July 2014 and in August 2014 in the EU and other countries worldwide, addressing the medical need for an efficacious and safe long-lasting anti-VEGF treatment in patients losing vision from this condition, who are on average younger than the patients suffering from neovascular AMD or RVO. DME patients are often still in working age, frequently overwhelmed by the many medical appointments for different specialties related to complications of diabetes. Therefore, a close medical follow-up and retreatment as frequent as monthly is an even greater challenge for this patient population. VIVID DME, VISTA DME and VIVID EAST demonstrated at the primary endpoint (Week 52) robust efficacy results for monthly and every other months aflibercept treatment regimens over laser control. The superior effect of either aflibercept regimen over laser was maintained through Week 148 (final results) in VIVID DME and VISTA DME.

With regards to safety, aflibercept was generally well tolerated with a similar overall incidence of AEs, ocular serious AEs, and non-ocular serious AEs across the treatment groups and the laser control group. AEs were typical of those seen in other studies in patients with diabetes receiving IVT anti-VEGF therapy. These results indicate that aflibercept leads to clinically important treatment benefits in patients with DME and thus it adds to the currently available therapeutic armamentarium for DME management.

The recently published results of the independently funded Protocol T study confirmed the benefits of aflibercept as observed in the clinical trial program and demonstrated at Year 2, an improvement of mean VA by 12.8, 10.0, and 12.3 letters, for aflibercept, bevacizumab, and ranibizumab respectively. Treatment group differences varied by baseline VA ($P = 0.02$ for interaction). With worse baseline VA (20/50 to 20/320), mean improvement was 18.1, 13.3,

and 16.1 letters, respectively (aflibercept vs. bevacizumab, P = 0.02; aflibercept vs. ranibizumab, P = 0.18; ranibizumab vs. bevacizumab, P = 0.18). With better baseline VA (20/32 to 20/40), mean improvement was 7.8, 6.8, and 8.6 letters, respectively (P > 0.10, for pairwise comparisons).

Protocol T study utilized a flexible treatment regimen for all treatment arms, including aflibercept, which was based on strict re-treatment criteria using OCT and vision. Such treatment regimens outside of the labeled posology are frequently used by ophthalmologists in clinical practice. Despite the flexible regimen, the number of aflibercept injections administered during the first year of treatment under DRCR.net Protocol T was similar to the total number of injections given the in the MAH's clinical trials and as expected based on the EU posology.

18.10 Myopic Choroidal Neovascularization

Previously, verteporfin photodynamic therapy (PDT) was the only approved treatment of myopic CNV in Europe, USA, and some Asian countries, however it resulted only in prevention of further vision loss but did not restore vision acutely. Preliminary results from uncontrolled clinical studies suggested a benefit of the treatment of myopic CNV with PDT with verteporfin. However, data from a randomized, sham-controlled trial on 120 patients did not show a statistically significant difference between outcomes from the active and the sham-treated groups at 24 months. Evidence of the effectiveness of anti-vascular endothelial growth factor (VEGF) therapies other than aflibercept has accumulated from a series of mostly non-randomized, uncontrolled, and partly retrospective studies and, from a 12-month, phase III, randomized, double-masked, multicenter, and active-controlled trial which compared two ranibizumab treatment groups with a control group receiving PDT with verteporfin, randomized 2:2:1, n=277.

MYRROR (study 15170) was a randomized, double-masked, sham-controlled, phase III study of efficacy and safety of repeated IVT administration of aflibercept in Asian patients with mCNV. All of the 122 randomized patients received at least one study treatment; there were 91 randomized subjects in the aflibercept 2 mg group and 31 in the control group. After Week 24, patients of the control group were treated with aflibercept and all patients were followed until Week 48.

In conclusion, in the MYRROR study aflibercept 2 mg was shown to be effective in the treatment of visual impairment due to myopic CNV. For a detailed discussion see section 17.1.

From a safety perspective, treatment with aflibercept 2 mg in both treatment groups (aflibercept 2 mg and control/ aflibercept 2 mg), up to Week 48 was not associated with unexpected safety events and was generally well tolerated. The observed safety profile was overall consistent with the other approved aflibercept indications.

18.11 Neovascular Glaucoma

Bayer was investigating Eylea treatment in NVG in an ongoing randomized, double-masked, sham-controlled phase 3 study in Japanese patients with NVG (VEGA Study, 17584). The difference between the treatment groups in least square mean change of IOP from baseline to Week 1 (primary endpoint) was −4.9 mmHg, with a 95% CI of −10.2 to 0.3 mmHg with an upper limit of the CI above zero (p = 0.0644, analysis of covariance model, including treatment group and stage of NVG for randomization as fixed effect and baseline IOP as a covariate). Thus statistically, the superiority of the aflibercept group over the sham group was not demonstrated. However, the change in IOP in the aflibercept group was −9.9 mmHg (LS mean change), which was comparable to the expected clinically meaningful reduction used to design the study (assumption for the determination of sample size: mean ± SD of −10 ± 12 mmHg for the aflibercept group). The PPS analysis provided the upper limit of the 95% CI lower than zero (LS mean difference in change in IOP was −5.5 mmHg with 95% CI of −10.8 to −0.2, p=0.0423), showing numerical significance.

In this study, aflibercept did not show a different safety profile in subjects with NVG compared to the safety profile in patients in the pivotal studies of the other indications wet AMD, RVO, DME and myopic CNV. It was generally well tolerated, and none of the reported events raised any safety concerns.

An additional phase 3, single-arm, non-randomized and open-label study evaluating the efficacy, safety and tolerability of a single injection of 2 mg aflibercept IVT aflibercept at baseline in a total of 16 Japanese patients with neovascular glaucoma was completed (VENERA study). The primary endpoint (change in IOP from baseline to Week 1) showed a significant reduction in IOP of 8.3 ± 7.3 mmHg with a two-sided 95% CI of -12.2 to -4.4 mmHg (p = 0.0004). No new safety signals were derived from this study.

Conclusions

Overall, given the treatment benefits of aflibercept with improvement of visual and associated outcomes in approved indications and its safety profile as demonstrated in the pivotal studies, it is concluded that the benefits of aflibercept given IVT outweigh the risks and the benefit-risk profile is considered favorable.

The newly received safety data from the post-marketing setting is in line with expected safety profile of Eylea. No new or unexpected risks were identified.

During the PBRER reporting period the MAH evaluated 9 safety topics cumulatively:

1. Arteriothromboembolic events (ATEs)
2. Ischemic colitis
3. Venous thromboembolic events (VTEs)
4. Non-ocular hemorrhages
5. Hypertension
6. Artery dissection/aneurysm

7. Macular Hole (MH)
8. Macular atrophy (MA)/geographic atrophy (GA)
9. Retinal Hemorrhages (RH)

Bases on the cumulative reviews no causal association to aflibercept therapy could be confirmed.

Overall, no new information has become available during the period of this PBRER/PSUR which would have an impact on the benefit-risk profile of aflibercept. The benefit-risk profile of aflibercept remains favorable.

Since the international birth date of aflibercept on 18 NOV 2011, therapeutic efficacy and the safety of aflibercept has been assessed routinely on an ongoing basis. Based on information available to date from post-marketing experience, including spontaneous reports, and from the scientific literature, the benefit-risk ratio of aflibercept treatment in approved indications remains positive.

19. Conclusions and Actions

No new information has arisen during the reporting interval that would change the overall evaluation of benefit-risk for aflibercept when used in the approved indications. The risks associated with aflibercept are clinically acceptable and outweighed by the benefits of the treatment with aflibercept in the approved indications.

There is currently no need for any new additional risk minimization activities.

The company’s assessment of the benefit-risk balance for aflibercept remains favorable.

20. Appendices

Appendix 1	Marketing Authorization Status
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Appendix 5	
Appendix 5a	List of ongoing interventional Clinical Trials
Appendix 5b	List of completed interventional Clinical Trials
Appendix 6	Cumulative safety evaluation: Macular atrophy (MA)/geographic atrophy (GA)
Appendix 7	Cumulative safety evaluation: Retinal Hemorrhages (RH)
Appendix 8	Cumulative safety evaluation: Macular Hole (MH)
Appendix 9	Final Signal Management Document for closed signal: Intraocular inflammations in the US
Appendix 10	Final Signal Management Document for closed signal: artery dissection/aneurysm
Appendix 11	Part II Module SVII Identified and potential risks- from EU RMP Version 26.1
Appendix 12	Cumulative safety evaluations on systemic safety topics (PRAC request for this PSUR):
	Cumulative safety evaluation: Arteriothromboembolic events (ATEs)
	Cumulative safety evaluation: Ischemic colitis
	Cumulative safety evaluation: Venous thromboembolic events (VTEs)

List of Regional Appendices (as appropriate)

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