SILDENAFIL CITRATE (ED) OVER-THE-COUNTER (OTC) RISK MANAGEMENT PLAN

RMP Version number: 3.2

Data lock point for this RMP: 30 June 2019

Date of final sign off: 10 September 2020

Rationale for submitting an updated RMP:

The Risk Management Plan (RMP) was updated at the request of the Norwegian and Polish Health Authorities (HAs) to modify the summary of safety concerns in accordance with Good Pharmacovigilance (GVP) Module V (rev 2), to include the background and results of the post-authorisation safety study A1481334 (pharmacist survey in the United Kingdom) and include the pharmacist checklist, educational materials for pharmacists and patient checklist as examples of additional risk minimisation measures (RMMs).

Summary of significant changes in this RMP:

RMP Part/Module	Major Changes
PART II: SAFETY SPECIFICATION	
Module SI. Epidemiology of the Indications and Target Population	Added epidemiological data based on new publications through the updated data-lock point (DLP) of 30 June 2019.
Module SII. Non-Clinical Part of the Safety Specification	Updated in accordance with the guidance in GVP Module V (Rev 2).
Module SIII. Clinical Trial Exposure	Updated in line with GVP Module V (Rev 2).
Module SIV. Populations Not Studied in Clinical Trials	Updated according to the proposed changes made to the safety concerns for sildenafil citrate (ED) in Module SVII.
Module SV. Post-Authorisation Exposure	Estimated post-marketing exposure for sildenafil (ED) prescription (Rx) was updated through the DLP of 30 June 2019. Estimated sales data for sildenafil (ED) OTC through the DLP of 30 June 2019 was added.
Module SVI. Additional EU Requirements for the Safety Specification	No updates.
Module SVII. Identified and Potential Risks	Updated based on proposed changes to the safety concerns for sildenafil citrate (ED) OTC. The marketing authorisation holder (MAH) is proposing to update the naming of the important identified risk of "Hypotension when used with BP lowering drugs" to focus specifically on the risk of symptomatic hypotension in men who are not stabilized on alpha blocker therapy. The MAH is proposing to rename the important identified risk of "Hypotension/increase hypotensive effect in patients taking nitrates or NO donors, including recreational nitrites (e.g., 'poppers')" to "Symptomatic hypotension/increase hypotensive effect in men taking nitrates or NO donors, including nitrites (e.g., amyl nitrite or 'poppers' for recreational use)" to reflect the fact that not all use of nitrites

RMP Part/Module	Major Changes
	are for recreational use. The MAH is proposing to remove the important potential risks of "Vision loss due to eye haemorrhage", "Serious CV events associated with sexual activity in men with pre-existing or undiagnosed CVD and/or risk factors", "Use in in patients with severe renal impairment" [for sildenafil (ED) OTC 50 mg], "Use in patients with hepatic impairment" [for sildenafil (ED) OTC 50 mg] and "Use in patients with severe hepatic impairment" [for sildenafil (ED) OTC 25 mg] as well as "Use in men with CV contraindications" and "Use in men with hereditary retinal disorders" as missing information in accordance with the guidance in GVP Module V (Rev 2). The MAH is proposing to upgrade "Use in patients with hypotension" from missing information to an important potential risk of "Symptomatic hypotension in men with pre-existing hypotension" based on the known hypotensive effects of sildenafil (ED). Also, post-marketing safety data for all important risks for sildenafil (ED) Rx was updated through 30 June 2019, clinical trial data for the proposed risk of "Symptomatic Hypotension/Increased Hypotensive Effect in Men: Who Are Not Stabilized on Alpha-Blocker Therapy" was added and post-marketing safety data for sildenafil (ED) OTC was added.
Module SVIII. Summary of the Safety Concerns	The list of the safety concerns has been aligned with the proposal presented in Module SVII.
PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)	Added the background and results of the post-authorisation safety study A1481334 (pharmacist survey in the United Kingdom).
PART IV. PLANS FOR POST-AUTHORISATION EFFICACY STUDIES	No updates.
PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)	Updated according to the proposed changes made to the safety concerns for sildenafil (ED) OTC in Module SVII. Included the pharmacist checklist, educational materials for pharmacists and patient checklist as examples of additional risk minimisation measures.
PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN	Text has been updated to reflect changes in Part II (modules SVII, SVIII), Part III and Part V.
PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN	Annex 2: added study A1481334 Annex 4: removed data capture aides for Eye haemorrhage and Serious CV events associated with sexual activity in men with pre-existing or undiagnosed CVD and/or risk factors Annex 6: added details for proposed additional risk minimisation activities Annex 7: updated with background and results from study A1481334 and updated RMP references Annex 8: updated consistently with changes in respective RMP section.

Other RMP versions under evaluation: None

Details of the currently approved RMP in the United Kingdom:

Version number: 1.4

Approved with procedure: UK/H/6416/01/DC

Date of approval (opinion date): 29 November 2017

QPPV name: Barbara De Bernardi, MD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s/applicant´s QPPV. The electronic signature is available on file.

LIST OF ABBREVIATIONS

ADP	Adenosine Diphosphate
ADR	Adverse Drug Reaction
AE	Adverse Event
AMI	Acute Myocardial Infarction
aRMM	Additional Risk Minimisation Measures
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Time-Concentration Curve
BID	Two Times a Day ("bis in die")
BP	Blood Pressure
cGMP	Cyclic Guanosine Monophosphate
C_{max}	Peak Concentration
CHMP	Committee for Medicinal Products for Human Use
CV	Cardiovascular
CVD	Cardiovascular Disease
CYP	Cytochrome P
DCA	Data Capture Aide
ED	Erectile Dysfunction
EEA	European Economic Area
ERG	Electroretinogram
EMA	European Medicines Agency
EU	European Union
FSAD	Female Sexual Arousal Disorder
GTN	Glyceryl Trinitrate
GVP	Good Pharmacovigilance
HCP	Healthcare Professional
HED	Human Equivalent Dose
HLT	MedDRA High-Level Term
HIV	Human Immunodeficiency Virus
INN	International Nonproprietary Name
IRI	Information Resources UK Ltd
IUGR	Intrauterine Growth Restriction
IV	Intravenous
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
NAION	Non-arteritic Anterior Ischaemic Optic Neuropathy
NO	Nitric Oxide
NOAEL	No Observed Adverse Effect Level
OTC	Over The Counter
PAH	Pulmonary Arterial Hypertension
PDE5	Phosphodiesterase Type 5
PL	Package Leaflet

PK	Pharmacokinetic
PM	Post-Marketing
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term
QD	Once a Day (“quaque die”)
RMP	Risk Management Plan
Rx	Prescription
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SNP	Sodium Nitroprusside
TID	“Ter in die”, ie, three times a day
UK	United Kingdom
USA	United States of America
WHO	World Health Organisation

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PART I. PRODUCT OVERVIEW

Active substance International Nonproprietary Name ([INN] or common name)	Sildenafil citrate
Pharmacotherapeutic group(s) (ATC Code)	G04B E03
Marketing Authorisation Holder Applicant	Pfizer Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Viagra Reseptfri, Viagra Connect
Marketing authorisation procedure	Decentralised procedure, National procedure
Brief description of the product:	Chemical class Sildenafil is a potent and selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific PDE5, which is responsible for degradation of cGMP.
	Summary of mode of action Sildenafil has a peripheral site of action on erections. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum but potently enhances the relaxant effect of NO on this tissue. When the NO/cGMP pathway is activated, as occurs with sexual stimulation, inhibition of PDE5 by sildenafil results in increased corpus cavernosum levels of cGMP. Therefore sexual stimulation is required in order for sildenafil to produce its intended beneficial pharmacological effects.
	Important information about its composition: None.
Hyperlink to the Product Information:	Sildenafil citrate (ED) OTC 50 mg: Module 1.3.1 Sildenafil citrate (ED) OTC 25 mg: Module 1.3.1
Indication(s) in the EEA	Current: Sildenafil ED (OTC) is indicated in adult men with ED, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance. In order for sildenafil ED (OTC) to be effective, sexual stimulation is required. Proposed: Not applicable
Dosage in the EEA	Current: The recommended dose is 1 50 mg tablet taken with water approximately 1 hour before sexual activity. The maximum recommended dosing frequency is once per day. If Viagra Connect is taken with food, the onset of activity may be delayed compared to the fasted state. Patients should be advised that they may need to take

	Viagra Connect a number of times on different occasions (a maximum of 1 50 mg tablet per day), before they can achieve a penile erection satisfactory for sexual activity. If after several attempts on different dosing occasions patients are still not able to achieve a penile erection sufficient for satisfactory sexual activity, they should be advised to consult a doctor. Proposed: Not applicable
	Current (in Poland): The recommended dose is one 25 mg tablet taken with water approximately one hour before sexual activity. The maximum recommended dosing frequency is once per day. If Viagra Connect is taken with food, the onset of activity may be delayed compared to the fasted state. Patients should be advised that they may need to take Viagra Connect a number of times on different occasions (a maximum of one 25 mg tablet per day), before they can achieve a penile erection satisfactory for sexual activity. If after several attempts on different dosing occasions patients are still not able to achieve a penile erection sufficient for satisfactory sexual activity, they should be advised to consult a doctor. Proposed (in Poland): Not applicable
Pharmaceutical form(s) and strengths	Current:50 mg film-coated, blue, rounded-diamond shaped tablets measuring 11.2 mm x 8.1 mm, marked “PFIZER” on 1 side and “V50” on the other. Proposed: Not applicable
	Current (in Poland): 25 mg film-coated, blue, rounded diamond-shaped tablets measuring 9.2 mm x 6.7 mm, marked “PFIZER” on one side and “V-25” on the other. Proposed (in Poland): Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

ATC = Anatomical Therapeutic Chemical; cGMP = Cyclic Guanosine Monophosphate; ED = Erectile Dysfunction; NO = Nitric Oxide; PDE5 = Phosphodiesterase Type 5.

PART II. SAFETY SPECIFICATION

Module SI. Epidemiology of the Indication(s) and Target Population (s)

Indication:

Viagra Connect is indicated in adult men with Erectile Dysfunction (ED), which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.

In order for Viagra Connect to be effective, sexual stimulation is required.

Incidence:

Estimating the frequency of male ED can be difficult given the reluctance of patients to seek treatment. Treatment-seeking behaviour of European patients with ED has been the subject of observational studies. These studies have shown that in Europe, men are reluctant presenting to their physician for an embarrassingly perceived sex-related issue.[1,2,3] As a result, only a small proportion of men suffering from ED symptoms ever visit their physician or other Healthcare Professionals (HCPs) to request treatment, and those who do may wait, on average, more than 2 years to do so,[4] and are often reluctant to put themselves through the ordeal of returning every time they need a new prescription (Rx). An analysis of the IMS Health patient claims dataset identified 6,228,509 US men with an ED diagnosis (not necessarily a new diagnosis) during a 1-year period, of these men only 25.4% were treated, whereas 74.6% were untreated.[5] Furthermore, even among men who are actively seeking information on ED, many resist discussing their condition with either their partner or their physician.[6] Besides their own embarrassment, 71% of men with ED thought that their physician would be unsympathetic, and 68% were afraid that asking for help for sexual dysfunction would embarrass their physician, as well.[7]

Reported incidence rates of ED vary. Among the population-based studies that provided data on the incidence of ED in men in Europe and US, the incidence rate (cases per 1000 man-years) ranged from 11 to 39, with rates increasing with age (Table 1). [8,9,10,11,12,13]

Table 1. Incidence of Erectile Dysfunction reported in Population-based Studies in Europe or North America

Author	Study Years	Country	Measurement Technique	Follow-up (years)	N	Incidence (Cases per 1000 man-years)
Europe						
Egeberg et al, 2017[8]	2008-2012	Denmark	Nationwide administrative registries	5	1,577,234	Age 30+: 11
Schouten et al, 2005[9]	1995-2002	The Netherlands	Self-administered questionnaire with 1 ED question	2.1	1432	Overall: 33 Age 50-59: 21 Age 60-69: 34 Age 70-78: 97

Table 1. Incidence of Erectile Dysfunction reported in Population-based Studies in Europe or North America

Author	Study Years	Country	Measurement Technique	Follow-up (years)	N	Incidence (Cases per 1000 man-years)
				4.2	1432	Overall: 19 Age 50-59: 10 Age 60-69: 24 Age 70-78: 64
Shiri et al, 2003 & 2004[10,11]	1994-1999	Finland	Self-administered questionnaire with 2 ED questions	5	1130	Overall: 39 Age 50-55: 22 Age 60-65: 49 Age 70-75: 84
US						
Gades et al, 2009[12]	1996-2004	USA	Self-administered questionnaire	8	1827	Overall: 28 Age 40-49: 6 Age 50-59: 12 Age 60-69: 38 Age 70+: 118
Johannes et al, 2000[13]	1987-1995	USA	Self-administered questionnaire with 1 ED question	8.8	847	Overall: 26 Age 40-49: 12 Age 50-59: 30 Age 60-69: 46

Prevalence:

Prevalence rates of ED vary substantially across published studies depending on age ranges studied (e.g., prevalence rates are higher in older men), diagnostic tools used (e.g., single question, validated questionnaires), population sampled (e.g., random digit dialing, self-administered questionnaire), and time period in which erectile problems were assessed. As such, prevalence estimates should be interpreted with caution.

The overall prevalence of ED ranged from 9% to 77% in Europe[8,14,15,16,17,18,19,20,21,22,23,24,25,26] and 5.6% to 52% in the US,[27,28,29,30,31,32] with increased rates reported in older men (as seen in Table 2). Among the studies that provided an age breakdown in Europe, prevalence rates of ED ranged from 6% to 29% in men aged 40-49, 3% to 67% in men aged 50-59, and 11% to 81% in men aged 60-69, 26% to 89% in men aged 70+.[15,17,19,24,25,33,34,35] Furthermore, severity of ED ranged from 16%-48% for mild, 2%-42.4% for moderate, and 0.6%-13% for severe, with severity increasing with age.[15,17,19,24,25,26] Similar results were reported in US studies.

Outside of Europe and the US, ED affects a sizeable proportion of men as well. Prevalence estimates obtained from surveys of men living in Australia, Hong Kong, Qatar, South Africa, and Nigeria range from 44% to 68%.[36,37,38,39,40]

Table 2. Prevalence of Erectile Dysfunction reported in Population-based Studies in Europe or North America

Author	Study Years	Country	Measurement Technique	N	Prevalence (%)
Multinational					
Rosen et al, 2004[14]	2001	Multinational: UK, Germany, France, Italy, Spain, USA, Mexico, Brazil	Self-administered questionnaire	27,839	Overall: 16% UK: 13% Germany: 13% France: 11% Italy: 13% Spain: 10% USA: 22% Mexico: 14% Brazil: 14%
Rosen et al, 2003[41]	2001	Multinational: UK, France, Germany, the Netherlands, Italy, Spain, USA	Self-administered questionnaire	12,815	Overall: 49% Age 50-59: 31% Age 60-69: 55% Age 70-80: 76%
Europe					
Dumbraveanu et al, 2018[26]	2015-2016	Republic of Moldova	Representative questionnaire	1,186	Overall: 47.1% Age 18-29: 8.1% Age 30-39: 12.5% Age 40-49: 25.2% Age 50-64: 37.2% >65: 17%
Egeberg et al, 2017[8]	1994-2008	Denmark	Nationwide administrative registries	1,727,770	Age 30+: 9%
Ettala et al, 2014[15]	2004-2007	Finland	Self-administered questionnaire	1000	Overall: 57% Age 45-49: 28% Age 50-54: 44% Age 55-59: 62% Age 60-64: 69% Age 65+: 81%
Stranne et al, 2013[16]	1992	Sweden	Self-administered questionnaire	7763	Age 45+ 44%
	2003	Sweden	Self-administered questionnaire	7349	Age 45+: 51%
Corona et al, 2010[17]	Not Stated	Europe: Italy, Belgium, UK, Spain, Poland, Hungary, Estonia	Self-administered questionnaire	3369	Overall: 30% Age 40-49: 6% Age 50-59: 19% Age 60-69: 38% Age 70+: 64%
Buvat et al, 2009[18]	2001-2002	France	Telephone survey (random dialed digit)	750	Age 40-80: 15%
Teles et al, 2008[19]	2004-2005	Portugal	Self-administered questionnaire	3067	Overall: 48% Age 40-49: 29% Age 50-59: 50% Age 60-69: 74%
Moreira et al, 2008[20]	2001-2002	UK	Telephone survey (random dialed digit)	750	Age 40-80: 18%
Moreira et al, 2005[21]	2001-2002	Germany	Telephone survey (random dialed digit)	750	Age 40-80: 78%

Table 2. Prevalence of Erectile Dysfunction reported in Population-based Studies in Europe or North America

Author	Study Years	Country	Measurement Technique	N	Prevalence (%)
Moreira et al, 2005[22]	2001-2002	Spain	Telephone survey (random dialed digit)	750	Age 40-80: 13%
Laumann et al, 2005[23]	Not Stated	Northern Europe	Telephone survey (random dialed digit)	2151	Age 40-80: 13%
		Southern Europe	Telephone survey (random dialed digit)	2160	Age 40-80: 13%
Shiri et al, 2003[24]	1994 & 1999	Finland	Self-administered questionnaire	3787	Overall: 77% Age 50: 67% Age 75: 89%
Martin-Morales et al, 2001[25]	1998-1999	Spain	Self-administered questionnaire	2476	Overall: 19% Age 25-39: 8% Age 40-49: 14% Age 50-59: 26% Age 60-70: 48%
Blanker et al, 2001[33]	1995-1998	The Netherlands	Self-administered questionnaire	1688	Age 50-54: 3% Age 55-59: 5% Age 60-64: 11% Age 65-69: 19% Age 70-78: 26%
Macfarlene et al, 1996[34]	1992	France	Self-administered questionnaire	1734	Age 50-59: 20% Age 60-69: 33% Age 70-79: 38%
Helgason et al, 1996[35]	1993-1994	Sweden	Self-administered questionnaire	319	Age 50-59: 3% Age 60-69: 24% Age 70-80: 49%
United States					
Goldstein et al., 2018[42]	2011-2014	USA	MarketScan claims database	9,839,578	Overall: 6%
Mulhall et al, 2016[27]	2007-2014	USA	MarketScan claims database	19,833,939	Overall: 6% Age 18-29: 0.4% Age 30-39: 2% Age 40-49: 6% Age 50-59: 10% Age 60-69: 12% Age 70-79: 11% Age 80-89: 5% Age 90+: 0.9%
Farag et al, 2016[28]	2001-2004	USA	Interviewer administered questionnaire with 1 ED question	3390	Age 20-85: 15%
Lee et al, 2015[43]	2001-2010	USA	Medicare claims data	Not Stated	Age <65: 26% Age 65-69: 28% Age 70-74: 21% Age 75-79: 13% Age 80-84: 7% Age 85+: 3%
Foster et al, 2013[29]	2011	USA	Self-administered survey	27,337	Overall: 25% Age 40-44: 10% Age 45-54: 27% Age 55-64: 30% Age 65-74: 19% Age 75+: 14%

Table 2. Prevalence of Erectile Dysfunction reported in Population-based Studies in Europe or North America

Author	Study Years	Country	Measurement Technique	N	Prevalence (%)
Laumann et al, 2009[30]	2001-2002	USA	Telephone survey (random dialed digit)	742	Age 40-80: 23%
Laumann et al, 1999[31]	1992	USA	Structured Interview	1244	Overall: 10% Age 18-29: 7% Age 30-39: 9% Age 40-49: 11% Age 50-59: 18%
Panser et al, 1995[44]	1989-1990	USA	Self-administered questionnaire	2155	Age 40-49: 1% Age 50-59: 6% Age 60-69: 22% Age 70-79: 44%
Feldman et al, 1994[32]	1987-1989	USA	Self-administered questionnaire	1290	Overall: 52% Age 40: 23% Age 50: 32% Age 60: 40% Age 70: 49%

Demographics of the population in the authorised proposed indication–age, gender, racial and/or ethnic origin and risk factors for the disease:

Age: The incidence and prevalence of ED increases with age (as seen in the Incidence and Prevalence sections above).

Race/Ethnic Origin: In the US, among those with ED, 73% to 81% were white 9% to 14% were black, 2% to 15% were Mexican American or other Hispanic, 0.6% to 2% were Asian, and 0.6% to 1% were Native American.[28,29,43]

Risk Factors: As most epidemiology data arise from cross-sectional surveys, the temporal relationship between factors that increase the risk and the occurrence of ED cannot be satisfactorily addressed. Information on underlying co-morbidities, including diabetes, obesity, hypertension, and the clinical manifestations of atherosclerosis (see Important co-morbidities below), are relevant to the assessment of ED risk, as ED is often associated with a vascular disease and is often a marker of the progression of the underlying conditions exemplified above.[45]

ED shares a number of risk factors with CVD and premature mortality, including increasing age, diabetes, hypertension, dyslipidaemia, smoking, and excessive alcohol consumption.[32,42,46,47,48,49] ED is often a vascular condition and is often a marker of a more advanced stage of each of these diseases. A recent meta-analysis found that severe ED compared with no ED was associated with a statistically significant increased risk of all-cause mortality.[50] Another systematic review and meta-analysis reported a positive association between ED and subclinical CVD.[51] Another study found an inverse association between physical activity and ED among diabetics.[52]

The main existing treatment options:

Currently employed medical interventions for the management of ED include oral therapies that exhibit their mode of action through PDE5 inhibition and intrapenile therapies (intra-urethral suppositories and intracavernous injections). The vacuum constriction device is a noninvasive mechanical device. Surgical therapies include implantation of prosthetic devices and vascular intervention. Psychosexual therapy may be useful in combination with both medical and surgical treatment for men with ED. For some patients, brief education, support, and reassurance may be sufficient to restore sexual function, while for others, referral to more specialised and intensive counselling may be necessary. Oral PDE5 inhibitors including sildenafil, tadalafil, and vardenafil are considered first-line of therapy for ED, unless contraindicated.[53]

Natural history of the indicated condition in the untreated population

Many doctors do not usually raise the subject of sexual health. It is not part of formal health screening for men in the majority of countries and is generally not considered a medical priority.[54] For many men the loss of erectile function can have significant consequences for their relationship with their partners and their self-esteem.[55,56] ED is associated with depression[57,58] and can adversely influence personal relationships.[1] Consequently, the benefits of a successful treatment of ED extend beyond the restoration of sexual function, as indicated by improved depression rating scores, a general improvement in couple relationships, and an overall improved quality of life.[59,60,61,62,63]

In two recent studies, Massachusetts Male Aging Study (follow-up: 7 years) and Men's Attitudes to Life Events and Sexuality (follow-up: 3 years), 28% to 51% reported ED progression and 21% to 25% reported remission.[64] Current PDE5i use was only reported in 14% to 23% of subjects. Progression of ED was associated with increasing age and BMI.

Important co-morbidities:

Important co-morbidities among patients with erectile dysfunction include the following: hypertension, heart condition, diabetes, high cholesterol, stroke, cancer, overactive bladder, benign prostatic hyperplasia, prostate disease, sleep difficulties, atrial fibrillation, subclinical CVD, and depression or anxiety.[14,17,27,29, 42, 43,48,49,65]

Module SII. Non-Clinical Part of the Safety Specification

SII.1. General

Sildenafil is a selective inhibitor of PDE5. It enhances vascular smooth muscle relaxation in the penile corpus cavernosa in erectile tissue by increasing the levels of Cyclic Guanosine Monophosphate (cGMP). The main potential or theoretical safety issues for sildenafil relate to the pharmacological effects arising from the elevation of cGMP in other tissues such as systemic vascular smooth muscle, the retina, platelets, and gastrointestinal smooth muscle. The safety pharmacology studies are unremarkable except for a moderate antagonist affinity of sildenafil for adenosine A2a receptors, although this finding is unlikely to have any functional consequences.

Oral absorption of sildenafil is rapid and high in all species. Systemic bioavailability is attenuated by pre-systemic hepatic metabolism to an extent consistent with the plasma clearance value in each species. UK-103,320 is the major metabolite of sildenafil. A species-specific gender difference in Pharmacokinetics (PKs) in the rat reflects the more rapid metabolism to UK-103,320 in males. Volume of distribution is similar in rodents and humans but is higher in the dog, probably reflecting the lower plasma protein binding in this species. The pattern of tissue distribution of drug-derived radioactivity in the rat is as expected for a lipophilic weak base, including an affinity for melanin, which is believed to be of no toxicological significance. In all species studied, clearance of sildenafil is via 5 principal pathways of oxidative metabolism, the majority of the dose being excreted in the faeces over 48 hours. Plasma drug concentrations in man increase linearly over the clinical dose range and metabolism is mediated by cytochrome P3A4 (CYP3A4) and CYP2C9, the former appearing to be more important at clinical doses. Circulating metabolites are present, but only 1 (UK-103,320) would be expected to make a contribution to therapeutic activity and, moreover, a minor contribution relative to sildenafil itself. Interactions with co-administered agents are unlikely to be of clinical significance since both sildenafil and UK-103,320 are only weak inhibitors of major human drug-metabolising P450s. Toxicokinetic data for both sildenafil and UK-103,320 indicate a large separation between plasma exposure to drug-related components in man and that associated with toxicity in the rat and the dog. Table 3 provides a summary of the results from non-clinical studies.

Table 3. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Acute Toxicity Single dose The administration of single oral doses of sildenafil indicated a minimal lethal dose of 500-1000 mg/kg in mice and 300-500 mg/kg in rats.	No relevance to human usage as these are single doses studies to determine actual doses for more relevant repeated dosing studies.
Sub-acute and Chronic Toxicity Repeated Dose In a one-month rat study, isolated deaths were observed at 200 mg/kg. The main effects of treatment in rats were adaptive liver changes (associated with thyroid follicular hypertrophy) at lower doses. The oral No Observed Adverse Effect Level (NOAEL) was 60 mg/kg with a Human Equivalent Dose (HED) of 10 mg/kg (60 mg/kg 6.2 conversion factor).[66] This is equivalent to 600 mg for a 60 kg human.	No relevance to human usage as the 60 mg/kg dose is 6 times above the highest human therapeutic dose of 100 mg.
Repeated oral dose studies in rats and dogs, doses were limited by isolated deaths at 200 mg/kg in rats and by gastric intolerance in dogs at 80 mg/kg. The HEDs for the rat and dog are 32 mg/kg (200 mg/kg ÷ 6.2) and 44 mg/kg (80 mg/kg ÷ 1.8) [66] respectively and equivalent to 1935 and 2666 mg. In dogs, heart rate was moderately increased in all studies, with no consistent changes in blood pressure (BP).	No relevance to human usage as the 200 mg/kg in rat and 80 mg/kg in dog are 19 and 26 times above the 100 mg human dose. In addition, the rat deaths were isolated, the gastric intolerance (emesis, salivation) was mild and the BP changes inconsistent.
In chronic dog studies, 50 mg/kg was associated with Idiopathic Juvenile Arteritis (Beagle Pain Syndrome), a syndrome thought to be an expression of a latent disease precipitated by stress, rather than a direct toxic effect of the compound. The oral NOAEL was 15 mg/kg.	There is no human relevance to this finding as this arteritis is specific only to beagle dogs.[67,68]
Genotoxicity Sildenafil did not induce mutations in bacterial or mammalian cells in vitro, nor did it cause clastogenic activity in vivo or in vitro.	Sildenafil is not a genotoxicant.
Carcinogenicity Mice Doses of 1, 3 and 5 mg/kg, and 3, 10, 30 mg/kg were studied. Mortality in mice at 5, 10 and 30 mg/kg was often associated with gastrointestinal dilation. Investigative studies have shown that mice are particularly sensitive to effects of sildenafil on the gastrointestinal tract. The HED of 30 mg/kg is	Sildenafil is not a carcinogen at 1.5 - 6 times the highest human dose.

Table 3. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
2.43 mg/kg (30 mg/kg ÷ 12.3 conversion factor) [66] and 150 mg for a 60 kg human. This is 1.5 times the human dose of 100 mg/day. Sildenafil was shown not to be carcinogenic in mice. Rat Doses of 1.5, 5 and 60 mg/kg were studied. The 60 mg/kg dose produced an increased incidence of proliferative changes in the thyroid, resulting from the liver adaptive changes. HED of 60 mg/kg = 10 mg/kg and 600 mg for a 60 kg human. [66] Sildenafil was shown not to be carcinogenic in rats.	
Reproductive toxicity There were 3 types of oral reproductive toxicity studies conducted: a) fertility in rats b) teratogenicity/embryotoxicity in rats and rabbits c) pre- and postnatal development in rats.	Sildenafil is not a reproductive toxicant in both human sexes.
a) Fertility in rats Doses of 3, 12, 60 mg/kg were studied. Sildenafil had no adverse effects on fertility at up to the NOAEL of 60 mg/kg. HED of 60 mg/kg = 10 mg/kg and 600 mg for a 60 kg human. [66]	No adverse effect on human fertility at up to 6 times the highest human dose is expected.
b) Teratogenicity i) Rats Doses of 50, 100 and 200 mg/kg were studied. Sildenafil at 200 mg/kg produced light maternal toxicity without embryotoxicity but a slight toxicity in male fetuses only. There was no maternal, fetal or embryotoxicity with 10 or 50 mg/kg. No teratogenic effects were seen at any dose. NOAEL was 50 mg/kg in dams and fetuses, with slight toxic effects at 200 mg/kg. HED of 50 mg/kg = 8 mg/kg and 480 mg for a 60 kg human. [66] ii) Rabbits Doses of 10, 50, 200 mg/kg were studied. At 200 mg/kg, there were reductions in body weight and body weight gain late in gestation, compared to the control group indicative of minimal maternal toxicity. Reduction in food intake could be the cause. No teratogenic effects at any dose with NOAEL of 200 mg/kg. NOAEL was 50 mg/kg for dams, given the effect on body weight at 200 mg/kg. HED of 50 mg/kg = 16 mg/kg (50 mg/kg ÷ 3.1	Sildenafil is not teratogenic at 5 - 10 times highest human dose. It is unlikely to produce birth defects in humans.

Table 3. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
conversion factor) and 970 mg for a 60 kg human. [66]	
c) Pre- and postnatal development Doses of 10, 30 and 60 mg/kg were studied. Sildenafil at 60 mg/kg produced minimal toxicity to dams with a decrease in the ratio of viable pups at birth and a consequent reduction in the litter size of viable pups. There was a lower F_1 pup body weight at birth and a decrease in the 4-day survival index. Body weight gain of this group was similar to controls. There were no adverse effects on the maternal function of the F_1 generation or on the postnatal development of the F_2 generation. Treatment at doses of 10 and 30 mg/kg produced no adverse effects. The minimal perinatal effects at 60 mg/kg may be related to inhibition of oxytocin-induced contractions in the rat uterus, demonstrated in vitro. F_0 females and F_1 pups NOAEL was 30 mg/kg. F_2 NOAEL was 60 mg/kg. HED of 30 mg/kg = 5 mg/kg and 290 mg for a 60 kg human. [66]	Sildenafil does not produce any adverse pre- or postnatal developmental effects at 3 times highest human dose.
Paediatric Toxicity	Sildenafil is not indicated for use in a paediatric patient population (ie, <18 years of age). Refer to the sildenafil (PAH) RMP for further discussion of clinical studies conducted to support the clinical development of sildenafil (PAH) in the paediatric patient population affected by PAH.
Cardiovascular safety Unlike the PDE3 inhibitor milrinone, sildenafil had no inotropic action on the dog-isolated trabeculae or rabbit isolated papillary muscle, at up to 10 µM." Preclinical studies demonstrate that sildenafil is a pulmonary vasodilator over a therapeutic concentration range with only small systemic vasodilator effects.[69] This results in decreased pulmonary artery pressure and a reduction in pulmonary vascular resistance. Therefore, outflow resistance from the right ventricle is ameliorated and the load on the right ventricular muscle is relieved. Furthermore, left heart filling pressures will also be reduced, thereby helping to maintain left ventricular performance. The haemodynamic profile of sildenafil in PAH patients (Study 1481024)	There is no evidence of cardiovascular adverse effects in non-clinical studies. These studies therefore have no relevance to human usage. Serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, cerebrovascular haemorrhage, transient ischaemic attack, hypertension and hypotension have been reported post-marketing in temporal association with the use of sildenafil. Most, but not all, of these patients had pre-existing cardiovascular risk factors. Many events were reported to occur during or shortly after sexual intercourse and a few were reported to occur shortly after the use of sildenafil without sexual activity. It is not possible to determine whether these

Table 3. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
confirms that pulmonary artery pressure and pulmonary vascular resistance are indeed reduced.	events are related directly to these factors or to other factors.
Ocular Nonclinical Safety Specification The expression of phosphodiesterase-6 has been confirmed in the retina of man, dog and rat, and is inhibited by sildenafil over the same concentration range.[69] Functional changes to the retina with sildenafil have been investigated using ERG recordings in the dog and have demonstrated effects which were reversible and proportional to plasma sildenafil concentrations. However, sildenafil only affected the ERG at plasma concentrations higher than those active on the pulmonary vasculature in the anaesthetised dog. Furthermore, in rat and dog toxicology studies, plasma exposure levels of sildenafil, which are pharmacologically active on the retina, did not cause structural changes to the retina.[70] Ophthalmologic examinations have revealed no unusual findings in rats, mice or dogs treated up to 24, 18 or 12 months respectively. A thorough in-depth histopathological assessment of the structural integrity of the retina was conducted in rat and dog toxicology studies of up to 2 years in duration. A detailed qualitative examination of histologic sections of eyes was performed together with a histomorphometric analysis of the nuclear layers of the retina in the 6-month and carcinogenicity rat studies, and in the 6- and 12-month dog studies. There was no evidence of an alteration of the integrity of the retina. Nuclear assessment has been carried out for Study Nos. 91098 (6-month oral rat,) and 94092 (24-month carcinogenicity). The results indicate that there is no evidence of an effect of treatment on the retina in either study.[71,72] Similarly, the retina of dogs which contains both rods and cones, from Study Nos. 91099 (6-month oral dog) and 95039 (12-month oral dog) also had no effect.[73,74] Both the inner and outer nuclear layers were counted in dogs because damage to cones is reflected in the inner nuclear layer. The results	No relevance to human usage as the nonclinical data did not predict human ocular effects as described in the product label.

Table 3. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
indicate that there is no evidence of an effect of treatment on the retina in either study. The rat retina is dominated by rods and thus counting of the inner nuclear layers is not appropriate. In conclusion, the integrity of the retina, including the photoreceptor cells, was directly fully assessed by histopathological examination of the retina conducted in rat and dog toxicology studies of up to 2 years in duration. There was no evidence of an adverse effect of sildenafil in the retina of rat or dog.	
Non-arteritic anterior ischaemic optic neuropathy (NAION) Histopathological examination in rat and dog toxicology studies of sildenafil involved all the major structures of the visual pathways with the exception of the optic radiation in the rat brain due to its short longitudinal dimension. These included all layers of the retina and the optic nerve. Histopathology did not reveal any evidence of a treatment-related effect, there being no evidence of morphological alterations or clinical abnormalities. There was no evidence of an effect of treatment on the retina, optic nerve or associated blood vessels in either species. There were no pathological changes that would suggest the occurrence of a syndrome similar to that in the rat model of NAION described by Bernstein et al (2003).[75] The absence of effect was confirmed by an independent peer review of the histopathology sections of eye from 4 toxicity studies in dogs, from 1 month to 1 year in duration, and 1 6-month toxicity study in rats. Importantly, mice, rats and dogs were exposed for prolonged periods to plasma concentrations of sildenafil or its active metabolite, UK-103,320, which are known to affect retinal function (ERG or isolated retina) in the dog. Sildenafil in excess of those shown to be pharmacologically active in the retina, daily for up to 24 months, did not result in any treatment-related toxicity of the retina or eye. NAION has been rarely reported post marketing (PM) in temporal association with the use of all PDE5 inhibitors, including sildenafil citrate. It	The nonclinical data do not have relevance to human usage as sildenafil did not produce NAION in rat and dog studies. It also did not result in any treatment-related toxicity of the retina or eye. Cases of NAION have been reported spontaneously and in an observational study in connection with the intake of sildenafil and other PDE5 inhibitors. NAION is considered an important potential risk (see Section SVII.3.1.3).

Table 3. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors.	
Bleeding In preclinical studies, sildenafil at 0.3 mg/kg IV (t = 25 min) increased the rat tail bleeding time by approximately 60 %, although this change was not statistically significant. In rabbits 1 mg/kg IV significantly prolonged bleeding time. Sildenafil's increase in bleeding time was additive with that of heparin but not synergistic with heparin or aspirin. The doses used were approximately 20 times higher than the effective dose on the corpus cavernosum pressure in dogs conducted to support the use of sildenafil for male. Sildenafil had no effect on clotting time in rats and rabbits. Clinical experience with sildenafil citrate provides more useful data on bleeding risk in man than further laboratory animal studies. Overall, single oral doses of sildenafil citrate above 15 mg were generally associated with a potentiation of the anti-aggregatory effects of SNP, on ADP aggregation of ex vivo platelets (Studies 148-201, 148-201A and 148-206). Sildenafil citrate had no effect on other ex vivo tests (ADP-induced platelet aggregation of whole blood and ADP-induced aggregation of platelet-rich plasma in the absence of SNP). These findings confirm that sildenafil citrate has no direct effect on platelet function ex vivo, but will potentiate the action of a NO donor, SNP. These data are consistent with the need for a NO drive to exist before sildenafil citrate produces its pharmacological effect (Study 148-206) on platelets. These modest effects on platelet activity, ex vivo, did not result in a clinically significant effect on bleeding time in healthy volunteers (Study 148-206). The absence of a clinical effect on bleeding time was also demonstrated when sildenafil citrate was co-administered with aspirin (Studies 148-216 and 148-222, discussed in the sildenafil citrate MAA).[76] Consistent with its known effects on the NO/cGMP pathway, sildenafil citrate was shown to potentiate the hypotensive effects of nitrates, and its co-	The non-clinical data do not have relevance to human usage as there is no evidence that sildenafil affects human bleeding time or platelet aggregation on its own. There have been post-marketing reports of bleeding events in patients who have taken sildenafil. A causal relationship between sildenafil and these events has not been established. In humans, sildenafil has no effect on bleeding time when taken alone or with aspirin. However, in vitro studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside (a nitric oxide donor). In addition, the combination of heparin and sildenafil had an additive effect on bleeding time in the anesthetized rabbit, but this interaction has not been studied in humans.

Table 3. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
administration with NO donors or nitrates in any form is therefore contraindicated. A potential safety risk exists in relation to anti-platelet effects of sildenafil citrate in the presence of an NO donor. However, as nitrates are contraindicated with sildenafil citrate, a bleeding risk should remain a potential one. In conclusion, there is no evidence that sildenafil citrate prolongs bleeding time or inhibits platelet aggregation on its own in humans, and in this respect, the animal data do not predict the human situation.	

ADP= Adenosine diphosphate; cGMP= Cyclic guanosine monophosphate; ERG=Electroretinogram; HED= Human Equivalent Dose; IV=Intravenous; MAA= Marketing authorisation application; NOAEL= No Observed Adverse Effect Level; NAION= Non-arteritic Anterior Ischaemic Optic Neuropathy; NO= Nitric oxide; PAH= Pulmonary Arterial Hypertension; PDE=Phosphodiesterase; PM= Post-marketing; SNP=Sodium nitroprusside

Module SIII. Clinical Trial Exposure

Table 4 to Table 7 present the patient exposure data from all 136 completed sildenafil citrate (ED) studies, including placebo-controlled, double-blinded, as well as non-placebo-controlled, parent and extension studies in the MAH's clinical trial repository. The 136 sildenafil (ED) studies are from the clinical development program for sildenafil RX; there were no additional interventional clinical trials conducted for the OTC application.

Of note, the clinical trial data presented in SVII.3 to characterise the important risks is based on 75 double-blinded placebo-controlled clinical trials in men which have been used to characterise the safety profile of sildenafil citrate (ED).

Sildenafil citrate has also been approved for the treatment of PAH, classified as World Health Organization (WHO) functional class II and III. Data from sildenafil citrate (PAH) exposure in adult and paediatric clinical trial patients is included for completeness.

SIII.1. Clinical Trial Exposure in All Completed Sildenafil Citrate for Erectile Dysfunction (ED) Studies, by Duration, Dose, Age, and Race (N = 136)[1]

Table 4. Duration of Exposure (Totals)

Duration of Exposure (at Least)	Persons	Person Time (Years)[a]
Total Exposed Population in ED Studies		
Cumulative up to 1 month	6186	700.90
Cumulative up to 3 months	19,731	3641.42
Cumulative up to 6 months	21,931	5089.51
Cumulative up to 12 months	23,101	8338.01
Cumulative >12 months[b]	81	4627.18

ED = Erectile Dysfunction

Exposure was episodic, as needed, during the reported exposure period.
Note: Subjects enrolled in more than 1 study (i.e., parent study and 1 or more follow-up studies) are counted only once. Their exposure to sildenafil citrate (ED) is reported as cumulative number of days/years across both parent and follow-up study.

a. Duration = (date of the last dose of study medication in the study) - (date of first dispensing study medication in the study) + 1. Total duration in years = total duration in days/365.25.
b. Only includes subjects who were exposed to sildenafil citrate for erectile dysfunction (ED) for more than 12 months.

[1] Source: 148-101B, 148-101C, 148-102, 148-102C, 148-103, 148-103C, 148-104, 148-104C, 148-105, 148-105C, 148-106, 148-106C, 148-107, 148-108, 148-109, 148-110, 148-351, 148-353, 148-354A, 148-354B, 148-354C, 148-355, 148-356, 148-357, 148-358, 148-359, 148-360, 148-361, 148-363, 148-364, 148-365, 148-350, 148-366, 148-367, 148-367B, 148-369, 148-369C, 148-370, 148-373, 148-378, 148-379, 148-803, 166-301, A1481006, A1481030, A1481036, A1481041, A1481042, A1481074, A1481084, A1481085, A1481090, A1481122, R-0529, R-0530, R-0538, R-0539, R-0540, SDN-AFME-98-001, SDN-AFME-98-003, SDN-AFME-98-004, SDN-B-98-001, SDN-BRA-98-001, SDN-BRA-98-002, SDN-BRA-98-003, SDN-BRA-98-004, SDN-BRA-98-006, SDN-BRA-98-007, SDN-CDN-98-001, SDN-CDN-98-002, SDN-CZ-98-001, SDN-D-98-002, SDN-E-98-001, SDN-E-98-002, SDN-E-98-003, SDN-JP-96-601, SDN-JP-96-602, SDN-K-98-001, SDN-LA-97-001, SDN-LA-97-003, SDN-MEX-98-001, SDN-NL-98-002, SDN-NY-96-002, SDN-NY-96-003, SDN-NY-96-004, SDN-NY-96-005, SDN-NY-96-006, SDN-NY-97-001, SDN-NY-97-002, SDN-NY-97-004 SDN-NY-98-001, SDN-NY-98-002, SDN-NY-98-003, SDN-RU-98-001, SDN-S-98-001, SDN-F-98-001, SDN-BRA-98-005, A1481104, A1481118, A1481119, A1481120, A1481137, A1481031, A1481146, A1481177, A1481217, A1481179, A1481068, A1481132, A1481163, A1481183, A1481037, A1481103, A1481161, SDN-E-98-004, SDN-E-98-005, A1481195, A1481222, A1481230, A1481236, A1481240, A1481239, A1481247, A1481025, A1481048, A1481238, A1481237, A1481210, A1481251, A1481110, A1481047, SDN-F-98-002, SDN-98-F-003, A1481070, A1481108, A1481187.

Table 5. By Modal Dose (Totals)

Dose of Exposure (Modal Dose) [a]	Persons	Person Time (Years)[b]
Total Population in ED studies		
5 mg	27	12.40
10 mg	38	4.44
25 mg	637	529.49
50 mg	9831	3605.62
75 mg	43	20.10
100 mg	12558	8739.33
200 mg	48	11.32
Total	23182	12965.19

Exposure was episodic, as needed, during the reported exposure period.

Note: Subjects enrolled in more than 1 study (i.e., parent study and 1 or more follow-up studies) are counted only once. Their exposure to sildenafil for erectile dysfunction (ED) is reported as cumulative number of days/years across both parent and follow-up study

a. Modal dose = the dose that the subject was exposed to the longest period of time. If there were ties, the highest dose (between the 2) was selected. Modal dose for subjects participating in both parent and follow-up studies was estimated based on cumulative exposure across parent and follow-up study.
b. Duration = (date of the last dose of study medication in the study) - (date of first dispensing study medication in the study) + 1. Total duration in years = total duration in days/365.25.

Table 6. By Age Group (Totals)

Age Group	Persons (Total number of UNIQUE subjects)	Person Time (Years)[a]
Total Population in ED Studies		
≤65 years	19176	10593.25
>65 years	3937	2362.21
Missing[b]	69	9.72
Total	**23182**	**12965.19**
≤18 years	4	0.87
>18 to ≤65 years	19172	10592.39
>65 to ≤75 years	3573	2190.84
>75 years	364	171.84
Missing[b]	**69**	**9.72**

ED = Erectile Dysfunction

Exposure was episodic, as needed, during the reported exposure period.

Note: Subjects enrolled in more than 1 study (i.e., parent study and 1 or more follow-up studies) are counted only once. Their exposure to sildenafil for erectile dysfunction (ED) is reported as cumulative number of days/years across both parent and follow-up study.

a. Duration = (date of the last dose of study medication in the study) - (date of first dispensing study medication in the study) + 1. Total duration in years = total duration in days/365.25.
b. Age information was missing/not available for these subjects.

Table 7. By Ethnic or Racial Origin (Totals)

Ethnic/racial Origin	Persons	Person Time (Years)[a]
Total Population in ED Studies		
Caucasian	16044	10996.62
Black	1517	692.07
Asian	1695	371.06
American Indian	1174	346.96
Latin American	925	225.81
Missing[b]	1827	332.67
Total	23182	12965.19

ED = Erectile Dysfunction.

Exposure was episodic, as needed, during the reported exposure period.

Note: Subjects enrolled in more than 1 study (i.e., parent study and 1 or more follow-up studies) are counted only once. Their exposure to sildenafil for erectile dysfunction (ED) is reported as cumulative number of days/years across both parent and follow-up study.

a. Duration = (date of the last dose of study medication in the study) - (date of first dispensing study medication in the study) + 1. Total duration in years = total duration in days/365.25.
b. Ethnic/racial origin information was missing/not available for these subjects.

SIII.2. Clinical Trial Exposure in All Completed Sildenafil Citrate (PAH) Studies, by Age, Gender, Race, Dose, and Duration

Table 8. Clinical Trial Exposure to Sildenafil for Pulmonary Arterial Hypertension by Duration, in Completed Adult Phase 2, 3, and 4 Studies

Duration of Exposure[a]	Persons[b]	Person time (years)[c]
Less than 1 month	136	3.461
≥1 to <3 months	39	7.411
≥3 to <6 months	133	58.568
≥6 to <12 months	91	73.881
≥12 to <18 months	93	109.697
≥18 to <24 months	32	56.991
≥24 months	369	1342.894
Total	893	1652.903

PAH = Pulmonary Arterial Hypertension.

Studies included: Phase 2: A1481024 and A1481130; Phase 3: A1481140, A1481141, and A1481252; Long Term Extension: A1481142 and A1481153; Phase 4: A1481243 and A1481244.

Study A1481243: Includes subjects who were randomised to bosentan/sildenafil and bosentan/placebo in the double-blind phase, and participated in an open label phase receiving bosentan/sildenafil.

a. Exposure is to any dose of sildenafil for pulmonary arterial hypertension (PAH).
b. A subject is counted only once if the subject participated in both a short-term Phase 2, 3 or 4 study and also a Long Term Extension study, and 'person time' for the subject is cumulative treatment duration on sildenafil in both short term and Long Term Extension studies.
c. 'Persons' represent the number of subjects whose total exposure to sildenafil falls under a particular duration category. Person time: calculated as 'Last Dose Date - First Dose Date + 1'.

Table 9. Clinical Trial Exposure to Sildenafil Citrate (PAH) by Duration, in Completed Paediatric Sildenafil (PAH) Phase 2 and 3 Studies

Duration of Exposure[a]	Persons[b]	Person time (years) [c]
Less than 1 month	57	0.630
≥1 to <3 months	1	0.225
≥3 to <6 months	8	2.877
≥6 to <12 months	10	7.934
≥12 to <18 months	13	16.079
≥18 to <24 months	11	19.080
≥24 months	181	951.305
Total	281	998.130

PAH = Pulmonary Arterial Hypertension.

Studies included: Phase 2: A1481157 and A1481276; Phase 3: A1481131 and A1481134; Long term extension: A1481156.

a. Exposure is to any dose of sildenafil for pulmonary arterial hypertension (PAH).
b. A subject is counted only once if the subject participated in both a short-term Phase 2, 3 or 4 study and also a Long Term Extension study, and 'person time' for the subject is cumulative treatment duration on sildenafil in both short term and Long Term Extension studies.
c. 'Persons' represent the number of subjects whose total exposure to sildenafil falls under a particular duration category. Person time: calculated as 'Last Dose Date - First Dose Date + 1'.

Table 10. Clinical Trial Exposure to Oral Sildenafil Citrate (PAH) in Completed Phase 2, 3, and 4 Studies, by Dose, Age, and Gender

Dose (All TID[a])	Age Group	Persons[b]			Person Time (years)[c]		
		Male	Female	Total	Male	Female	Total
1 mg	<18	-	-	-	-	-	-
	18-<65	12	24	36	2.730	5.273	8.003
	65-<75	-	3	3	-	0.695	0.695
	≥75	1	1	2	0.230	0.230	0.460
	Total	13	28	41	2.960	6.198	9.158
5 mg	<18	-	-	-	-	-	-
	18-<65	7	29	36	1.659	6.409	8.068
	65-<75	2	2	4	0.381	0.457	0.838
	≥75	1	2	3	0.011	0.326	0.337
	Total	10	33	43	2.051	7.192	9.243
20 mg	<18	-	1	1	-	0.903	0.903
	18-<65	125	382	507	41.749	180.594	222.344
	65-<75	18	60	78	11.529	35.997	47.526
	≥75	5	15	20	2.426	7.923	10.349
	Total	148	458	606	55.704	225.418	281.123
40 mg	<18	-	-	-	-	-	-
	18-<65	88	301	389	30.804	160.613	191.417
	65-<75	18	43	61	3.781	21.013	24.794
	≥75	4	9	13	0.419	3.379	3.797
	Total	110	353	463	35.003	185.005	220.008
60 mg	<18	-	-	-	-	-	-
	18-<65	-	1	1	-	0.131	0.131
	65-<75	-	-	-	-	-	-
	≥75	-	-	-	-	-	-

Table 10. Clinical Trial Exposure to Oral Sildenafil Citrate (PAH) in Completed Phase 2, 3, and 4 Studies, by Dose, Age, and Gender

Dose (All TID[a])	Age Group	Persons[b]			Person Time (years)[c]		
		Male	Female	Total	Male	Female	Total
	Total	-	1	1	-	0.131	0.131
80 mg	<18	-	-	-	-	-	-
	18-<65	90	309	399	236.060	762.519	998.579
	65-<75	14	44	58	32.988	90.508	123.496
	≥75	1	10	11	1.246	19.483	20.728
	Total	105	363	468	270.294	872.509	1142.804

BID = Two Times a Day ("bis in die"); PAH = Pulmonary Arterial Hypertension; QD = Once a Day ("quaque die"); TID = Three Times a Day.

Note: Subject 10012001 from A1481252 who entered the study at age 16 years old is included on this table.

Studies included: Phase 2: A1481130; Phase 3: A1481140, A1481141, and A1481252; Phase 4: A1481243 and A1481244; Long Term Extension studies: A1481142 and A1481153.

a. Subjects were summarised under prescribed dosing frequency of TID. Subjects may have taken QD, BID, or other dosing frequencies on some days during the study.
b. A subject is counted only once if the subject participated in both a short term Phase 2, 3 or 4 study and also a Long Term Extension study, and the 'person time' for the patient is the cumulative treatment duration on sildenafil in both the short term and Long Term Extension studies.
c. Person time: calculated as 'Last Dose Date - First Dose Date + 1'.

Table 11. Clinical Trial Exposure to Oral Sildenafil Citrate (PAH) in Completed Phase 2, 3, and 4 Studies, by Dose and Race

Dose (All TID[a])	Ethnicity	Persons[b]	Person Time (years)[c]
1 mg	White	11	2.593
	Black	2	0.465
	Asian	27	5.867
	Other	1	0.233
5 mg	White	11	2.445
	Black	2	0.452
	Asian	30	6.346
	Other	-	-
20 mg	White	403	189.780
	Black	20	4.537
	Asian	145	68.274
	Other	38	18.533
40 mg	White	386	183.217
	Black	19	8.323
	Asian	21	7.116
	Other	37	21.352
60 mg	White	-	-
	Black	-	-
	Asian	-	-
	Other	1	0.131
80 mg	White	389	934.152
	Black	19	37.465
	Asian	26	77.708
	Other	34	93.478

Table 11. Clinical Trial Exposure to Oral Sildenafil Citrate (PAH) in Completed Phase 2, 3, and 4 Studies, by Dose and Race

Dose (All TID[a])	Ethnicity	Persons[b]	Person Time (years)[c]

BID=Two Times a Day; PAH = Pulmonary Arterial Hypertension; QD=Once a Day; TID=Three Times a Day.

Note: Subject 10012001 from A1481252 who entered the study at age 16 years old is included on this table.

Studies included: Phase 2: A1481130; Phase 3: A1481140, A1481141, and A1481252; Phase 4: A1481243 and A1481244; Long Term Extension studies: A1481142 and A1481153.

a. Subjects were summarised under prescribed dosing frequency of TID. Subjects may have taken QD, BID, or other dosing frequencies on some days during the study.
b. A subject is counted only once if the subject participated in both a short-term Phase 2, 3 or 4 study and also a Long Term Extension study, and the 'person time' for the subject is the cumulative treatment duration on sildenafil in both the short term and Long Term Extension studies.
c. Person time: calculated as 'Last Dose Date - First Dose Date + 1'.

The number of adult PAH subjects treated with oral and Intravenous (IV) sildenafil (PAH) in completed clinical trials is summarised in Table 12 and Table 13, respectively.

Table 12. Number of Adult Subjects Treated in Completed Phase 2, 3, and 4 Sildenafil Citrate (PAH) Oral Studies

Study Phase	Sildenafil (PAH)	Placebo	Total
Phase 2[a]	33	30	33
Phase 3[b]	567	201	586
Phase 4[c]	227	0	227

PAH = Pulmonary Arterial Hypertension

Subjects in long term extension studies were previously enrolled in the short-term Phase 3 studies, and were not new subjects.

a. Studies included: A1481130 (crossover study with N = 33 enrolled and treated).
b. Studies included: A1481140, A1481141, A1481142, A1481153, and A1481252. 259 subjects from Study A1481180 entered its long-term extension Study A1481142; 242 subjects from Study A1481141 entered its long-term extension Study A1481153.
c. Studies included: A1481243 and A1481244. Study A1481243 included subjects who were randomised to bosentan/sildenafil and bosentan/placebo in the double-blind phase, and participated in an open label phase receiving bosentan/sildenafil.

Table 13. Number of Adult Subjects Treated in Completed Phase 2 and 3 Sildenafil Citrate (PAH) Intravenous Studies

Study Phase	Sildenafil (PAH)	Placebo	Total
Phase 2[a]	66	19	85
Phase 3	0	0	0

PAH = Pulmonary Arterial Hypertension

There were no Phase IV studies for the IV formulation.

a. Studies included: Study A1481024.

The number of paediatric PAH subjects treated with oral and IV sildenafil (PAH) in completed clinical trials is summarised in Table 14 and Table 15, respectively.

Table 14. Number of Paediatric Subjects Treated in Completed Phase 2 and 3 Sildenafil Citrate (PAH) Oral Studies

Study Phase	Sildenafil (PAH)	Placebo	Total
Phase 2	0	0	0
Phase 3[a]	229	60	234

PAH = Pulmonary Arterial Hypertension

Subjects in long term extension studies were previously enrolled in the short-term Phase 3 studies and were not new subjects.

a. Studies included: A1481131 and A1481156. 220 subjects from Study A1481131 entered its long-term extension study (Study A1481156).

Table 15. Number of Paediatric Subjects Treated in Completed Phase 2 and 3 Sildenafil Citrate (PAH) Intravenous Studies

Study Phase	Sildenafil (PAH)	Placebo	Total
Phase 2[a]	40	0	40
Phase 3[b]	12	5	17

PAH = Pulmonary Arterial Hypertension.

a. Studies included: A1481157 and A1481276.
b. Studies included: A1481134.

Module SIV. Populations Not Studied In Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Table 16. Exclusion Criteria Across the Development Programme

Criterion	Reason for Exclusion	Missing Information (Yes/No)	Rationale (if not included as missing information)
Subjects who have a known hypersensitivity to sildenafil citrate for erectile dysfunction (ED) or any component of the study medication; subjects who have had any previous treatment-related intolerable side effects to sildenafil citrate (ED).	The incidence of hypersensitivity to sildenafil citrate (ED) is not known, but estimated to be low.	No	This exclusion criterion is a contraindication in the SmPC. Hypersensitivity to the active substance or to any of the excipients is not considered to be missing information as patients who are hypersensitive to sildenafil citrate (ED) or any of the excipients should not be exposed to sildenafil citrate (ED) due to the possibility of a hypersensitivity reaction.
Subjects who are currently prescribed, taking, and/or likely to be treated with nitrates or NO donors in any form on either a regular or an intermittent basis.	Consistent with its known effects on the NO/cGMP pathway, sildenafil citrate (ED) was shown to potentiate the hypotensive effects of nitrates.	No	This exclusion criterion is a contraindication in the SmPC. The risk of hypotensive effects when sildenafil citrate (ED) is administered with nitrates or NO donors is well characterized and symptomatic hypotension/increase hypotensive effect in men taking nitrates or NO donors, including nitrites (e.g., amyl nitrite or 'poppers' for recreational use) is considered an important identified risk.
Subjects who are receiving concomitant treatment with ritonavir.	Sildenafil citrate (ED) metabolism is principally mediated by the CYP isoforms 3A4 (major route) and 2C9 (minor route). Therefore, inhibitors of these isoenzymes may reduce sildenafil citrate (ED) clearance.	No	Pharmacokinetic studies have shown that co-administration of ritonavir, at steady state (500 mg twice daily) with sildenafil (100 mg single dose) resulted in a 300% (4-fold) increase in sildenafil C_{max} and a 1,000% (11-fold) increase in sildenafil plasma AUC. At 24 hours, the plasma levels of sildenafil were still approximately 200 ng/mL, compared to approximately 5

Table 16. Exclusion Criteria Across the Development Programme

Criterion	Reason for Exclusion	Missing Information (Yes/No)	Rationale (if not included as missing information)
			ng/mL when sildenafil was administered alone. Based on these pharmacokinetic results, co-administration of sildenafil citrate (ED) with ritonavir is a contraindication.
Subjects with significant CVD in the last 3 months, including cardiac failure, stroke, MI, unstable angina and symptomatic or clinically significant cardiac arrhythmias.	Because exertional activity (including sexual activity) may be associated with some degree of cardiac risk in subjects with significant CVD, the CV status of men should be considered prior to initiation of therapy. Agents for the treatment of ED, including sildenafil, should not be used by those men for whom sexual activity may be inadvisable, and these patients should be referred to their doctor. This includes patients with severe CV disorders such as a recent AMI or stroke (6 months), unstable angina or severe cardiac failure.	No	This exclusion criterion is a contraindication in the SmPC. Use in subjects with significant CVD in the last 3 months, including cardiac failure, stroke, MI, unstable angina and symptomatic or clinically significant cardiac arrhythmias is not considered missing information as it is known that exertional activity (including sexual activity) may be associated with some degree of cardiac risk in these patients.
Subjects with a known history of retinitis pigmentosa.	Patients with a history of retinitis pigmentosa were excluded because a minority of these patients have genetic disorders of retinal phosphodiesterases (and sildenafil citrate [ED] is a phosphodiesterase inhibitor). .	No	This exclusion criterion is a contraindication in the SmPC. Sildenafil should not be used in patients with known hereditary degenerative retinal disorders such as retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).
Subjects with a known history hypotension (BP<90/50 mm Hg).	In clinical trials, sildenafil has been shown to have systemic vasodilatory properties that result in transient decreases in blood pressure; as such, patients with hypotension (BP<90/50 mm Hg) were excluded from clinical trials	No	This exclusion criterion is a contraindication in the SmPC. Symptomatic hypotension in men with pre-existing hypotension is considered an important potential risk.
Subjects who have loss of vision in 1 eye because of NAION.	Cases of NAION, a rare condition, have been reported spontaneously and	No	This exclusion criterion is a contraindication in the SmPC. This is not

Table 16. Exclusion Criteria Across the Development Programme

Criterion	Reason for Exclusion	Missing Information (Yes/No)	Rationale (if not included as missing information)
	in an observational study in connection with the intake of sildenafil citrate (ED) and other PDE5 inhibitors, therefore sildenafil citrate (ED) is contraindicated in patients with prior history of NAION.		considered missing information as cases of NAION have been reported spontaneously and in observational studies. NAION is considered an important potential risk.
Subjects with severe hepatic impairment.	Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. Subjects with severe hepatic impairment were excluded from clinical trials because sildenafil clearance is reduced in individuals with hepatic impairment (eg, cirrhosis); impaired clearance of sildenafil citrate (ED) may result in higher systemic exposure with increased risk of toxicity.	No	This exclusion criterion is a contraindication in the SmPC. This is not considered missing information because sildenafil clearance has been shown to be reduced in individuals with hepatic impairment.
Men with penile deformities.	Patients with penile deformities (such as angulation, cavernosal fibrosis or Peyronie's disease) were excluded from clinical trials due to the mechanism of sildenafil citrate (ED) which ultimately results in an inflow of blood into the corpus cavernosum of the penis. For patients with penile deformities, the fibrous tissue in the corpus cavernosum may be damaged.	No	This exclusion criterion is a contraindication in the SmPC. This is not considered missing information due to the known mechanism of sildenafil and its potential effects on patients with penile deformities.
Subjects currently taking any other commercially available drug or non-drug treatments for ED (i.e., intraurethral agents, prostheses, injection therapy, topical applications, herbal or alternative medications, or	Other concomitant ED treatments were excluded from use in clinical studies to ensure that the efficacy assessment was not confounded by the effects of these agents.	No	The concomitant use of other ED treatments with sildenafil citrate (ED) is cautioned in Section 4.4 of the SmPC under the subheading "Concomitant use with other treatments for ED". This is not considered missing information because the

Table 16. Exclusion Criteria Across the Development Programme

Criterion	Reason for Exclusion	Missing Information (Yes/No)	Rationale (if not included as missing information)
vacuum-assisted erection devices). Such treatments must be terminated at or before the screening visit and must not be taken at any time during the study.			counselling HCP should use his/her judgement of risk/benefit when treating individual patients with sildenafil ED and additional drug or non-drug treatments for ED.
Subjects with severe renal impairment	Sildenafil citrate (ED) clearance is reduced in patients with severe renal impairment (creatinine clearance <30 mL/min).	No	Due to the known reduction of sildenafil clearance in patients with severe renal impairment (creatinine clearance <30 mL/min), this exclusion criteria is not considered missing information.
Subjects with hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.	The film coating of sildenafil citrate (ED) tablets contains lactose.	No	This exclusion criterion is not considered missing information because it is known that the film coating of the tablet contains lactose and Section 4.4 of the SmPC includes a warning that sildenafil should not be administered to men with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.
Subjects with active peptic ulceration	Subjects with active peptic ulceration were excluded from clinical trials because studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside (SNP) in vitro.	No	This exclusion criterion is not considered missing information based on the studies with human platelets that indicate that sildenafil potentiates the antiaggregatory effect of SNP in vitro. Section 4.4 of the SmPC includes a warning that the use of sildenafil is not recommended in those patients with history of bleeding disorders or active peptic ulceration, and should only be administered after consultation with a doctor.

AMI = Acute Myocardial Infarction; AUC= Area Under the Curve; BP = Blood Pressure; C_{max}= Maximum concentration; CV = Cardiovascular; CVD = Cardiovascular Disease; CYP = Cytochrome P450; ED = Erectile Dysfunction; MI = Myocardial Infarction; NAION = Non-Arteritic Anterior Ischaemic Optic Neuropathy; NO = Nitric Oxide; PDE5 = Phosphodiesterase Type 5; SmPC = Summary of Product Characteristics; SNP: sodium nitroprusside.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, or those caused by prolonged or cumulative exposure. Given the short half-life of sildenafil (ED) and studied dose regimen (intermittent use on an as needed basis), adverse drug reactions (ADRs) with long latency periods are not anticipated.

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 17. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Children	Paediatric patients were not studied in the sildenafil citrate for ED clinical programme. Note that sildenafil citrate for PAH has been studied in children as part of the PAH clinical programme and was approved for the treatment of paediatric PAH in the EU in May 2011 (see SIII.2 for clinical exposure data). Sildenafil citrate (ED) is not indicated for patients <18 years of age. No paediatric investigational program for sildenafil citrate (ED) is planned.
Elderly	There were 3937 subjects ≥65 years of age enrolled in the clinical programme with the total exposure duration of 2362 years. Cumulative analysis of double-blind placebo-controlled clinical studies confirmed that sildenafil citrate (ED) is well tolerated in men with ED overall and in those aged ≥65 years and ≥75 years. No dosage adjustment is required in elderly patients (≥65 years of age).
Pregnant women	Pregnant women have not been studied in the development program. Sildenafil citrate (ED) is not indicated for use by women.
Breastfeeding women	Nursing women have not been studied in the development program. Sildenafil citrate (ED) is not indicated for use by women.
Population with relevant different racial and/or ethnic origin	Different ethnic groups were included in the clinical study programme. In the 136 completed sildenafil citrate (ED) studies, including placebo-controlled, double-blinded, as well as non-placebo-controlled, parent and extension studies, the majority of the recruited subjects on sildenafil citrate (ED) were Caucasian (16044 persons; 10996.62 person time [years]). Other ethnic groups included Blacks (1517 persons; 692.07 person time [years]), Asians (1695 persons; 371.06 person time [years]), American Indians (1174 persons; 346.96 person time [years]) and Latin Americans (925 persons; 225.81 person time [years]). Information about race was missing for 1827 persons (332.67 person time [years]). Efficacy and safety of sildenafil citrate (ED) was investigated in Black Americans (study A1481006); in Chinese men (A148-803), in men with ED in the Republic of South Korea (SDN-K-98-001), in men with ED in Latin America (SDN-LA-97-001; SDN-LA-97-003; SDN-LA-97-004), and in men with ED in Asia (SDN-NY-96-002; SDN-NY-96-003; SDN-NY-96-006).

Table 17. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
	No notable differences were seen in safety or efficacy in the populations studied.
Patients with a disease severity different from inclusion criteria in clinical trials	Sildenafil citrate (ED) is indicated for male patients with ED and does not have limitations on the degree of the disease severity.
Subpopulations carrying known and relevant genetic polymorphisms	No studies have been carried out to assess populations with polymorphisms that could affect treatment with sildenafil citrate (ED).
Patients with relevant co-morbidities: • **Patients with hepatic impairment**	In volunteers with mild to moderate hepatic cirrhosis (Child-Pugh A and B), sildenafil citrate (ED) clearance was reduced. Sildenafil citrate (ED) has not been studied in patients with severe hepatic impairment (Child-Pugh C); therefore, the use of sildenafil citrate (ED) is contraindicated in these patients. In the 75 double-blinded placebo-controlled trials, there were 38 subjects (6.74 person-time [years]) with hepatic impairment.
• **Patients with renal impairment**	In volunteers with mild to moderate renal impairment (creatinine clearance = 30-80 mL/min), the pharmacokinetics of sildenafil were not altered after receiving a 50 mg single oral dose. The same has been shown for the 25 mg dose. The mean AUC and C_{max} of the N-desmethyl metabolite increased 126% and 73% respectively, compared to age-matched volunteers with no renal impairment. However, due to high inter-subject variability, these differences were not statistically significant. In volunteers with severe renal impairment (creatinine clearance < 30 mL/min), sildenafil clearance was reduced, resulting in mean increases in AUC and C_{max} of 100% and 88% respectively compared to age-matched volunteers with no renal impairment. In addition, N-desmethyl metabolite AUC and C_{max} values were significantly increased 200% and 79% respectively. In the 75 double-blinded placebo-controlled trials, there were 107 subjects (18.07 person-time [years]) with renal impairment.
• **Patients with other relevant co-morbidity such as CVD**	Though subjects with significant CVD in the last 3 months were not studied in clinical program, based on the cumulative analysis of the double-blind studies there is no causal link between sildenafil citrate (ED) and CV events. However, because exertional activity (including sexual activity) may be associated with some degree of cardiac risk in subjects with significant CVD, it is recommended that HCPs consider the CV status of patients prior to counselling them about suitability of taking ED medications.

AUC= Area Under the Concentration-time Curve; C_{max}= Maximum Observed Concentration; CV = Cardiovascular; CVD = Cardiovascular Disease; ED = Erectile Dysfunction; HCP = Healthcare Professional; PAH = Pulmonary Arterial Hypertension

Module SV. Post-Authorisation Experience

SV.1. Post-Authorisation Exposure

SV.1.1. Sildenafil (ED) Rx Estimated Post-Authorisation Exposure

Estimated exposure for Rx sildenafil citrate (ED) is provided for informational purposes.

It is estimated that 88,740,410 patients were exposed to sildenafil (ED) worldwide since the product was first approved (05 February 1998) through 30 June 2019. The current estimated cumulative exposure is calculated by adding the cumulative exposure (05 February 1998 - 02 February 2018) from the most recent sildenafil (ED) PSUR to the interval exposure of 03 February 2018 through 30 June 2019.

Table 18. Cumulative and Interval Patient Exposure from Marketing Experience for Sildenafil (ED)

Reporting Period	Patient Exposure
IBD to 02 February 2018	84,533,849
03 February 2018 to 30 June 2019	4,206,561
IBD to 30 June 2019	88,740,410

It is estimated that 4,206,561 patients were exposed to sildenafil (ED) worldwide from 03 February 2018 through 30 June 2019 (the reporting interval for the most recent sildenafil [ED] PSUR through the data-lock point of the RMP). United States (US) patient exposure during the reporting interval (814,223 patients) was projected from IQVIA's Total Patient Tracker (a source for estimating patient level data which includes 55% coverage of US retail pharmacies and projects to the US retail pharmacy universe). Since patients' data are not available outside the US, to calculate non-US patient exposure, IQVIA standard units' data were used to extrapolate the number of non-US sildenafil (ED) patients, with assumptions that usage and treatment patterns were consistent worldwide. US and non-US sildenafil (ED) standard units were obtained from IQVIA Midas data available at time of the report (first quarter 2018 through second quarter 2019). The ratio of non-US (102,885,308 standard units) to US standard units (24,694,345 standard units) was multiplied by the number of US patients to arrive at an estimate of non-US sildenafil (ED) patients. This calculation yields a total non-US patient count of 3,392,338 patients receiving sildenafil (ED) cumulatively. United States estimated cumulative exposure (814,223 patients) was added to non-US estimated cumulative exposure (3,392,338 patients) to arrive at a cumulative estimate of the worldwide sildenafil (ED) post-marketing experience of 4,206,561 patients.

Table 19. Cumulative Estimated Exposure for Sildenafil (05 February 1998 through 30 June 2019) - Patients (in Thousands)

Indication[a]	Age(years)				Gender			Region				Form	Dose			
	0-16	17-65	>65	UNK	M	F	UNK	EU	Japan	NA	ROW	Oral	25 mg	50 mg	100 mg	UNK
Other disorders of penis	-	37,192	11,563	668	49,420	3	0	1,752	-	46,716	956	49,423	2,829	14,606	29,295	2,693
Sexual dysfunction, not caused by organic disorder or disease	16	22,462	10,575	-	32,451	600	2	12,142	11,036	2,000	7,875	33,053	3,283	22,988	6,594	187
Total Others	2	3,856	2,406	-	6,116	149	-	4,552	115	1,258	340	6,265	551	2,188	3,459	67

EU: European Union; F: Female; Form: Formulation; M: Male; Mg: Milligram; NA: North America; ROW: Rest of World; UNK: Unknown
Gender, age, dose data available from 4th quarter 2014 through 3rd quarter 2017. Formulation and region data available from 4th quarter 2011 through 3rd quarter 2017.

a. Indication data are based on selected World Health Organization (WHO) International Classification of Disease (ICD)-10 codes obtained from doctor diaries and may not be reflective of the actual patient diagnoses.

A review of the estimated post-authorisation exposure of the approved sildenafil citrate (ED) Rx product cumulatively through 30 June 2019 indicates that in general, the data appears to be consistent with on-label use of sildenafil citrate (ED); however, there is some use of sildenafil citrate (ED) in unapproved populations (i.e., paediatric and female patients). Paediatric patients were not studied in the sildenafil citrate for ED clinical programme. Of note, sildenafil for PAH has been studied in children as part of the PAH clinical programme and was approved for the treatment of paediatric PAH in the EU in May 2011. The MAH had conducted a number of investigational studies for the indication of female sexual arousal disorder (FSAD). While the clinical studies confirmed the safety of the drug in females, it did not generate data that would unequivocally support the efficacy of sildenafil citrate (ED) in the treatment of women with FSAD and the clinical program was terminated.

SV.1.2. Viagra Connect (sildenafil [ED] OTC) Estimated Post-Authorisation Exposure

Viagra Connect, sildenafil [ED] OTC 50 mg was launched in the United Kingdom on 27 March 2018.[2]

Sales data for Viagra Connect is obtained from IRI (Information Resources UK Ltd) Infoscan service, directly from the retailer electronic point of sales data, which records all sales going through the store check-out via the scanned barcodes. The sales data from IRI is available from 21 April 2018 through 29 June 2019[3] and is estimated to be 1,417,680 units. One unit is equal to one pack of Viagra Connect.

As Viagra Connect is used on an "as needed" basis, it is not possible to estimate patient exposure based on the IRI sales data (e.g., patients may have purchased more than one pack of Viagra Connect during the reporting period).

[2] Viagra Reseptfri has not been launched in Norway.

[3] Sales data for Viagra Connect could not be provided through 30 June 2019 because IRI data is available by week and not by day.

Module SVI. Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

Sildenafil citrate (ED) has no ingredients that can be used for the manufacturing of controlled or illicit substances. Sildenafil citrate (ED) does not alter the level of consciousness, does not have any effects on behavioural inhibition or decision-making. Therefore, there does not appear to be a potential for its use in the commission of a crime.

There is no evidence from preclinical studies or Phase I-IV clinical studies to suggest that sildenafil citrate (ED) has the potential for abuse. There are no underlying pharmacological mechanisms, or neural or behavioural signs and symptoms that suggest that sildenafil citrate (ED) would induce drug-seeking behaviour. There have been no reports of drug abuse or drug dependence associated with the use of sildenafil citrate (ED) in clinical trials.

Inappropriate recreational use of sildenafil citrate (ED) and other PDE5 inhibitors has been reported; and the MAH is aware that all PDE5 inhibitors including sildenafil citrate (ED) have been used by some non-sufferers for recreational purposes shortly after their introduction in the market, first in the US and then in other countries including the EU, thus prompting an early debate about the safety of the inappropriate usage of these compounds.[77,78] However, most of these sildenafil citrate (ED) consumers proved to be drug abusers, who reported having taken the compound simultaneously with illicit drugs, eg, cocaine, cannabis, methylenedioxymethamphetamine, amyl nitrite, and γ-hydroxybutyric acid.[79,80,81,82,83,84]

Module SVII. Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Not applicable as this is not an initial submission.

SVII.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

There are no new safety concerns identified for sildenafil (ED) OTC since approval of the RMP version 1.4 dated 08 September 2017.

The MAH is proposing to update the safety concerns for sildenafil (ED) OTC in accordance with the guidance in GVP Module V (Rev 2). The proposed updates to the safety concerns and the rationale for the proposals are outlined below.

1) Proposed update of the naming of the important identified risks of "hypotension/increase hypotensive effect in patients taking nitrates or NO donors, including recreational nitrites (e.g., 'poppers')" and "hypotension when used with BP lowering drugs".

The MAH is proposing to update the naming of the important identified risk of "hypotension when used with BP lowering drugs" to focus specifically on the risk of symptomatic hypotension in men who are not stabilized on alpha blocker therapy. Section 4.4 of the sildenafil (ED) OTC 50 mg and 25 mg SmPCs, Special warnings and precautions for use, specifically cautions that patients taking alpha-blockers should be stabilized on alpha-blocker therapy prior to initiating therapy with sildenafil (ED) OTC. Furthermore, Section 4.5 of the sildenafil (ED) OTC 50 mg and 25 mg SmPCs, Interaction with other medicinal products and other forms of interaction, includes the following data regarding concomitant use of sildenafil and anti-hypertensives: *"Pooling of the following classes of antihypertensive medication; diuretics, betablockers, ACE inhibitors, angiotensin II antagonists, antihypertensive medicinal products (vasodilator and centrally-acting), adrenergic neurone blockers, calcium channel blockers and alpha-adrenoceptor blockers, showed no difference in the side effect profile in patients taking sildenafil compared to placebo treatment. In a specific interaction study, where sildenafil (100 mg) was co-administered with amlodipine in hypertensive patients, there was an additional reduction on supine systolic blood pressure of 8 mmHg. The corresponding additional reduction in supine diastolic blood pressure was 7 mmHg. These additional blood pressure reductions were of a similar magnitude to those seen when sildenafil was administered alone to healthy volunteers."*

The MAH is proposing to rename the important identified risk of "hypotension/increase hypotensive effect in patients taking nitrates or NO donors, including recreational nitrites (e.g., 'poppers')" to " symptomatic hypotension/increase hypotensive effect in men taking nitrates or NO donors, including nitrites (e.g., amyl nitrite or 'poppers' for recreational use)" to reflect the fact that not all use of nitrites are for recreational use. Of note, symptomatic hypotension is defined as a decrease in blood pressure such that symptoms of hypotension are manifested such as dizziness, syncope or orthostatic hypotension.

The MAH is proposing to combine the important identified risk of "hypotension/increase hypotensive effect in patients taking nitrates or NO donors, including nitrites (e.g., amyl nitrite or 'poppers' for recreational use)" with the proposed risk of "hypotension in patients who are not stabilized on alpha blocker therapy" to reflect the risk of symptomatic hypotension when sildenafil is used concomitantly with nitrates/NO donors/nitrites or in men who are not stabilized on alpha-blocker therapy. However, to keep the distinction between the two drug interactions (sildenafil (ED) use with nitrates/NO donors/nitrites is a contraindication whereas use of sildenafil (ED) with alpha-blockers is a warning/precaution), the risk will be presented as two sub-bullet points as follows:

- *Symptomatic hypotension/increase hypotensive effect in men:*
  - taking nitrates or NO donors, including nitrites (e.g., amyl nitrite or 'poppers' for recreational use)
  - who are not stabilized on alpha-blocker therapy

2) Proposal to remove the important potential risk of "Vision loss due to eye haemorrhage".

In 2013, the Marketing Authorisation Holder received the following request from EMA PRAC: "The MAH is requested to provide the cumulative overview of cases reporting chorioretinopathy as well as hemorrhagic events of the eye grouped under the main eye hemorrhage categories, e.g. subconjunctival haemorrhage, hyphema, vitreous hemorrhage, subretinal hemorrhage, and submacular hemorrhage." The conclusion from the review was that in the majority of cases, pre-existing conditions or other concomitant medications more plausibly caused or contributed to the events of interest and that a comprehensive review of the spontaneous reports does not support a direct causal association with sildenafil use. Therefore, the MAH did not believe there was sufficient justification for any revisions to sildenafil product labeling at the time. However, in June 2013, the Committee for Medicinal Products for Human Use (CHMP) provided its assessment of the Marketing Authorisation Holder (MAH)'s cumulative review of the topic of chorioretinopathy and eye haemorrhage and concluded that "Due to the number of cases involving eye haemorrhage events and a plausible mechanism of action as described in the SmPC, the Viagra RMP should be updated to include eye haemorrhage events as Important Potential Risk subject to close monitoring."

Eye haemorrhage has been monitored regularly during post-marketing signal detection activities and has been reviewed in the Viagra Periodic Safety Update Reports following its inclusion as an important potential risk in the Viagra RMP as per the CHMP recommendation in 2013; no new significant safety information have been identified to date. Cumulatively, through 30 June 2019, there were 308 cases (Tradename reported as Viagra), reporting 1223 events[4], reported to the MAH safety database for sildenafil (ED) that related to the potential risk of Eye haemorrhage. Of these, the terms indicative of haemorrhage were Eye haemorrhage (85), Retinal haemorrhage (51), Conjunctival haemorrhage (16), Vitreous haemorrhage (14), and Optic disc haemorrhage (1).

Retinal haemorrhage is considered a more specific and informative adverse event term, which is included as an adverse drug reaction term in the sildenafil (ED) EU SmPC. Fewer cases reported specific terms of Conjunctival haemorrhage (9 cases involved patients with a medical history of cardiovascular disease, diabetes or hypertension or underlying ocular condition such as macular degeneration or cataract; 3 cases in which a causal association could not be ruled out [reported for 2 cases that no action was taken and patient recovered]; and 4 cases provided insufficient information for a meaningful assessment), Vitreous haemorrhage (7 cases in patients with medical history for cardiovascular disease, diabetes or hypertension; 1 case in a patient who was not receiving treatment at the time of the event; 3 cases in which a causal association could not be ruled out and 3 cases reporting too little information for a meaningful assessment) and Optic disc haemorrhage (1 case in a patient diagnosed with optic ischaemic neuropathy with hypotension and a small cup-to-disc ratio).

Of the 85 cases reporting an event of Eye haemorrhage 24 cases lacked sufficient case detail for a meaningful assessment. Five (5) cases co-reported a more specific haemorrhage-related event: Conjunctival haemorrhage (2), Retinal haemorrhage (2) and Optic disc haemorrhage

[4] Search terms included: MedDRA High-Level Terms (HLTs: (1) HLT Anterior Chamber Bleeding and Vascular Disorders; (2) HLT Choroid and Vitreous Haemorrhages and Vascular Disorders; (3) HLT conjunctival and Corneal Bleeding and Vascular Disorders; (4) HLT Ocular Bleeding and Vascular Disorders (not elsewhere classifiable); and (5) HLT Retinal Bleeding and Vascular Disorders (Excluding Retinopathy).

(1). In 33 cases the event was associated with underlying confounding medical conditions including cardiovascular disease, hypertension, diabetes and existing eye conditions, including retinopathy, glaucoma, cataract (involving surgery[85]), macular degeneration, retinal vein occlusion, and ischaemic optic neuropathy, which likely contributed to the event of eye haemorrhage. For 6 cases, the event was reported as occurring after discontinuation of treatment, making a temporal causal association unlikely. For other cases an alternative explanation is provided: industrial accident (1), overdose with induced strained vomiting (1), and strenuous manual lifting in a patient with pulmonary arterial hypertension (1). The remaining cases include those reporting 'blood shot eyes' without a formal examination and cases in which a causal association to treatment could not be ruled out; in 3 of the cases it is reported that the physician told the patient that there was not an association to treatment, but the event was considered 'normal' in the patient population.

The MAH considers that important eye-related events, including visual disturbances, and the risk of non-arteritic ischaemic optic neuropathy (NAION) are well characterised in the currently approved product label for sildenafil (ED). The event term of Eye haemorrhage is a broad term that is likely to be caused by a number of other risk factors and underlying medical conditions in this patient population (e.g., diabetes and cardiovascular disease) and not specifically to sildenafil treatment. The more specific and informative term of Retinal haemorrhage is included as an adverse drug reaction in the currently approved label to best guide the prescriber. Therefore, the MAH proposes to remove the non-specific safety concern of Vision loss due to eye haemorrhage as an important potential risk for sildenafil (ED) OTC. The MAH continues to conduct routine pharmacovigilance for all events reported.

3) The MAH proposes to remove "Serious cardiovascular (CV) events associated with sexual activity in men with pre-existing or undiagnosed cardiovascular disease (CVD) and/or other risk factors" as an important potential risk in line with the recommendation from the Type II variation preliminary Final Variation Assessment Report of the sildenafil (ED) OTC version 3.1 (NO/H/0307/001/II/001) received from the Norwegian Medicines Agency (NoMA).

In men with significant CVD, serious CV events can be associated with sexual activity. Therefore, the association to sildenafil (ED) is indirect due to sildenafil (ED) allowing the patient to facilitate exertional activity, which in turn may be associated with some degree of cardiac risk in patients with significant CVD. The EU SmPC communicates this risk in Section 4.4 "*Since there is a degree of cardiac risk associated with sexual activity, the cardiovascular status of men should be considered prior to initiation of therapy…Serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, cerebrovascular haemorrhage, transient ischaemic attack, hypertension and hypotension have been reported post-marketing in temporal association with the use of sildenafil. Most, but not all, of these patients had pre-existing cardiovascular risk factors. Many events were reported to occur during or shortly after sexual intercourse and a few were reported to occur shortly after the use of sildenafil without sexual activity. It is not possible to determine whether these events are related directly to these factors or to other factors."*

Accordingly, this risk does not meet the definition of a potential risk of the GVP module V rev.2 and therefore the MAH is proposing to remove this safety concern.

4) Proposal to remove "Use in patients with severe renal impairment" and "Use in patients with hepatic impairment" as safety concerns for sildenafil (ED) OTC 50 mg and "Use in patients with severe hepatic impairment" as a safety concern for sildenafil (ED) OTC 25 mg.

The MAH is proposing to remove "Use in patients with severe renal impairment" and "Use in patients with hepatic impairment" as safety concerns for sildenafil (ED) OTC 50 mg and "Use in patients with severe hepatic impairment" as a safety concern for sildenafil (ED) OTC 25 mg. The potential risks associated with the use of sildenafil (ED) OTC in these patient populations are generally increased incidence/severity of listed events such as headache, flushing, dizziness, dyspepsia, nasal congestion, altered vision. The clinical impact of these events is considered minimal in relation to the severity of the indication and therefore are not considered important risks. In addition, use in patients with severe hepatic impairment is a contraindication in Section 4.3 of the sildenafil (ED) OTC 50 mg and 25 mg SmPCs. Section 4.4 of the sildenafil (ED) OTC 50 mg SmPCs further recommends that patients with hepatic impairment or severe renal impairment (creatinine clearance <30 mL/min) should consult with their doctor before taking sildenafil (ED) 50 mg OTC as the 25 mg tablet may be more suitable for them.

5) Proposal to remove "Use in men with CV contraindications" as missing information.

The MAH is proposing to remove "Use in men with CV contraindications" as missing information. It is known that exertional activity (including sexual activity) may be associated with some degree of cardiac risk in patients with cardiovascular contraindications. Section 4.3 of the SmPC states that *"agents for the treatment of erectile dysfunction, including sildenafil, should not be used by men for whom sexual activity may be inadvisable and these patients should be referred to their doctor including patients with severe cardiovascular disorders such as a recent (6 months) acute myocardial infarction (AMI) or stroke, unstable angina or severe cardiac failure."*

6) Proposal to remove "Use in men with hereditary retinal disorders" as missing information.

The MAH is proposing to remove "Use in men with hereditary retinal disorders" as missing information. Use in men with known hereditary degenerative retinal disorders such as *retinitis pigmentosa* is a contraindication in Section 4.3 of the SmPC. It is not expected that there will be significant off-label use in this sub-population as hereditary degenerative retinal disorders are rare and sildenafil (ED) OTC is contraindicated in this patient population.

7) Proposal to upgrade "Use in patients with hypotension" from missing information to an important potential risk.

The MAH is proposing to upgrade "Use in patients with hypotension" from missing information to an important potential risk of "Symptomatic hypotension in men with pre-existing hypotension" based on the known hypotensive effects of sildenafil.

Of note, the MAH does not consider concomitant use of riociguat with sildenafil as an important risk in the RMP given it is contraindicated in the label and usage is in a patient population unsuitable to receive Viagra Connect. Riociguat is indicated for the treatment of patients with chronic thromboembolic pulmonary hypertension (CTEPH) (WHO Group 4) treated with surgery but who continue to have high pulmonary blood pressure (persistent) or it comes back after surgery (recurrent), or that cannot be treated with surgery (inoperable) and patients with pulmonary arterial hypertension (PAH) (WHO Group 1). It acts in a similar mechanism to that of sildenafil and is therefore, contraindicated due to the risk of symptomatic hypotension. Among the first symptoms of PAH are shortness of breath with everyday activities, such as climbing stairs, fatigue, dizziness, and fainting spells. PAH is a progressive disease with a poor prognosis. Diagnosis is often late as the early signs and symptoms can be mistaken for other less serious conditions. This patient population is, therefore, under the direct care of physicians within the healthcare system prior to receiving a diagnosis and appropriate treatment with riociguat or an alternative agent for PAH. As such, the potential for off label use of Viagra Connect for the treatment for PAH is very limited and patients are well placed to receive any additional treatment for co-morbidities, including erectile dysfunction, from physicians with expertise in treating this patient population. As part of the pharmacy educational materials it is stated clearly that men who get very breathless or experience chest pains with light or moderate physical activity, such as walking briskly for 20 minutes or climbing 2 flights of stairs should be referred to their physician and not receive Viagra Connect within a pharmacy setting. The symptoms described align with an early diagnosis of PAH. Therefore, these patients are not suitable to take Viagra Connect and will be directed into the healthcare system. As a result, additional information is not likely to be received to further characterise the risk.

SVII.3. Details of Important Identified, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

The clinical trial data presented in SVII.3 to characterise the important risks are based on 75 double-blinded placebo-controlled trials which have been used to characterise the safety profile of sildenafil citrate (ED).

SVII.3.1.1. Important Identified Risk: Symptomatic Hypotension/Increased Hypotensive Effect in Men: Taking Nitrates or NO Donors, including Nitrites (e.g., amyl nitrite or 'poppers' for recreational use); Who Are Not Stabilized on Alpha-blocker Therapy

SVII.3.1.1.1. Important Identified Risk: Symptomatic Hypotension/Increased Hypotensive Effect in Men: Taking Nitrates or NO Donors, including Nitrites (e.g., amyl nitrite or 'poppers' for recreational use)

VII.3.1.1.1.1. Potential Mechanisms

NO induces the formation of intracellular cGMP by guanylate cyclase.[86] Sildenafil selectively inhibits PDE5, effectively blocking the degradation of cGMP. When nitrates and sildenafil were co-administered in preclinical studies larger but similarly transient effects on BP were observed, consistent with their known effects on the NO/cGMP pathway.

VII.3.1.1.1.2. Evidence Source and Strength of Evidence

In preclinical studies, in anaesthetised dogs, sildenafil was shown to potentiate nitroglycerin induced postural hypotension. A study (148-209) conducted in human volunteers to assess the effects of sildenafil (25 mg) on the haemodynamic responses to Glyceryl Trinitrate (GTN) using a tilt table under laboratory conditions showed that sildenafil (multiple daily dosing) potentiated the hypotensive effects of sublingual and IV GTN (Study 148-209). Following this Phase I study, use in patients on chronic nitrates was contraindicated in all subsequent sildenafil ED studies.

Hypotension/increased hypotensive effect in patients taking sildenafil and nitrates or nitric oxide donors has also been observed in the post-marketing setting.

VII.3.1.1.1.3. Characterisation of the Risk

Post-marketing Data

Sildenafil (ED) Rx

Cumulatively, through 30 June 2019, there were 101 sildenafil (ED) Rx cases (0.1% of all post-marketing cases) that reported concomitant use of a nitrate or nitric oxide donor with sildenafil citrate (ED) and also reported an event indicative of hypotension. The 101 cases reported 117 relevant events coded to the PTs Hypotension (54), Dizziness (32), Syncope (16), Circulatory collapse (10), Shock (3) and Presyncope (2). The nitrates/nitric oxide donors reported as co-suspect medications were nitroglycerin (30), organic nitrates (16), isosorbide mononitrate (8), glyceryl trinitrate (4), amyl nitrite, isosorbide dinitrate (3 each) and propatylnitrate (1). The nitrates/nitric oxide donors reported as concomitant medications were glyceryl trinitrate (21), cardiac therapy (6), isosorbide dinitrate, isosorbide mononitrate, organic nitrates (4 each), nicorandil (2) amyl nitrite and isosorbide (1 each).

Seriousness and outcomes for the 117 relevant AEs are presented in the table below.

Table 20. Seriousness and Outcomes of Events Indicative of Hypotension in Cases Reporting Concomitant Administration of a Nitrate/NO Donor and Sildenafil Citrate (ED) Rx Cumulative through 30 June 2019

MedDRA PT	Number of Events	Serious Events	Fatal	Resolving/ Resolved/Resolved with Sequelae	Not Resolved	Unknown
Hypotension	54[a]	40	7	20	1	29
Dizziness	32	8	0	17	0	15
Syncope	16	8	0	7	2	7
Circulatory collapse	10	6	0	4	1	5
Shock	3	3	2	0	0	1
Presyncope	2	1	0	1	0	1

ED= Erectile dysfunction; MedDRA = Medical Dictionary for Regulatory Activities; NO= Nitric oxide; PT= Preferred Term; Rx= Prescription

a. Cases may report multiple events coded to the same PT

Sildenafil (ED) OTC:

Cumulatively, through 30 June 2019, there were no cases involving sildenafil (ED) OTC [Tradename: Viagra Connect] reporting concomitant use of a nitrate or nitric oxide donor and an event indicative of hypotension.

VII.3.1.1.1.4. Risk Factors and Risk Groups

Patients taking NO donors or nitrates.

VII.3.1.1.1.5. Preventability

This interaction can be prevented by avoiding co-administration of sildenafil citrate (ED) and nitrates or other NO donors. In some member states, additional risk minimisation measures (RMMs) such as a pharmacist check-list, educational materials for pharmacists and/or patient check-lists are in place (see Part V Section V.2).

VII.3.1.1.1.6. Impact on the Risk-Benefit Balance of the Product

While the impact to an individual patient may have significant clinical consequences (i.e., symptomatic hypotension could lead to risk of injury and risk of end organ damage including fatality), this drug interaction is already well-known to healthcare professionals (including pharmacists) and RMMs are in place (contraindication in the SmPC and in some member states, additional RMMs such as pharmacists checklist, educational materials for pharmacists and/or patient checklists). Thus, due to the RMM in place, little impact on the overall risk-benefit balance of sildenafil (ED) OTC is expected.

VII.3.1.1.1.7. Public Health Impact

The public health impact is expected to be minimal as measures are in place (e.g., contraindications in the SmPC and in some member states, additional RMMs) to prevent co-administration.

SVII.3.1.1.2. Important Identified Risk: Symptomatic Hypotension/Increased Hypotensive Effect in Men: Who Are Not Stabilized on Alpha-Blocker Therapy

VII.3.1.1.2.1. Potential Mechanisms

PDE5-inhibitors, including sildenafil (ED) and alpha-adrenergic blocking agents are both vasodilators with blood pressure lowering effects.

VII.3.1.1.2.2. Evidence Source and Strength of Evidence

Hypotension/increased hypotensive effects in patients taking sildenafil (ED) and alpha-blocker have been observed in the clinical trial and post-marketing setting.

VII.3.1.1.2.3. Characterisation of the Risk

Clinical Trial Data

In three specific drug-drug interaction studies, the alpha-blocker doxazosin (4 mg and 8 mg) and oral sildenafil (25 mg, 50 mg, or 100 mg) were administered simultaneously to patients

with benign prostatic hyperplasia stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine systolic and diastolic blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, respectively, and mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively were observed. When sildenafil and doxazosin were administered simultaneously to patients stabilized on doxazosin therapy, there were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and lightheadedness, but not syncope.

In the 75- double-blinded clinical trials, there were 510 subjects who received an alpha-blocker concomitantly with sildenafil citrate (ED). Among the subjects (n = 510) exposed to sildenafil citrate (ED) and a BP lowering drug, a total of 13 subjects experienced a hypotension-related AE (2.55%; 95% CI: 1.36, 4.32), compared to 10 subjects (2.16%, 95% CI: 1.04, 3.94) exposed to placebo and an alpha-blocker (n = 463). Among the subjects (n = 9158) who were exposed to sildenafil citrate (ED) and did not receive an alpha -blocker, a total of 233 subjects experienced a hypotension-related AE (2.54%; 95% CI: 2.23, 2.89) compared with 82 subjects (1.19%, 95% CI: 0.95, 1.48) exposed to placebo and did not receive an alpha-blocker (n = 6880).

Among the 13 subjects who were received an alpha-blocker concomitantly with sildenafil citrate (ED) and experienced a hypotension-related AEs, the events were coded to the PTs Dizziness (12) and Syncope (1).

Among those 13 subjects, the co-administered alpha-blocker in the sildenafil group was doxazosin, terazosin (6 each), tamsulosin (2) and prazosin (1). Among those 10 subjects, the co-administered alpha-blocker in the placebo group was terazosin (4), doxazosin (3), tamsulosin (2) and prazosin (1). Of note subjects may have been exposed to more than one alpha-blocker.

Seriousness/Outcomes:

Among 13 subjects reporting concomitant use of an alpha-blocker with sildenafil citrate (ED), 1 of the subjects experienced hypotension-related AEs (PT Syncope) that were assessed as an SAE. The subject was a 72-year-old male patient who experienced syncope while taking sildenafil (ED) 100 mg. The outcome of the event was not reported.

Severity:

Of the 13 hypotension-related AEs reported, 84.6% (11/13) were considered mild, 7.7% (1/13) were considered moderate and 7.7% were considered severe (1/13).

Table 21. Incidence and Severity of Treatment-Emergent AEs

MedDRA PT	N=510	Severity		
		Mild	Moderate	Severe
Dizziness	12 (2.4%)	11	1	0
Syncope	1 (0.2%)	0	0	1

AE = Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred term; N= Number

Post-marketing Data

Sildenafil (ED) Rx

Cumulatively through 30 June 2019, there were 51 sildenafil (ED) Rx cases (0.1% of all post-marketing cases) that reported concomitant use of an alpha blocker with sildenafil citrate (ED) and also reported an event indicative of hypotension. The 51 cases reported 57 relevant events coded to the PTs Dizziness (29), Hypotension (9), Syncope (7), Presyncope (6), Orthostatic hypotension (4) and Circulatory collapse (2). The alpha blocker that was reported as a co-suspect medication was tamsulosin (13). The alpha-blockers reported as concomitant medications were tamsulosin (18), doxazosin (8), terazosin (6), alfuzosin (3), prazosin (2) and indoramin (1).

Seriousness and outcomes for the 57 relevant AEs are presented in the table below.

Table 22. Seriousness and Outcomes of Events Indicative of Hypotension in Cases Reporting Concomitant Administration of an Alpha Blocker and Sildenafil Citrate (ED) Rx Cumulative through 30 June 2019

MedDRA PT	Number of Events	Serious Events	Fatal	Resolving/ Resolved/Resolved with Sequelae	Not Resolved	Unknown
Dizziness	29	7	0	15	2	12
Hypotension	9	5	0	2	3	4
Syncope	7	2	0	2	0	5
Presyncope	6	3	0	6	0	0
Orthostatic hypotension	4	1	0	1	0	3
Circulatory collapse	2	1	0	0	0	2

MedDRA = Medical Dictionary for Regulatory Activities; PT= Preferred Term

Sildenafil (ED) OTC:

Cumulatively, through 30 June 2019, there were no cases involving sildenafil (ED) OTC [Tradename: Viagra Connect] reporting concomitant use of an alpha blocker and an event indicative of hypotension.

VII.3.1.1.2.4. Risk Factors and Risk Groups

Patients taking alpha blockers who are not haemodynamically stabilised on alpha-blocker therapy prior to initiating sildenafil treatment.

VII.3.1.1.2.5. Preventability

In order to minimise the potential for developing postural hypotension, patients should be haemodynamically stablise on alpha-blocker therapy prior to initiating sildenafil treatment.

In some member states, additional RMMs such as a pharmacist check-list, educational materials for pharmacists and/or patient check-lists are in place (see Part V Section V.2).

VII.3.1.1.2.6. Impact on the Risk-Benefit Balance of the Product

Co-administration of sildenafil (ED) and an alpha-blocker may lead to symptomatic hypotension (e.g. dizziness, syncope or orthostatic hypotension) in a few susceptible individuals and in order to minimise this risk it is cautioned that patients should be stabilised on alpha-blocker therapy prior to initiation of treatment with sildenafil.

Risk minimisation measures are in place (warnings and precautions in the SmPC and in some member states, additional RMMs). Thus, minimal impact on the overall risk-benefit balance of sildenafil (ED) OTC is expected.

VII.3.1.1.2.7. Public Health Impact

The public health impact is expected to be minimal as RMMs are in place (e.g., warnings and precautions in the SmPC and in some member states, additional RMMs) warning patients to use caution when taking sildenafil (ED) with an alpha-blocker and advising patients to ensure they are haemodynamically stable on alpha-blocker therapy prior to initiating sildenafil (ED) treatment.

SVII.3.1.2. Important Identified Risk: Penile Tissue Damage and/or Permanent Loss of Potency Due to Priapism

SVII.3.1.2.1. Potential Mechanisms

Priapism results from a derangement of the penile haemodynamics, affecting the arterial component or the veno-occlusive mechanism. This mechanism explains the 2 types of priapism-high flow and low flow types. High flow (non-ischaemic) priapism commonly follows an episode of trauma to the perineum or the genitalia resulting in increased flow through the arteries. This leads to the formation of arteriocavernous shunts, resulting in increased arterial flow into the cavernous tissue. In ischaemic priapism, there is an abnormality in the venoocclusive mechanism, resulting in venous stasis and accumulation of de-oxygenated blood within the cavernous tissue.[87]

Sildenafil citrate results in increased levels of cGMP which produces smooth muscle relaxation in the corpus cavernosum, allowing inflow of blood. It is unknown whether sildenafil citrate (ED) causes ischaemic or non-ischaemic priapism although certain risk factors may predispose a patient to 1 form of priapism over the other.

SVII.3.1.2.2. Evidence Source and Strength of Evidence

Prolonged erections and priapism have been occasionally reported with sildenafil in post-marketing experience.

SVII.3.1.2.3. Characterisation of the Risk

Clinical Trial Data

Among all subjects (N = 9668) exposed to sildenafil citrate (ED) in 75 double-blinded clinical trials, a total of 12 priapism-related AEs were reported in 12 subjects (0.1%; 95% CI: 0.06, 0.22), compared with 1 AE reported in 1 subject (<0.1%) exposed to placebo (N = 7343). Treatment-emergent all-causality priapism-related AEs reported by subjects in the sildenafil arm of these 75 clinical trials were coded to the following MedDRA PTs: Erection increased and Painful erection; notably, there were no cases of priapism in the clinical trials database.

Seriousness/outcomes:

None of the 12 priapism-related AEs reported were SAEs.

The following outcomes were reported for all 12 priapism-related AEs: resolved/cleared (8 events) and unknown (4 events).

Severity:

Of the 12 priapism-related AEs reported (none were actual cases of true priapism), 58.3% (7/12) were considered mild and 41.7% (5/12) were considered moderate.

Table 23. Incidence and Severity of Treatment-Emergent AEs

MedDRA PT	N=12	Severity		
		Mild	Moderate	Severe
Erection increased	9	5	4	0
Painful erection	3	2	1	0

AE= Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities; PT= Preferred Term; N= Number

Post-marketing Data

Sildenafil (ED) Rx

Cumulatively through 30 June 2019, there were 4,600 sildenafil (ED) Rx cases (5.7% of all post-marketing cases) reporting 4,754 relevant AEs that reported events coded to PTs Erection increased (3,984), Priapism (506), and Painful erection (264).

Seriousness and outcomes for the 4,754 relevant AEs are presented in the table below.

Table 24. Seriousness and Outcomes of Priapism-Related Events (PM Data through 30 June 2019)

MedDRA PT	Number of Events	Serious Events	Fatal	Resolving/Resolved/Resolved with Sequelae	Not Resolved	Unknown
Erection increased	3,984[a]	2,338	0	407	1,061	2,523
Priapism	506	483	0	215	43	248
Painful erection	264	100	0	57	64	143

MedDRA = Medical Dictionary for Regulatory Activities; PT= Preferred Term
a. Cases may report multiple events coded to the same PT

Sildenafil (ED) OTC:

Cumulatively, through 30 June 2019, there were 3 cases (8.6% of the 35 Viagra Connect cases received cumulatively) involving sildenafil (ED) OTC [Tradename: Viagra Connect] reporting priapism-related AEs. All 3 cases reported an event coded to the PT Erection increased. Event outcome was not reported in any of the cases. Two (2) cases were assessed as serious. The first serious case involved a male patient (age unspecified) who reported experiencing an erection for 14 hours even after sexual contact. Action taken with sildenafil (ED) OTC, total number of doses taken, medical history, concomitant medications and treatment information was not reported. The second serious case involved a male patient who reported that he "felt fine" after taking 1 tablet of Viagra Connect; however, when he took 2 tablets a few days later, the patient "kept getting erections for the next 10-12 hours/multiple erections". The action taken with sildenafil (ED) OTC, medical history, concomitant medications and treatment information were not reported. There was no information reported in these 3 cases regarding penile tissue damage or permanent loss of potency due to priapism.

SVII.3.1.2.4. Risk Factors and Risk Groups

Patients at risk include those with sickle cell anaemia[88,89,90,91,92], who use psychotropic agents[89,90,91,] or intracorporeal injections of drugs for the treatment for ED[93,88,89,91,94], who are older[95,93], who have experienced a penile trauma[91], and who have a history of previous recurrent attacks of prolonged erection or priapism.[96] In addition, patients who are Black or Hispanic are at a greater risk but this might be due to the fact that they are more likely to be diagnosed with sickle cell disease.[91]

SVII.3.1.2.5. Preventability

Patients who have conditions which may predispose them to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia), should consult a doctor before using agents for the treatment of erectile dysfunction, including sildenafil citrate (ED). In the event of an erection that persists longer than 4 hours, the patients are instructed to seek immediate medical assistance. In some member states, additional RMMs such as a pharmacist check-list, educational materials for pharmacists and/or patient check-lists are in place (see Part V Section V.2).

SVII.3.1.2.6. Impact on the Risk-Benefit Balance of the Product

The risk, whilst a rare event, is described in the warnings and precautions in the label as it has been observed in post-marketing reports. The warning includes a patient specific action to consult the doctor before using the product if the patient has condition that predisposes them to priapism. The SmPC also instructs the patient to seek immediate medical assistance in the event that they experience an erection that persists longer than 4 hours. In some member states, priapism is communicated in the aRMMs as agreed at a national level.

Due to the rarity of the event and RMMs in place, minimal impact on the overall benefit-risk balance of sildenafil (ED) OTC is expected.

SVII.3.1.2.7. Public Health Impact

Penile tissue damage and/or permanent loss of potency due to priapism is a rare event that would require a patient to seek medical assistance. Minimal public health impact is anticipated, based on the current data from the development programme and PM data.

SVII.3.1.3. Important Potential Risk: Non-arteritic Anterior Ischaemic Optic Neuropathy (NAION)

SVII.3.1.3.1. Potential Mechanism

There is no firmly established mechanistic explanation for the occurrence of NAION associated with the use of sildenafil citrate (ED).

SVII.3.1.3.2. Evidence and Source and Strength of Evidence

NAION has been observed with PDE-5 inhibitors in non-interventional studies as well as in the post-marketing setting.

SVII.3.1.3.3. Characterisation of the Risk

Clinical Trial Data

Ischaemic optic neuropathy (the MedDRA PT including the low level term NAION) was not reported as an AE in any of the 9668 subjects who were exposed to sildenafil citrate (ED) in 75 double-blinded clinical studies of ED. However, PTs possibly representing NAION were reported in 8 subjects (<0.1%; 95% CI: 0.04, 0.16) subjects (coded to PTs Blindness, Visual acuity reduced, and Visual field defect), compared with 3 AEs in 3 subjects (<0.1%) exposed to placebo (N = 7343).

Seriousness/outcomes:

Of the 8 NAION-related AEs reported, 1 event (PT Blindness) was a SAE (outcome: cleared).

The following outcomes were reported for all 8 NAION-related AEs: cleared (2 events), still present at the time of last reporting (2 events), and unknown (4 events).

Severity:

Of the 8 NAION-related AEs reported, 62.5% (5/8) were considered mild, 12.5% (1/8) were considered moderate, and 25.0% (2/8) were considered severe.

Table 25. Incidence and Severity of Treatment-Emergent AEs

MedDRA PT	N=8	Severity		
		Mild	Moderate	Severe
Blindness	1	0	0	1
Visual acuity reduced	4	2	1	1
Visual field defect	3	3	0	0

AE = Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; N= Number

Post-marketing Data

Sildenafil (ED) Rx

A prospective cohort study (the International Men's Health Study) that enrolled 3813 men for 2935 patient-years of follow-up identified no NAION cases.[97] In another PM study (the Sildenafil PEM study) that enrolled over 28000 patients (5601 patients, for a mean follow-up of 6 months and 22473 patients for a mean of almost 18 months), 1 case of NAION was reported, corresponding to unadjusted incidence of NAION of 2.8 per 100000 person-years.[98] This is in line with expected prevalence of NAION in middle-aged/older men.

An observational non-interventional, case-crossover study (A1481259) was conducted to examine whether as needed use of PDE5 inhibitors, as a class (including sildenafil citrate (ED), vardenafil, or tadalafil), triggers the onset of acute NAION within a pharmacokinetically-defined time period (approximately 5 half-lives) following drug ingestion. The primary analysis of "definite NAION" cases suggests an approximately 2-fold increased risk of NAION within 5 half-lives of PDE5 inhibitor use. To put these findings into context, the absolute risk (i.e., risk difference) was estimated by applying the estimated OR of 2.36 based on subjects adjudicated as definite or possible NAION cases to an estimate of the background annual risk of NAION and accounting for the average proportion of days in a given year that a PDE5 inhibitor user is exposed. Using conservative assumptions, PDE5 inhibitor use is estimated to add 3 to 8 cases per 100000 males 50 years and older per year.

Cumulatively through 30 June 2019, there were 1224[5] (1.5% of all post-marketing cases) cases reporting 1661 relevant AEs that reported events coded to MedDRA PTs Blindness

[5] In the sildenafil citrate (ED) OTC RMP version 1.4 there were 1245 post-marketing cases reporting NAION-related events cumulatively through 15 December 2015. The number of cases reporting NAION-related events has decreased in the current sildenafil citrate (ED) OTC RMP version 3.0 (1224 cases received cumulatively through 30 June 2019) due to changes as a result of a MedDRA up-version. The MedDRA version in effect for the sildenafil citrate (ED) OTC RMP version 1.4 was MedDRA version 18.1. In MedDRA version 18.1, the lowest level term (LLT) Vision decreased coded up to PT Visual acuity reduced. In MedDRA

(473), Optic ischaemic neuropathy (403), Visual field defect (170), Visual acuity reduced (146), Blindness unilateral (133), Blindness transient (90), Retinal vein occlusion (71), Optic nerve disorder (36), Retinal artery occlusion (33), Retinal vein thrombosis (25), Optic neuropathy (16), Retinal artery thrombosis (12), Retinal vascular occlusion (11), Amaurosis fugax , Retinal vascular thrombosis (9 each), Retinal ischaemia , Sudden visual loss (5 each), Optic nerve infarction, Retinal artery embolism , Retinal infarction (4 each), and Amaurosis (2).

Seriousness and outcomes for the 1661 AEs are presented in the table below.

Table 26. Seriousness and Outcomes of NAION-Related Events (PM data through 30 June 2019)

MedDRA PT	Number of Events	Serious Events	Fatal	Resolving/ Resolved/ Resolved with Sequelae	Not Resolved	Unknown
Blindness	473[a]	462	0	33	137	305
Optic ischaemic neuropathy	403[a]	402	0	27	75	302
Visual field defect	170[a]	138	0	27	54	93
Visual acuity reduced	146[a]	82	0	32	47	68
Blindness unilateral	133	133	0	17	58	58
Blindness transient	90	72	0	52	6	32
Retinal vein occlusion	71	68	0	8	19	44
Optic nerve disorder	36	32	0	1	13	22
Retinal artery occlusion	33	32	0	6	11	16
Retinal vein thrombosis	25	25	0	4	13	8
Optic neuropathy	16	16	0	1	6	9
Retinal artery thrombosis	12	12	0	3	5	4
Retinal vascular occlusion	11	10	0	2	3	6
Amaurosis fugax	9	9	0	5	0	4

22.0 (the MedDRA version in effect for the sildenafil [ED] OTC RMP version 3.0), LLT Vision decreased now codes up to PT Visual impairment which is a term that is not used to characterise the risk of NAION.

Table 26. Seriousness and Outcomes of NAION-Related Events (PM data through 30 June 2019)

MedDRA PT	Number of Events	Serious Events	Fatal	Resolving/ Resolved/ Resolved with Sequelae	Not Resolved	Unknown
Retinal vascular thrombosis	9	9	0	1	4	4
Retinal ischaemia	5	5	0	0	1	4
Sudden visual loss	5	4	0	2	1	2
Optic nerve infarction	4	4	0	0	0	4
Retinal artery embolism	4	3	0	0	1	3
Retinal infarction	4	4	0	0	0	4
Amaurosis	2	2	0	1	1	0

MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; N= Number
a. Cases may report multiple events coded to the same PT

Sildenafil (ED) OTC:

Cumulatively, through 30 June 2019, there were no cases involving sildenafil (ED) OTC [Tradename: Viagra Connect] reporting events indicative of NAION.

SVII.3.1.3.4. Risk Factors and Risk Groups

NAION shares several risk factors with ED, such as ischaemic heart disease, hypertension, hypercholesterolemia, diabetes, and increased age.[99,100,101] Other potential risk factors for NAION are sleep apnoea, hyperhomocystinemia, the presence of a disc at risk (ie, a crowded optic nerve head), cataract extraction and intraocular lens surgery, disorders of blood coagulation and specifically thrombotic tendency.[102,103] Patients who have experienced an episode of NAION in 1 eye are at higher risk of having it occur in the opposite eye, as well as those who have had cataract extraction, intraocular lens surgery, or who have a 'disc at risk'.

SVII.3.1.3.5. Preventability

Sildenafil (ED) is contraindicated in patients who have loss of vision in one eye because of NAION, regardless of whether this episode was in connection or not with previous PDE-5 inhibitor exposure. In some member states, additional RMMs such as a pharmacist check-list, educational materials for pharmacists and/or patient check-lists are in place (see Part V Section V.2).

SVII.3.1.3.6. Impact on the Risk-Benefit Balance of the Product

NAION is a rare condition and a cause of decreased vision or loss of vision that has been reported in post-marketing with the use of all PDE5 inhibitors, including sildenafil. Most patients that experience NAION while taking a PDE-5 inhibitor had risk factors such as low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidaemia and smoking.

The risk, whilst rare, may lead to serious damage to the optic nerve[104] and has been appropriately communicated in the aRMMs in some member states as agreed at the national level.

Given the low frequency of occurrence and the presence of RMMs, it is expected that NAION will have a minimal impact on the overall benefit risk balance of sildenafil citrate (ED) OTC.

SVII.3.1.3.7. Public Health Impact

NAION is a rare event that would require a patient to consult their physician immediately. Minimal public health impact is expected given the low frequency of the event.

SVII.3.1.4. Important Potential Risk: Sudden Hearing Loss

SVII.3.1.4.1. Potential Mechanism

No biologically plausible mechanism for sildenafil citrate (ED) inducing hearing loss has been identified.

SVII.3.1.4.2. Evidence Source and Strength of Evidence

Sudden decrease or loss of hearing has been reported in a small number of post-marketing and clinical trial cases with the use of all PDE5 inhibitors, including sildenafil.

SVII.3.1.4.3. Characterisation of the Risk

Clinical Trial Data

Among all subjects (N = 9668) exposed to sildenafil citrate (ED) in 75 double-blinded clinical trials, a total of 22 sudden hearing loss-related AEs were reported in 22 subjects (0.2%; 95% CI: 0.14, 0.34), compared with 2 AEs reported in 2 subjects (<0.1%) exposed to placebo (N = 7343). Treatment-emergent all-causality sudden hearing loss-related AEs reported by subjects in the sildenafil arm of these 75 clinical trials were coded to the following PTs: Deafness, Deafness unilateral, Hypoacusis, Tinnitus, and Barotitis media; 18 of the 22 subjects reported tinnitus.

Seriousness/Outcomes:

Of the 22 sudden hearing loss-related AEs reported, 2 events (PT Deafness unilateral, Barotitis media) were SAEs. Outcome for both SAEs was unknown.

The following outcomes were reported for all 22 sudden hearing loss-related AEs: resolved/cleared (5 events), still present at the time of last reporting (3 events), and unknown (14 events).

Severity:

Among the 22 sudden hearing loss-related AEs reported, 68.2% (15/22) were considered mild, 27.3% (6/22) were considered moderate, and 4.5% (1/22) were considered severe.

Table 27. Incidence and Severity of Treatment-Emergent AEs

MedDRA PT	N= 22	Severity		
		Mild	Moderate	Severe
Deafness	1	1	0	0
Deafness unilateral	1	0	0	1
Hypoacusis	1	1	0	0
Tinnitus	18	13	5	0
Barotitis media	1	0	1	0

AE = Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred term; N= Number

Post-marketing Data

Sildenafil (ED) Rx

Cumulatively through 30 June 2019, there were 736 cases reporting (0.9% of the dataset) 825 relevant AEs that reported events coded to MedDRA PTs Tinnitus (274), Hypoacusis (242), Deafness (158), Deafness unilateral (54), Sudden hearing loss (34), Deafness neurosensory (18), Auditory disorder (14), Deafness transitory (13), Hyperacusis (5), Deafness bilateral (4), Middle ear effusion (3), Eustachian tube disorder (2) and 1 event each of Acoustic neuritis, Barotitis media, Ototoxicity and Tympanic membrane perforation.

Seriousness and outcomes for the 825 AEs is presented in the table below.

Table 28. Seriousness and Outcomes of Sudden Hearing Loss-Related Events (PM data through 30 June 2019)

MedDRA PT	Number of Events	Serious Events	Fatal	Resolving/ Resolved/ Resolved with Sequelae	Not Resolved	Unknown
Tinnitus	274	53	0	54	101	119
Hypoacusis	242	117	0	17	65	160
Deafness	158	150	0	24	42	92
Deafness unilateral	54	52	0	8	20	26
Sudden hearing loss	34	33	0	4	15	15
Deafness neurosensory	18	18	0	1	11	6

Table 28. Seriousness and Outcomes of Sudden Hearing Loss-Related Events (PM data through 30 June 2019)

MedDRA PT	Number of Events	Serious Events	Fatal	Resolving/ Resolved/ Resolved with Sequelae	Not Resolved	Unknown
Auditory disorder	14	3	0	3	3	8
Deafness transitory	13	13	0	10	0	3
Hyperacusis	5	1	0	1	2	2
Deafness bilateral	4	4	0	0	2	2
Middle ear effusion	3	2	0	2	1	0
Eustachian tube disorder	2	0	0	1	1	0
Acoustic neuritis	1	1	0	1	0	0
Barotitis media	1	0	0	0	0	1
Ototoxicity	1	1	0	0	0	1
Tympanic membrane perforation	1	1	0	0	0	1

MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred term.

Sildenafil (ED) OTC:

Cumulatively, through 30 June 2019, there was 1 case (2.9% of the 35 Viagra Connect cases received cumulatively) involving sildenafil (ED) OTC [Tradename: Viagra Connect] reporting a relevant event indicative of sudden hearing loss. This case involved a male patient (age unspecified) who took one tablet of Viagra Connect and experienced "faded hearing" (PT Hypoacusis) five minutes later. After a few hours, the event resolved. Medical history, concomitant medications and action taken with sildenafil (ED) OTC were not reported.

SVII.3.1.4.4. Risk Factors and Risk Groups

The occurrence of hearing loss rises with age, with some evidence that it is more likely in men than women.

SVII.3.1.4.5. Preventability

In some member states, additional RMMs such as educational materials for pharmacists are in place (see Part V Section V.2).

SVII.3.1.4.6. Impact on the Risk-Benefit Balance of the Product

Sudden decrease or loss of hearing has been reported in a small number of postmarketing and clinical trials cases with the use of all PDE5 inhibitors, including sildenafil. Most of these

patients had risk factors (e.g., older age, family history of hearing loss and concomitant ototoxic medications) for sudden decrease or loss of hearing. No direct causal relationship has been made between the use of PDE5 inhibitors and sudden decrease or loss of hearing. In case of sudden decrease or loss of hearing patients should be advised to stop taking sildenafil and consult a physician promptly.

Due to the potential seriousness of the event, this risk is communicated in aRMMs in some member states as agreed at the national level.

Given the rarity of the event and presence of RMMs, it is expected that this risk will have a minimal impact on the overall benefit risk balance of sildenafil citrate (ED) OTC.

SVII.3.1.4.7. Public Health Impact

Minimal public health impact is expected given the low frequency of the event.

SVII.3.1.5. Symptomatic Hypotension in Men with Pre-existing Hypotension

SVII.3.1.5.1. Potential Mechanism

Sildenafil (ED) has vasodilator properties, resulting in mild and transient decreases in blood pressure. Men with pre-existing hypotension (blood pressure < 90/50 mmHg) have a potential risk of experiencing symptomatic hypotension (i.e., a decrease in blood pressure such that symptoms of hypotension such as dizziness, syncope or orthostatic hypotension are manifested).

SVII.3.1.5.2. Evidence Source(s) and Strength of Evidence

Patients with hypotension (blood pressure <90/50 mmHg) were excluded from the clinical development program. However, based on the known vasodilator properties of sildenafil (ED), symptomatic hypotension (i.e., a decrease in blood pressure such that symptoms of hypotension such as dizziness, syncope or orthostatic hypotension are manifested) may occur in men with pre-existing hypotension.

SVII.3.1.5.3. Characterisation of the Risk

Sildenafil (ED) Rx

Post-marketing data:

Cumulatively through 30 June 2019, there were 11 cases involving men with pre-existing hypotension (0.01% of all post-marketing cases) reporting 11 relevant AEs that reported events coded to MedDRA PTs Dizziness (9), Hypotension and Orthostatic hypotension (1 each).

Seriousness and Outcomes for the 11 AEs is presented in the table below.

Table 29. Seriousness and Outcomes of Symptomatic hypotension in Men with Pre-existing Hypotension (PM data through 30 June 2019)

MedDRA PT	Number of Events	Serious Events	Fatal	Resolving/ Resolved/ Resolved with Sequelae	Not Resolved	Unknown
Dizziness	9	0	0	3	0	6
Hypotension	1	1	0	0	0	1
Orthostatic hypotension	1	0	0	1	0	0

MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred term.

Sildenafil (ED) OTC:

Cumulatively, through 30 June 2019, there were no cases involving sildenafil (ED) OTC [Tradename: Viagra Connect] involving symptomatic hypotension in men with pre-existing hypotension.

SVII.3.1.5.4. Risk factors and Risk Groups

Patients with hypotension (blood pressure <90/50 mmHg).

SVII.3.1.5.5. Preventability

In some member states, additional RMMs such as a pharmacist check-list, educational materials for pharmacists and patient check-lists are in place (see Part V Section V.2).

SVII.3.1.5.6. Impact on the risk-benefit balance of the product

Symptoms of hypotension include feeling light-headed, confused, tired or weak. In addition, a patient may experience blurred vision, headaches, neck or back pain, nausea or heart palpitations. In severe cases, hypotension can lead to shock. [105]

Given the low number of cases observed in the post-marketing safety database in relation to the cumulative exposure to sildenafil (ED) and the presence of aRMMs in some member states as agreed at the national level the risk is expected to have a minimal impact on the overall benefit-risk balance of sildenafil citrate (ED) OTC.

SVII.3.1.5.7. Public health impact

There was a low number of cases observed in the post-marketing safety database in relation to the cumulative exposure to sildenafil (ED). The public health impact is expected to be minimal.

SVII.3.2. Presentation of the Missing Information

There are no missing information for sildenafil (ED) OTC.

Module SVIII. Summary of the Safety Concerns

Table 30. Summary of Safety Concerns for Sildenafil Citrate (ED)

Summary of Safety Concerns	
Important identified risks	• Symptomatic hypotension[a]/increase hypotensive effect in men taking: -nitrates or NO donors, including nitrites (eg, amyl nitrite or 'poppers' for recreational use) -who are not stabilized on alpha-blocker therapy • Penile tissue damage and/or permanent loss of potency due to priapism
Important potential risks	• NAION • Sudden hearing loss • Symptomatic hypotension[a] in men with pre-existing hypotension
Missing information	None.

BP = Blood Pressure; NAION = Non-arteritic Anterior Ischaemic Optic Neuropathy; NO = Nitric Oxide.

a. Symptomatic hypotension is a decrease in blood pressure such that symptoms of hypotension such as dizziness, syncope or orthostatic hypotension are manifested.

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond ADR reporting and signal detection:

- **Specific adverse reaction follow-up questionnaires for safety concerns:**

  Targeted follow-up (FU) questionnaires (Data Capture Aides [DCAs]) for post-marketing reports are in place to better understand the nature of the following important risks: Penile tissue damage and/or permanent loss of potency due to priapism (DCA: Priapism/Peyronie's Disease); NAION (DCA: Visual events) and Sudden hearing loss (DCA: Hearing impairment). FU questionnaires are provided in Annex 4 of this RMP.

- **Other forms of routine pharmacovigilance activities for safety concerns:**

  Not applicable

III.2. Additional Pharmacovigilance Activities

There are no category 1-2 studies for sildenafil (ED).

In the United Kingdom (UK), a post-authorization safety study (protocol A1481334) was conducted from 28 January 2019 through 31 March 2019 to evaluate the effectiveness of additional risk minimization measures (aRMMs). The effectiveness was evaluated via a cross-sectional survey of pharmacists.

The study concluded that in this sample of pharmacists who supply Viagra Connect, there was generally a high level of knowledge and awareness of the Key Risk Messages. There are some areas that could benefit from more emphasis in the training modalities provided to pharmacists, including improved knowledge of the underlying health conditions of patients with ED, contraindicated medications, and that men using a different dose of sildenafil or other ED treatment may not also be supplied Viagra Connect.

Utilisation and satisfaction with the Viagra Connect Pharmacy Training and the voluntary pharmacist checklist was high. The stratified analyses indicate that participation in pharmacist training was associated with slightly higher rate of utilization of the voluntary checklist and tear-off slips and a greater proportion of pharmacists advising the patients to see their doctor within 6 months of supply. This along with the high proportion of pharmacists indicating that the aRMMs materials are their main source of knowledge coupled

with the overall high rate of correct responses to knowledge questions suggest that the aRMMs have been effective in ensuring patients are supplied Viagra Connect safely by pharmacists. Study data provide reasonable assurance that the pharmacist participants are representative of the wider pharmacist population in the UK with respect to type of pharmacy.

Additional information on study A1481334 is provided in Annex 2 and Annex 7.

III.3. Summary Table of Additional Pharmacovigilance Activities

There are no ongoing or planned category 1,2, or studies for sildenafil (ED) OTC.

III.3.1. On-Going and Planned Additional Pharmacovigilance Activities

None.

PART IV. PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no on-going post-authorisation efficacy studies for sildenafil citrate (ED), and none are planned.

The ED patient population who was enrolled in the pivotal Phase 3 studies of sildenafil citrate (ED) was intended to be reflective of the population who would be expected to be prescribed sildenafil citrate (ED) in clinical practice. The pre-registration clinical trial programme included patients with ED caused by a variety of underlying medical and other conditions and excluded subjects in the following sub-groups: severe hepatic impairment, hypotension (BP <90/50 mmHg), recent history of stroke or myocardial infarction and known hereditary degenerative retinal disorders such as retinitis pigmentosa. Post approval, the clinical trial programme continued with some individual trials further documenting the efficacy and safety of sildenafil in patients with specific causes of ED or risk factors for ED (eg, depression, multiple sclerosis, prostate cancer, diabetes, heart failure, hypertension etc.). Therefore, the overall clinical trial database is well representative of the subject population likely to use sildenafil citrate (ED).

PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

As expected for a non-Rx product, the SmPC, Package Leaflet (PL) and product label will be the key tools to ensure appropriate and effective use of OTC sildenafil. In accordance with national healthcare practice and policies, national training material, including a diagnostic tool (check-list) will be made available for pharmacists and patients, depending on the market to support the supply without Rx. These materials will be tailored and managed at a national level to meet national requirements.

V.1. Routine Risk Minimisation Measures

Table 31. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
Important Identified Risks	
Symptomatic hypotension/increase hypotensive effect in men taking: -nitrates or NO donors, including nitrites (eg, amyl nitrite or 'poppers' for recreational use) -who are not stabilized on alpha-blocker therapy	Routine risk communication SmPC Section 4.3 *Contraindications*, Section 4.4: *Special warnings and precautions for use*, Section 4.5: *Interaction with other medicinal products and other forms of interaction*. PL Section: 2. *What you need to know before you take Viagra Connect*, Section: 4. *Possible side effects* Product Label Section: 15. *Instructions on Use* Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for the contraindication for co-administration of sildenafil citrate (ED) with nitric oxide donors (such as amyl nitrate) or nitrates in any form is included in SmPC Section 4.3 and PL Section 2. SmPC Section 4.4 recommends that in order to minimise the potential for developing postural hypotension, patients should be haemodynamically stable on alpha-blocker therapy prior to initiating sildenafil treatment. Patients taking sildenafil (ED) 50 mg are advised to consult their doctor as a 25 mg tablet may be more suitable for them. For patients taking sildenafil (ED) 25 mg, a maximum daily dose of 25 mg is recommended. Treatment should be stopped if symptoms of postural hypotension occur, and patients should seek advice from their doctor on what to do. Other routine risk minimisation measures beyond the Product Information: None
Penile tissue damage and/or permanent loss of potency due to priapism	Routine risk communication SmPC Section 4.3: *Contraindications*, Section 4.4: *Special warnings and precautions for use*, Section 4.8: *Undesirable effects*

Table 31. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
	PL Section: 2. *What you need to know before you take Viagra Connect*, Section: 4. *Possible side effects* Product Label Section: 15. *Instructions on Use* <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> Recommendation for the contraindication of sildenafil citrate (ED) in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease) is included in SmPC Section 4.3 and PL Section 2. Recommendation that in the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance is included in SmPC Section 4.4 and PL Section 4. <u>Other routine risk minimisation measures beyond the Product Information:</u> None
Important Potential Risks	
NAION	<u>Routine risk communication</u> SmPC Section 4.3: *Contraindications*, Section 4.4: *Special warnings and precautions for use*, Section 4.8: *Undesirable effects* PL Section: 2. *What you need to know before you take Viagra Connect*, Section: 4. *Possible side effects* Product Label Section: 15. *Instructions on Use* <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> Recommendation for the contraindication of sildenafil citrate (ED) use in patients who have loss of vision in one eye because of NAION, regardless of whether this episode was in connection or not with a previous PDE5 inhibitor exposure is included in SmPC Section 4.3 and PL Section 2. Patients are advised in SmPC Section 4.4 and PL Section 4 that in an event of any sudden visual defect, they should stop taking sildenafil citrate (ED) and consult a physician immediately. <u>Other routine risk minimisation measures beyond the Product Information:</u> None
Sudden hearing loss	<u>Routine risk communication</u> SmPC Section 4.8 *Undesirable effects* PL Section 4. *Possible side effects*

Table 31. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None
Symptomatic hypotension in men with pre-existing hypotension	Routine risk communication SmPC Section 4.3 *Contraindications* PL Section 2. *What you need to know before you take Viagra Connect* Product Label Section 15. *Instructions on Use* Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation that sildenafil citrate (ED) should not be used in patients with hypotension (blood pressure < 90/50 mmHg) is included in SmPC Section 4.3 and PL Section 2. Other routine risk minimisation measures beyond the Product Information: None
Missing Information	
None.	

NAION = Non-arteritic Anterior Ischaemic Optic Neuropathy; NO = Nitric Oxide; PDE= Phosphodiesterase; PL = Package Leaflet; SmPC = Summary of Product Characteristics

V.2. Additional Risk Minimisation Measures

The need and content of additional risk minimization measures may vary across member states and are agreed at a national level. Examples of additional risk minimisation measures (aRMMs) that may be implemented in a member state depending on the pharmacy model in place include a pharmacist check-list, educational materials for pharmacists and/or a patient checklist. These examples of aRMMs may contain the following key elements:

Pharmacist Check-List

Objectives:

The objective of the proposed additional measure is to assist pharmacists in determining whether a patient is suitable for sildenafil (ED) OTC. The following safety concerns are addressed in the pharmacist check-list:

- Symptomatic hypotension/increase hypotensive effect in patients:

  - nitrates or NO donors, including nitrites (e.g., amyl nitrite or 'poppers' for recreational use)

  - who are not stabilized on alpha-blocker therapy

- Penile tissue damage and/or permanent loss of potency due to priapism
- NAION
- Symptomatic hypotension in men with pre-existing hypotension

Rationale for the additional risk minimisation activity:

The rationale for the proposed additional measure is to assist pharmacists in determining whether a patient is suitable for sildenafil (ED) OTC and to help mitigate the risks by ensuring that appropriate patients receive the medication.

Target audience and planned distribution path:

The target audience is pharmacists. The communication plan varies by local, legal and regulatory requirements.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Routine pharmacovigilance activities to identify new safety signals and monitor reporting trends.[6]

Risk minimisation measures are judged effective if no negative trends or worsening outcomes are identified.

[6] As noted in the Good Pharmacovigilance Practices Module XVI (Rev 2) dated 31 March 2017, there are well-known biases that affect reporting of suspected adverse reactions that may provide misleading results (e.g., the introduction of a risk minimisation measure in response to a safety concern detected in the post-authorisation phase of a medicinal product may raise awareness regarding related adverse reactions which ultimately may result in an increased reporting rate. In these circumstances an analysis of spontaneous reporting may lead to the erroneous conclusion that the intervention was ineffective. Decreasing reporting rates over time may also lead to the erroneous conclusion that the intervention was effective.*)*

The MAH plans to provide an evaluation of the effectiveness of routine pharmacovigilance activities in the next 5-year Period Safety Update Report (PSUR) scheduled to be submitted on 31 March 2022.

Educational materials for pharmacists

Objectives:

The objective of the proposed additional measure is to assist pharmacists in the assessment of whether a patient is suitable for sildenafil (ED) OTC and to provide additional information on erectile dysfunction, its causes, risk factors, co-morbid links, management, treatment options, sildenafil (ED) OTC product information and information on the pharmacist's role in supporting the patient. The following safety concerns are addressed in the educational materials for pharmacists:

- Symptomatic hypotension/increase hypotensive effect in patients:

  - nitrates or NO donors, including nitrites (e.g., amyl nitrite or 'poppers' for recreational use)

  - who are not stabilized on alpha-blocker therapy

- Penile tissue damage and/or permanent loss of potency due to priapism
- NAION
- Sudden hearing loss
- Symptomatic hypotension in men with pre-existing hypotension

Rationale for the additional risk minimisation activity:

The rationale for the proposed additional measure is to assist pharmacists in determining whether a patient is suitable for sildenafil (ED) OTC, to help mitigate the risks by ensuring that appropriate patients receive the medication and further support pharmacists in their role in managing ED.

Target audience and planned distribution path:

The target audience is pharmacists. The communication plan varies by local, legal and regulatory requirements.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Routine pharmacovigilance activities to identify new safety signals and monitor reporting trends.[6]

Risk minimisation measures are judged effective if no negative trends or worsening outcomes are identified.

The MAH plans to provide an evaluation of the effectiveness of routine pharmacovigilance activities in the next 5-year Period Safety Update Report (PSUR) scheduled to be submitted on 31 March 2022.

Patient Checklist

Objectives:

The objective of the proposed additional measure is to provide an appropriate tool designed to assist the patient in determining whether he is suitable for sildenafil (ED) OTC. In addition, the objective is to provide the patient with further direction with respect to the patient's general and sexual health. The following safety concerns are addressed in the patient check-list:

- Symptomatic hypotension/increase hypotensive effect in patients:

  - nitrates or NO donors, including nitrites (e.g., amyl nitrite or 'poppers' for recreational use)

  - who are not stabilized on alpha-blocker therapy

- Penile tissue damage and/or permanent loss of potency due to priapism
- NAION
- Symptomatic hypotension in men with pre-existing hypotension

Rationale for the additional risk minimisation activity:

The rationale for the proposed additional measure is to assist the patient in determining whether he is suitable for sildenafil (ED) OTC and to help mitigate the risks by ensuring that appropriate patients receive the medication.

Target audience and planned distribution path:

The target audience is the patient. The communication plan varies by local, legal and regulatory requirements.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Routine pharmacovigilance activities to identify new safety signals and monitor reporting trends.[6]

Risk minimisation measures are judged effective if no negative trends or worsening outcomes are identified.

The MAH plans to provide an evaluation of the effectiveness of routine pharmacovigilance activities in the next 5-year Period Safety Update Report (PSUR) scheduled to be submitted on 31 March 2022.

V.3. Summary of Risk Minimisation Measures

Table 32. Summary of Pharmacovigilance Activities and Risk Minimisation Measures by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Symptomatic hypotension/increase hypotensive effect in men taking: -nitrates or NO donors, including nitrites (eg, amyl nitrite or 'poppers' for recreational use) -who are not stabilized on alpha-blocker therapy	Routine risk minimisation measures: SmPC Section(s): 4.3: *Contraindications* 4.4: *Special warnings and precautions for use* 4.5: *Interactions with other medicinal products and other forms of interaction* PL Section(s): 2. *What you need to know before you take Viagra Connect* 4. *Possible side effects* Product Label Section(s): 15. *Instructions on Use* Examples of additional risk minimisation measures: Pharmacist checklist, Educational materials for pharmacists, Patient checklist	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Penile tissue damage and/or permanent loss of potency due to priapism	Routine risk minimisation measures: SmPC Section(s): 4.3: *Contraindications* 4.4: *Special warning and precautions for use* 4.8: *Undesirable effects* PL Section(s): 2. *What you need to know before you take Viagra Connect* 4. *Possible side effects* Product Label Section(s): 15. *Instructions on Use* Examples of additional risk minimisation measures: Pharmacist checklist,	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up (FU) questionnaires for post-marketing reports of priapism/Peyronie's disease Additional pharmacovigilance activities: None

Table 32. Summary of Pharmacovigilance Activities and Risk Minimisation Measures by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Educational materials for pharmacists, Patient checklist	
Important Potential Risks		
NAION	Routine risk minimisation measures: SmPC Section(s): 4.3: *Contraindications* 4.4: *Special warnings and precautions for use* 4.8: *Undesirable effects* PL Section(s): 2. *What you need to know before you take Viagra Connect* 4. *Possible side effects* Product Label Section(s): 15. *Instructions on Use* Examples of additional risk minimisation measures: Pharmacist checklist, Educational materials for pharmacists, Patient checklist	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted FU questionnaires for post-marketing reports of visual events. Additional pharmacovigilance activities: None
Sudden hearing loss	Routine risk minimisation measures: SmPC Section(s): 4.8: *Undesirable effects* PL Section(s): 4. *Possible side effects* Examples of additional risk minimisation measures: Educational materials for pharmacists	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted FU questionnaires for post-marketing reports of hearing impairment. Additional pharmacovigilance activities: None
Symptomatic hypotension in men with pre-existing hypotension	Routine risk minimisation measures: SmPC Section(s): 4.3: *Contraindications* PL Section(s): 2. *What you need to know before you take Viagra Connect*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Table 32. Summary of Pharmacovigilance Activities and Risk Minimisation Measures by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Product Label Section(s): 15. *Instructions on Use* <u>Examples of additional risk minimisation measures:</u> Pharmacist checklist, Educational materials for pharmacists, Patient checklist	
Missing Information		
None.		

FU= Follow-up; NAION = Non-arteritic Anterior Ischaemic Optic Neuropathy; NO = Nitric Oxide; PL = Package Leaflet; SmPC = Summary of Product Characteristics

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Viagra Reseptfri/Viagra Connect

This is a summary of the risk management plan (RMP) for Viagra Reseptfri and Viagra Connect, henceforth referred to as Viagra Reseptfri. The RMP details important risks of Viagra Reseptfri, how these risks can be minimised, and how more information will be obtained about Viagra Reseptfri 's risks and uncertainties (missing information).

Viagra Reseptfri 's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals (HCPs) and patients on how Viagra Reseptfri should be used.

I. The Medicine and What It Is Used For

Viagra Reseptfri is authorised for the treatment of adult men with erectile dysfunction (see SmPC for the full indication). It contains sildenafil citrate as the active substance and it is given by oral route of administration.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Viagra Reseptfri, together with measures to minimise such risks and the proposed studies for learning more about Viagra Reseptfri 's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine’s packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine’s legal status — the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Viagra Reseptfri, in some member states, depending on the pharmacy model in place, these measures may be supplemented with *additional risk minimisation* measures under relevant important risks, below.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Viagra Reseptfri is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Viagra Reseptfri are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Viagra Reseptfri. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long term use of the medicine).

Table 33. List of important risks and missing information for Viagra Reseptfri

Important identified risks	Symptomatic hypotension[a]/increase hypotensive effect in men taking: -nitrates or NO donors, including nitrites (eg, amyl nitrite or 'poppers' for recreational use) -who are not stabilized on alpha-blocker therapy Penile tissue damage and/or permanent loss of potency due to priapism
Important potential risks	Non-arteritic Anterior Ischaemic Optic Neuropathy (NAION) Sudden hearing loss Symptomatic hypotension[a] in men with pre-existing hypotension
Missing information	None

NAION= Non-arteritic Anterior Ischaemic Optic Neuropathy; NO=Nitric oxide;
a. Symptomatic hypotension is a decrease in blood pressure such that symptoms of hypotension such as dizziness, syncope or orthostatic hypotension are manifested.

II.B. Summary of Important Risks and Missing Information

Table 34. Summary of Important Risks and Missing Information

Important Identified Risk: Symptomatic Hypotension/increase Hypotensive Effect in Men: - taking nitrates or NO donors, including nitrites (eg, amyl nitrite or 'poppers' for recreational use) -who are not stabilized on alpha-blocker therapy	
Evidence for linking the risk to the medicine	In preclinical studies, in anaesthetised dogs, sildenafil was shown to potentiate nitroglycerin induced postural hypotension. A study (148-209) conducted in human volunteers to assess the effects of sildenafil (25 mg) on the haemodynamic responses to Glyceryl Trinitrate (GTN) using a tilt table under laboratory conditions showed that sildenafil (multiple daily dosing) potentiated the hypotensive effects of sublingual and IV GTN (Study 148-209). Following this Phase I study, use in patients on chronic nitrates was contraindicated in all subsequent sildenafil (ED) studies. Hypotension/increased hypotensive effect in patients taking sildenafil and nitrates or nitric oxide donors has also been observed in the post-marketing setting. Hypotension/increased hypotensive effects in patients taking sildenafil (ED) and alpha-blocker have been observed in the clinical trial and post-marketing setting.
Risk factors and risk groups	Patients taking NO donors or nitrates or patients who are not stabilized on alpha blocker therapy
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Section(s): 4.3: *Contraindications* 4.4: *Special warnings and precautions for use* 4.5: *Interactions with other medicinal products and other forms of interaction* PL Section(s): 2. *What you need to know before you take Viagra Connect* 4. *Possible side effects* Product Label Section(s): 15. *Instructions on Use* <u>Additional risk minimisation measures:</u> Pharmacist checklist, Educational materials for pharmacists, Patient checklist
Important Identified Risk: Penile Tissue Damage and/or Permanent Loss of Potency Due to Priapism	
Evidence for linking the risk to the medicine	Priapism results from a derangement of the penile haemodynamics, affecting the arterial component or the veno-occlusive mechanism. This mechanism explains the 2 types of priapism-high flow and low flow types. High flow (non-ischaemic) priapism commonly follows an episode of trauma to the perineum or the genitalia resulting in increased flow through the arteries. This leads to the formation of arteriocavernous shunts, resulting in increased arterial flow into the cavernous tissue. In ischaemic priapism, there is an abnormality in the venoocclusive mechanism, resulting in venous stasis and accumulation of de-oxygenated blood within the cavernous tissue.[87] Sildenafil citrate results in increased levels of cGMP which produces smooth muscle relaxation in the corpus cavernosum, allowing inflow of blood. It is unknown whether sildenafil citrate (ED) causes ischaemic or non-ischaemic

Table 34. Summary of Important Risks and Missing Information

	priapism although certain risk factors may predispose a patient to 1 form of priapism over the other.
Risk factors and risk groups	Patients at risk include those with sickle cell anaemia[88,89,90,91,92] who use psychotropic agents[88,90,91] or intracorporeal injections of drugs for the treatment for ED[88,89,91,93,94] who are older[93,95], who have experienced a penile trauma[91], and who have a history of previous recurrent attacks of prolonged erection or priapism.[96] In addition, patients who are Black or Hispanic are at a greater risk but this might be due to the fact that they are more likely to be diagnosed with sickle cell disease. [91]
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Section(s): 4.3: *Contraindications* 4.4: *Special warning and precautions for use* 4.8: *Undesirable effects* PL Section(s): 2. *What you need to know before you take Viagra Connect* 4. *Possible side effects* Product Label Section(s): 15. *Instructions on Use* <u>Additional risk minimisation measures:</u> Pharmacist checklist, Educational materials for pharmacists, Patient checklist
Important Potential Risk: NAION	
Evidence for linking the risk to the medicine	NAION has been observed with PDE-5 inhibitors in non-interventional studies as well as in the post-marketing setting.
Risk factors and risk groups	NAION shares several risk factors with ED, such as ischaemic heart disease, hypertension, hypercholesterolemia, diabetes, and increased age.[99,100,101] Other potential risk factors for NAION are sleep apnoea, hyperhomocystinemia, the presence of a disc at risk (ie, a crowded optic nerve head), cataract extraction and intraocular lens surgery, disorders of blood coagulation and specifically thrombotic tendency. [102,103]Patients who have experienced an episode of NAION in 1 eye are at higher risk of having it occur in the opposite eye, as well as those who have had cataract extraction, intraocular lens surgery, or who have a 'disc at risk'.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Section(s): 4.3: *Contraindications* 4.4: *Special warnings and precautions for use* 4.8: *Undesirable effects* PL Section(s): 2. *What you need to know before you take Viagra Connect* 4. *Possible side effects* Product Label Section(s): 15. *Instructions on Use*

Table 34. Summary of Important Risks and Missing Information

	Additional risk minimisation measures: Pharmacist checklist, Educational materials for pharmacists, Patient checklist
Important Potential Risk: Sudden Hearing Loss	
Evidence for linking the risk to the medicine	Sudden decrease or loss of hearing has been reported in a small number of post-marketing and clinical trial cases with the use of all PDE5 inhibitors, including sildenafil.
Risk factors and risk groups	The occurrence of hearing loss rises with age, with some evidence that it is more likely in men than women.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section(s): 4.8: *Undesirable effects* PL Section(s): 4. *Possible side effects* Additional risk minimisation measures: Educational materials for pharmacists
Important Potential Risk: Symptomatic Hypotension in Men with Pre-existing Hypotension	
Evidence for linking the risk to the medicine	Patients with hypotension (blood pressure <90/50 mmHg) were excluded from the clinical development program. However, based on the known vasodilator properties of sildenafil (ED), symptomatic hypotension (i.e., a decrease in blood pressure such that symptoms of hypotension are manifested such as dizziness, syncope or orthostatic hypotension) may occur in patients with pre-existing hypotension.
Risk factors and risk groups	Patients with hypotension (blood pressure <90/50 mmHg).
Risk minimisation measures	Routine risk minimisation measures: SmPC Section(s): 4.3: *Contraindications* PL Section(s): 2. *What you need to know before you take Viagra Connect* Product Label Section(s): 15. *Instructions on Use* Additional risk minimisation measures: Pharmacist checklist, Educational materials for pharmacists, Patient checklist
Missing Information	
None	

ED= Erectile dysfunction; EMA= European Medicines Agency; cGMP = Cyclic Guanosine Monophosphate; GTN= Glyceryl Trinitrate; IV= Intravenous; NAION = Non-arteritic Anterior Ischaemic Optic Neuropathy; NO = Nitric Oxide; PDE= Phosphodiesterase; PL = Package Leaflet; SmPC = Summary of Product Characteristics

II.C. Post-Authorisation Development Plan

II.C.1. Studies which are Conditions of the Marketing Authorisation

There are no on-going or planned studies which are conditions of the marketing authorisation or specific obligation of sildenafil citrate (ED) OTC.

II.C.2. Other Studies in Post-Authorisation Development Plan

There are no on-going or planned category 1-2-3 studies required for sildenafil citrate (ED) OTC.

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Annex 2 – Tabulated summary of planned, on-going, and completed pharmacovigilance study programme

Annex 3 – Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan

Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms

Annex 5 – Protocols for proposed and on-going studies in RMP Part IV

Annex 6 – Details of Proposed Additional Risk Minimisation Activities (if applicable)

Annex 7 – Other Supporting Data (Including Referenced Material)

Annex 8 – Summary of Changes to the Risk Management Plan over Time

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ANNEX 2. TABULATED SUMMARY OF PLANNED, ON-GOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAMME

Table 1. Summary of Completed Pharmacovigilance Studies For Sildenafil (ED) Rx

Study	Summary of Objectives	Safety Concerns Addressed	Protocol Link Milestones
Prescription Event Monitoring Study (Phase I and II) Cohort study	A population-based study conducted in 2 phases to measure the occurrence of safety outcomes, including selected short-term cardiovascular (CV) events, in patients prescribed sildenafil citrate (ED) in England	Safety outcomes, including selected short-term CV events	Link to final study report Final study report completed: November 2002
International Men's Health Study (IMHS) Cohort study	A prospective cohort study designed to assess the incidence of serious CVD events [ie, myocardial infarction (MI) and stroke] and all-cause mortality in men with erectile dysfunction (ED) who received prescriptions for sildenafil citrate (ED) in Germany, France, Spain, and Sweden	Serious CV events	Link to final study report Final study report completed: March 2005
A1481282	Large descriptive study of a US insurance claims database using medical record review to describe indicidence, natural history and potential risk factors of NAION	NAION	Link to final study report Final study report completed: March 2010
A1481259	Case-crossover study of PDE5 inhibitor exposure as a Potential "Trigger Factor" for acute NAION	NAION	Link to final study report Final study report completed: April 2013

Table 2. Summary of Completed Pharmacovigilance Studies For Sildenafil (ED) OTC

Study	Summary of Objectives	Safety Concerns Addressed	Protocol Link Milestones
A1481334	Survey of pharmacists to evaluate the effectiveness of the Viagra Connect national additional risk minimisation measures (aRMMs) in the United Kingdom (UK).	• Symptomatic hypotension/increase hypotensive effect in men taking: -nitrates or NO donors, including nitrites (eg, amyl nitrite or 'poppers' for recreational use) -who are not stabilized on alpha-blocker therapy • Penile tissue damage and/or permanent loss of potency due to priapism • NAION • Sudden hearing loss • Serious CV events associated with sexual activity in men with pre-existing or undiagnosed CVD and/or risk factors • Symptomatic hypotension in men with pre-existing hypotension	Link to final study report Final study report completed: 23 July 2019

ANNEX 3. PROTOCOLS FOR PROPOSED, ON-GOING, AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Not applicable.

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Not applicable.

Part C: Previously agreed protocols for on-going studies and final protocols not reviewed by the competent authority

Approved protocols:

Not applicable.

Final protocols not reviewed or not approved:

Not applicable.

ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Table of contents

Instructions for use:

Select questions as needed to obtain any DCA-defined information described below that was not included in the initial report.

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting special follow-up activities: _____

Priapism/Peyronie's Disease Event Follow-up Questions

Please provide additional details on a separate page if needed, and reference the question number.

1. Does the patient have a history of the adverse event(s)?

☐ No

☐ Yes (*If yes, provide details including frequency and duration*)

Details:

2. Please mark whether the patient has a history of any of the following (prior to or while taking the product):

☐ Pulmonary Arterial Hypertension (PAH) at time of event onset
☐ Anaemia
☐ Atherosclerotic / vascular disease (e.g., angina, MI, cerebrovascular accident, transient ischemic attack)
☐ Liver impairment
☐ Renal impairment [severe renal impairment (creatinine clearance (CLcr) < 30 mL/min]
☐ Hypertension / Hypotension
☐ Hyperlipidaemia / Hypercholesterolaemia / Hypertriglyceridaemia
☐ Blood platelet disorders (e.g., thrombocytopenia) or blood coagulation disorders
☐ Neurological disorders such as spinal trauma, multiple sclerosis
☐ Diabetes mellitus
☐ Haematological diseases (e.g., sickle cell anaemia and leukaemia)
☐ Previous penile trauma or injury
☐ Relevant social history including smoking, alcohol, IV drug use, illicit drug use (e.g., cocaine, amphetamines, marijuana), and use of anorexigens
☐ Previous use of other PDE5 inhibitors *(specify)*
☐ Previous use of other drug products *(specify)*

Details:

3. Was the patient taking any of the following medications at the time of the adverse event or within two weeks prior to the onset of the adverse event? *(please provide the specific dates of administration and dosage)*

☐ Nitrogen containing compounds (e.g., nitroglycerin, "poppers," amyl nitrate, nitropaste)
☐ Heart or blood pressure medications
☐ Other products in the treatment of PAH [e.g., bosentan (Tracleer®), epoprostenol (Flolan®), iloprost (Ventalis®, Cotherix®), beraprost sodium, treprostinil (Remodulin®); oral anticoagulants (e.g., warfarin); calcium channel blockers; diuretic use; or other investigational drug for PAH such as sitaxsentan, ambrisentan; Nitric oxide donors such as arginine
☐ Sexual stimulants
☐ Products used in the treatment of erectile dysfunction (e.g., Caverject®, papaverine, yohimbine, etc.) ☐ Disease modifying drugs, e.g., for connective tissue disease such as immunosuppressants
☐ Oral contraceptives
☐ Herbal preparations and/or dietary supplements (e.g., arginine)
☐ Over-the-counter drug (non-prescription)
☐ Other revelant products *(specify)*

Details:

4. Does the patient have other relevant personal medical history?

☐ No ☐ Yes (*provide details*)

Details:

5. Does the patient have other relevant family medical history?

☐ No ☐ Yes (*provide details*)

Details:

Additional Follow-up Question for Sildenafil

Please provide additional details on a separate page if needed, and reference the question number.

[1. Sildenafil] For patients who are being treated for Pulmonary Arterial Hypertension, what is the WHO functional class?

- ☐ I
- ☐ II
- ☐ III
- ☐ IV
- ☐ Unknown

Revision History

Revision	Effective Date	Summary of Revisions
1.0	03-Mar-2014	New DCA
2.0	19-Dec-2014	Addition of new product-specific question for sildenafil cases

Instructions for use:

Select questions as needed to obtain any DCA-defined information described below that was not included in the initial report.

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting special follow-up activities: _____

Visual Events Follow-up Questions

Please provide additional details on a separate page if needed, and reference the question number.

1. Is the reported adverse event a:
☐ New event
☐ Recurrence *(please provide details on previous events)*
☐ Exacerbation of underlying condition *(please provide details)*
Details:

2. Was an ophthalmologic condition diagnosed?
☐ Unknown ☐ No ☐ Yes
If Yes, what was the diagnosis and was the diagnosis provided by an ophthalmologist or another specialist?
Details:

3. Was the visual change 'sudden' or 'gradual'?
☐ Sudden ☐ Gradual *(please provide details)*
Details:

4. Was the visual event 'unilateral' or 'bilateral?
☐ Unilateral ☐ Bilateral ☐Unknown

5. Did the patient have a past medical history of eye disease/disorder?
☐ Unknown ☐ No ☐ Yes *(please provide details)*
Details:

6. Did the patient have a family history of eye disease / disorder?
☐ Unknown ☐ No ☐ Yes *(please provide details)*
Details:

7. If the patient experienced a retinal degeneration adverse event, please specify the type, pattern, and extension of the retinal lesions
Details:

8. If the patient experienced retinal vascular events including thrombosis, please provide details.
Details:

9. Please provide the date when an ophthalmologist or optometrist last performed a fundoscopic ('back of the eyes") examination on the patient (DD-MMM-YYYY):

10. Does the patient have a history of exposure to smoke conditions or other toxins including methyl alcohol (moonshine), ethylene glycol (antifreeze)?
☐ Unknown ☐ No ☐ Yes *(please provide details)*
Details:

11. Does the patient have a history of vitamin or nutritional deficiencies?
☐ Unknown ☐ No ☐ Yes *(please provide details)*
Details:

12. Please provide the name, address, and phone number of any ophthalmologist or other specialist to whom the patient was referred for further evaluation of the reported adverse event(s):
Details:

13. Please mark whether the patient was taking any of the following medications at the time of the adverse event or within two weeks prior to the onset of the adverse event: *(Please provide the specific dates of administration, dosage, and timing in relation to product)*

- ☐ Anti-malarial
- ☐ Clofazamine
- ☐ Deferoxamine
- ☐ Anti-arrhythmic
- ☐ Phenothiazines
- ☐ Quinine
- ☐ Tamoxifen
- ☐ Vigabatrin
- ☐ Didanosine
- ☐ Indomethacin
- ☐ Ibuprofen
- ☐ Other NSAIDs (e.g. aspirin)
- ☐ Cisplatin
- ☐ Ethambutol
- ☐ Nitrogen containing compounds
- ☐ Other heart or blood pressure medications
- ☐ Sexual stimulants and other PDE5 inhibitors
- ☐ Oral contraceptives
- ☐ Disease modifying drugs (e.g., for connective tissue disease)
- ☐ Herbal preparations
- ☐ Dietary supplements
- ☐ Over–the-counter drugs (non-prescription)
- ☐ Selective estrogen receptor modulators (SERMs)
- ☐ COX-2 inhibitors
- ☐ Other *(please specify)*

Details:

14. Please specify whether the patient has a history of any of the following: *(please specify date of onset / resolution):*

- ☐ Glaucoma
- ☐ Retinopathy
- ☐ Macular degeneration
- ☐ Amaurosis fugax
- ☐ Tilted optic disc
- ☐ Optic neuritis
- ☐ Thyroid eye disease
- ☐ Pseudotumor cerebri
- ☐ Papilloedema
- ☐ Sarcoidosis
- ☐ Head trauma
- ☐ Lupus
- ☐ Other autoimmune disease
- ☐ Multiple sclerosis (MS)
- ☐ Lyme disease
- ☐ Pituitary adenoma
- ☐ Smoking
- ☐ Sexual dysfunction
- ☐ HIV
- ☐ AIDS
- ☐ Hypercholesterolemia
- ☐ Cataract
- ☐ Ocular surgery
- ☐ Retinal laser photocoagulation
- ☐ Optic nerve hypoplasia
- ☐ Optic neuropathy
- ☐ Drusen syndrome
- ☐ Thrombocytopenia
- ☐ Hypertension
- ☐ Hypotension
- ☐ Alcohol or other substance use
- ☐ Hyperlipidemia
- ☐ Hypertriglyceridemia
- ☐ Diabetes mellitus
- ☐ Syphilis
- ☐ Aneurysm
- ☐ Obesity
- ☐ Neurofibromatosis
- ☐ Liver impairment
- ☐ Renal impairment

- ☐ Cancer *(please specify)*
- ☐ Progressive multifocal leukoencephalopathy (PML)
- ☐ Any neurologic disorder / disease *(please specify)*
- ☐ Any eye disorder / disease *(please specify)*
- ☐ Surgery *(please specify)*
- ☐ Other relevant history *(please specify)*
- ☐ Atherosclerotic / vascular disease *(please specify)*
- ☐ Blood platelet disorder or blood coagulation disorder
- ☐ Inherited clotting disorder (e.g. thrombophilic and/or hypofibrinolytic coagulation disorders)
- ☐ Stroke / Cerebrovascular accident (CVA)
- ☐ Transient ischemic attacks (TIA)
- ☐ Other heart disease *(please specify)*

Details:

Were any of the following laboratory tests or diagnostic studies performed? *Please specify laboratory data with units, date of test, and reference ranges; and please provide printouts and photographs if available*:

Laboratory Test	Date Performed (DD-MMM-YYYY)	Results with units if applicable	Reference Ranges if applicable
☐ Complete blood count (CBC) with differential			
☐ Sedimentation rate (ESR)			
☐ Antinuclear antibodies (ANA)			
☐ Venereal Disease Research Laboratories (VDRL)			
☐ Serum protein electrophoresis (SPEP)			
☐ Liver function tests			
☐ Formal visual field exam			
☐ Fundus photographs			
☐ Fundoscopioc exam			
☐ Fluorescin angiography			
☐ Color vision testing			
☐ Intraocular pressure			
☐ Visual acuity			
☐ Visual field			
☐ Doppler flowmetry			
☐ Electroretinography			
☐ Slit Lamp Exam			
☐ Cranial CT scan			
☐ Magnetic resonance imaging (MRI)			
☐ Lumbar puncture			
☐ Temporal artery biopsy			
☐ Other relevant test *(specify):*			

Additional Visual Event Follow-up Questions for Bazedoxifene

Please provide additional details on a separate page if needed, and reference the question number.

[1. Bazedoxifene] Please describe the patient's vision prior to the start of therapy, prior to the onset of the adverse event, after the adverse event resolved, and currently:
Details:

[2. Bazedoxifene] *Does the patient wear glasses/contact lenses to correct their vision?*
☐ Unknown ☐ No ☐ Yes *(please state for how long)*
Details:

[3.Bazedoxifene] Was their vision considered stable with their current lens prescription prior to starting treatment with bazedoxifene?
☐ Unknown ☐ Yes ☐ No *(please provide details)*
Details:

[4. Bazedoxifene] Does the patient have an intraocular lens or cataract? Could regression in vision be due to a cataract?
☐ Unknown ☐ No ☐ Yes
Details:
:

[5. Bazedoxifene] Does the patient have a history of atopy/allergy?
☐ Unknown ☐ No ☐ Yes
Details:
:

[6. Bazedoxifene] Did the patient previously experience any visual symptoms (e.g. contact lens intolerance, dry eyes, visual disturbance) during pregnancy or post-partum, or whilst taking oral contraceptive medication or hormonal therapy for menopausal symptoms?
☐ Unknown ☐ No ☐ Yes
Details:

Additional Follow-up Question for Sildenafil

Please provide additional details on a separate page if needed, and reference the question number.

[1. Sildenafil] For patients who are being treated for Pulmonary Arterial Hypertension, what is the WHO functional class?
☐ I
☐ II
☐ III
☐ IV
☐ Unknown

Revision History

Revision	Effective Date	Summary of Revisions
1.0	22-May-2014	New DCA
2.0	19-Dec-2014	Addition of new product-specific question for sildenafil cases

Instructions for use:

Select questions as needed to obtain any DCA-defined information described below that was not included in the initial report.

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting special follow-up activities: _____

Hearing Impairment/Hearing Loss Follow-up Questions

Please provide additional details on a separate page if needed, and reference the question number.

1. Please mark whether the patient had a history of any of the following prior to or while taking product:

- ☐ Hearing impairment
- ☐ Sudden hearing loss
- ☐ Conductive deafness
- ☐ Bilateral deafness
- ☐ Unilateral deafness
- ☐ Neurosensory deafness
- ☐ Transitory deafness
- ☐ Hypoacusis
- ☐ Previous exposure to ototoxic chemicals *(please specify)*
- ☐ Previous use of other ototoxic products *(please specify)*

2. Other relevant medical history

- ☐ Recent ear infection
- ☐ Ear trauma
- ☐ Repetitive or prolonged exposure to loud noises
- ☐ Neurological disorders (mulltiple sclerosis, acoustic neuroma, medulloblastoma and other types of brain tumors, cerebrovascular accident, transient ischemic attack, and other)
- ☐ Congenital or inherited form of hearing impairment
- ☐ Inherited clotting disorder (e.g. thrombophilic and/or hypofibrinolytic coagulation disorders)
- ☐ Others (please specify)

3. Did the patient experience any other relevant event that could account for the hearing impairment / hearing loss?

- ☐ No
- ☐ Yes *(please provide details)*

Details:

4. Was the hearing impairment/hearing loss 'sudden' or 'gradual'?

☐ Sudden ☐ Gradual *(please provide details)* ☐ Unknown

Details:

5. Was the hearingimpairment/hearing loss 'unilateral' or 'bilateral?'

☐ Unilateral ☐ Bilateral ☐ Unknown

6. Please mark whether the patient was taking any of the following medications at the time of the adverse event or within two weeks prior to the onset of the adverse event: *(Please provide the specific dates of administration, dosage, and timing in relation to product)*

- ☐ Aminoglycosides (e.g. gentamicin, tobramycin)
- ☐ Chemotherapeutic agents (e.g. cisplatin, oxaliplatin, vincristine)
- ☐ Loop diuretics
- ☐ Salicylate pain relievers (e.g., aspirin)
- ☐ Quinine
- ☐ Other PDE5 inhibitors
- ☐ Other (specify)

7. Did the patient have a family history of hearing impairment /hearing loss?

☐ Unknown ☐ No ☐ Yes *(please provide details)*

Details:

8. Were any of the following laboratory tests performed? *Please specify laboratory data, date of test, and reference ranges*:

Laboratory Test	Date of Test (DD-MMM-YYYY)	Test Result	Reference Range
☐ **Audiogram**			
☐ **Other audiometric tests** (specify)			
☐ **Magnetic resonance imaging (MRI)**			
☐ **Other** (specify)			

Additional Follow-up Question for Sildenafil

Please provide additional details on a separate page if needed, and reference the question number.

[1. Sildenafil] For patients who are being treated for Pulmonary Arterial Hypertension, what is the WHO functional class?

- ☐ I
- ☐ II
- ☐ III
- ☐ IV
- ☐ Unknown

Revision History

Revision	Effective Date	Summary of Revisions
1.0	25-Feb-2014	New DCA
2.0	19-Dec-2014	Addition of new product-specific question for sildenafil cases

ANNEX 5. PROTOCOLS FOR PROPOSED AND ON-GOING STUDIES IN RMP PART IV

Not applicable.

ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

Key messages of the additional risk minimisation measures:

In accordance with national healthcare practice and policies, national training material, including a diagnostic tool (check-list) will be made available for pharmacists or patients, depending on the market, to support the supply without a prescription. These materials will be tailored and managed at a national level to meet national requirements.

The need and content of additional risk minimization measures may vary across member states and are agreed at a national level. Examples of additional risk minimisation measures that may be implemented in a member state depending on the pharmacy model in place, include pharmacist educational materials, a pharmacist checklist and/or a patient checklist.

Pharmacist educational material:

In addition to the Summary of Product Characteristics, the following tools will form the pharmacist educational materials:

- Essential information for the supply of sildenafil (ED) OTC for pharmacists
- Pharmacist checklist

- **Essential information for the supply of sildenafil (ED) OTC for pharmacists (may contain the following key elements)**:
  - Relevant information of the safety concerns addressed by the aRMM (e.g. seriousness, severity, frequency, time to onset and reversibility of the AE as applicable).
  - Details of the population at higher risk for the safety concerns addressed by the aRMM (e.g. contraindications, risk factors, increased risk by interactions with certain medicines)
  - Details on how to minimise the safety concerns addressed by the aRMM through appropriate monitoring and management (i.e. what to do, what not do, and who is most likely to be impacted according to different scenarios, when to limit or stop supply, how to administer the medicine, when to seek additional advice from a doctor about ED, its underlying causes or to treat a different condition.)
  - Key messages to convey in patient counselling
  - Instructions on how to handle possible adverse events
  - Instructions on how to take the product correctly

- **Pharmacist checklist (may contain the following key elements)**:
  - Helps to identify who is an appropriate candidate for treatment.

- Covers who the product is indicated for and whether the enquirer is a man, 18 years or older and is presenting with a complaint of erectile dysfucnction i.e the inability to get or maintain an erection hard enough for satisfactory sexual intercourse.
- Covers key elements relating to a man's fitness for sex, especially focussing on his ability to perform light to moderate exercise as well as ascertaining if there are any other obvious reasons why the man is not fit enough for sexual intercourse.
- Covers a range of cardiovascular conditions including whether the patient has suffered a heart attack or stroke in the last 6 months.
- Covers contraindicated medicines in particular nitrates and other nitic oxide donors. This allows a check to be made on all drugs a man may be taking before he uses the product.
- Covers a list of contraindicated medical conditions, this includes Peyronies disease, sickle cell anaemia and any bledding issues.

Patient educational material:

In addition to the Summary of Product Characteristics and Patient Information Leaflet, the following tools will form the patient educational materials:

- The patient checklist

- **Patient checklist (may contain the following key elements)**:
  - Identify who is an appropriate candidate for treatment.
  - Covers who the product is indicated for; explaining the product is for men over the age of 18 presenting with a complaint of erectile dysfucnction i.e the inability to get or maintain an erection hard enough for satisfactory sexual intercourse
  - Covers key elements relating to a man's fitness for sex, especially focussing on his ability to perform light to moderate exercise as well as ascertaining if there are any other obvious reasons why the man is not fit enough for sexual intercourse.
  - Covers a range of cardiovascular conditions including whether the patient has suffered a heart attack or stroke in the last 6 months.
  - Covers contraindicated medicines in particular nitrates and other nitic oxide donors. This allows a check to be made on all drugs a man may be taking before he uses the product.
  - Covers a list of contraindicated medical conditions including Peyronies disease, sickle cell anaemia and any bleeding issues.

ANNEX 7. OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIALS)

RMP Version number: 3.2

Data lock point for this RMP: 30 June 2019

Date of final sign off: 10 September 2020

ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

A1481334- Completed

Study title:

Survey of pharmacists to evaluate the effectiveness of the Viagra Connect national additional risk minimisation measures (aRMMs) in the United Kingdom (UK).

Rationale and study objectives:

The pharmacy and trained pharmacist can play a key role in ensuring any CVD issues are identified earlier and that the man is directed to see his doctor for a check-up as soon as possible within 6 months of his initial enquiry, helping to improve his overall health prognosis. The doctor can then help determine the best course of action for the man and his future health management.

The MAH has developed a training programme in the UK for pharmacists, consisting of a training guide with essential information regarding the safe supply of Viagra Connect to the ED patient and an optional checklist which pharmacists can choose to use when a patient requests to purchase Viagra Connect behind the counter. The training guide and the checklist are considered UK national aRMM which, with agreement of the MHRA were put in place to minimise the risk of Viagra Connect being sold to patients who may be unsuitable to take the product without prior consultation with their doctor.

Study A1481334 was conducted to evaluate the effectiveness of these national aRMM activities in the UK.

The overall objective of the study was to evaluate the effectiveness of the Viagra Connect national aRMM by assessing:

- The pharmacists' knowledge of key risk messages contained in the Viagra Connect Training materials;
- The pharmacists' participation in Viagra Connect pharmacist training;

- The pharmacists' utilisation of the optional Viagra Connect Pharmacy Checklist at the point of dispensing.

The safety concerns addressed are:

- Symptomatic hypotension/increase hypotensive effect in patients taking:
  -nitrates or NO donors, including nitrites (eg, amyl nitrite or 'poppers' for recreational use)
  -who are not stabilized on alpha-blocker therapy
- Penile tissue damage and/or permanent loss of potency due to priapism
- NAION
- Sudden hearing loss
- Serious CV events associated with sexual activity in men with pre-existing or undiagnosed CVD and/or risk factors
- Symptomatic hypotensiona in men with pre-existing hypotension

Study design:

The study was a cross-sectional, non-interventional, web-based survey that was conducted in the UK among pharmacists who had received at least one patient request to supply Viagra Connect within the six months preceding the survey administration.

Study population:

This survey was conducted in the UK from 28 January 2019 through 31 March 2019 in a population of pharmacists who had received at least one patient request for the supply of Viagra Connect.

Inclusion Criteria

Pharmacists must meet all of the following inclusion criteria to be eligible for inclusion in the study:

- Willing/consent to participate in this self-administered survey (Answered "Yes" to a survey question asking "Do you agree to proceed with this survey");
- A practicing pharmacist in the UK;
- Received at least one patient face-to-face request to supply Viagra Connect in the past six months.

Exclusion Criteria

Pharmacists meeting the following criteria will not be included in the study:

- Pharmacists who answer affirmatively to a question asking if they or their immediate family members currently work for Pfizer, another pharmaceutical company, or the survey vendor (UBC), the European Medicines Agency (EMA) or the MHRA;

- Pharmacists who work only as on-line pharmacists and who do not participate in face-to-face consultations.

Milestones:

Table 1. Milestones for A1481334

Milestone	Date
Protocol Approval	June 2018
Start of data collection for the pilot survey	July 2018
End of data collection for the pilot survey	August 2018
Pilot results report and updated survey submitted to the Agency	October 2018
Feedback from the MHRA on the pilot results	December 2018
Registration in the EU PAS register	December 2018
Start of data collection for full survey (estimated)	January 2019
End of data collection for full survey (estimated)	March 2019
Final study report submitted to MHRA	July 2019

EU= European Union; MHRA= Medicines and Healthcare products Regulatory Agency; PAS= Post-Authorisation Study

Study Conclusions:

In this sample of pharmacists who supply Viagra Connect, there was generally a high level of knowledge and awareness of the Key Risk Messages. There are some areas that could benefit from more emphasis in the training modalities provided to pharmacists, including improved knowledge of the underlying health conditions of patients with ED, contraindicated medications, and that men using a different dose of sildenafil or other ED treatment may not also be supplied Viagra Connect. The MAH is committed to a continuous improvement of the aRMM program. The MAH will be reviewing the checklists and identifying areas for potential formatting changes as well as areas requiring additional emphasis within the pharmacist training package. The MAH will also take the opportunity to consult with outside pharmacy and medical practitioners in order to review the data generated with a view to improving outcomes in key areas.

Utilisation and satisfaction with the Viagra Connect Pharmacy Training and the voluntary pharmacist checklist was high. The stratified analyses indicate that participation in pharmacist training was associated with slightly higher rate of utilization of the voluntary checklist and tear-off slips and a greater proportion of pharmacists advising the patients to see their doctor within 6 months of supply. This along with the high proportion of pharmacists indicating that the aRMMs materials are their main source of knowledge coupled

with the overall high rate of correct responses to knowledge questions suggest that the aRMMs have been effective in ensuring patients are supplied Viagra Connect safely by pharmacists. Study data provide reasonable assurance that the pharmacist participants are representative of the wider pharmacist population in the UK with respect to type of pharmacy.

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ANNEX 8. SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Version	Approval date Procedure	Change
1.4	Procedure number in the United Kingdom: UK/H/6416/01/DC Approved in United Kingdom: 29 November 2017	Version 1.4 respresents the initial RMP for sildenafil (ED) OTC in the United Kingdom: Important identified risks: • Interaction with nitrates or NO donors, including recreational nitrites (eg, 'poppers') • Priapism • Hypotension when used with BP lowering drugs Important potential risks: • NAION • Sudden hearing loss • Eye haemorrhage • Serious CV events associated with sexual activity in men with pre-existing or undiagnosed CVD and/or risk factors • Interaction with CYP3A4 inhibitors including ritonavir (including grapefruit juice) • Use in patients with severe renal impairment • Use in patients with hepatic impairment Missing information: • Use in men with CV contraindications • Use in patients with hypotension • Use in men with hereditary retinal disorders
2.0	Not yet approved Procedure number in Poland (National): UR.DRL.RLN.4000.0154.2017	The RMP was updated at the request of the Polish HA, to include the 25 mg strength to Part I Product Overview. The important identified risk of "Interaction with nitrates or nitric oxide donors including recreational nitrites (eg, 'poppers')" was renamed to "Hypotension/increased hypotensive effect in patients taking nitrates or nitric oxide donors, including recreational nitrites (eg, 'poppers)" to reflect the clinical outcome of the drug interaction between nitrates/nitric oxide donors and sildenafil. The important identified risk of "Priapism" was renamed to "Penile tissue damage and/or permanent loss of potency due to priapism" to reflect the clinical outcome of the adverse drug reaction of priapism.
2.1	Not yet approved Procedure number in Poland (National):	The RMP was updated at the request of the Polish HA to modify the summary of safety concerns in accordance with GVP Module V (rev 2) and to update the summary of safety concerns specific to the 25 mg dose of sildenafil (ED) OTC. "Interaction with CYP3A inhibitors including ritonavir (including

	UR.DRL.RLN.4000.0154.2017	grapefruit juice)" was reclassified from an important potential risk to a risk not considered important and therefore removed from the list of safety concerns. The important potential risk of "Eye haemorrhage" was renamed to "Decrease in vision due to eye haemorrhage" to reflect the clinical outcome of the risk. The RMP was also updated to present the summary of safety concerns for the 25 mg dose separately from the 50 mg dose. The summary of safety concerns for the 25 mg dose are the same as for the 50 mg dose except that for the 25 mg dose, "Use in patients with severe renal impairment" is not considered a safety concern and "Use in patients with hepatic impairment" has been updated to "Use in patients severe hepatic impairment."
3.0	Not yet approved Procedure number in Norway: NO/H/0307/001/E/001 Procedure number in Poland (National): UR.DRL.RLN.4000.0154.2017	The Risk Management Plan (RMP) was updated at the request of the Norwegian and Polish Health Authorities (HAs) to modify the summary of safety concerns in accordance with GVP Module V (rev 2), to include the background and results of the post-authorisation safety study A1481334 (pharmacist survey in the United Kingdom) and include the pharmacist checklist, pharmacist educational materials and patient checklist as examples of additional risk minimisation measures. The marketing authorisation holder (MAH) is proposing to update the naming of the important identified risk of "Hypotension when used with BP lowering drugs" to focus specifically on the risk of symptomatic hypotension in men who are not stabilized on alpha blocker therapy. The MAH is proposing to rename the important identified risk of "Hypotensive/increase hypotensive effect in patients taking nitrates or NO donors, including recreational nitrites (e.g., 'poppers')" to "Symptomatic hypotensive/increase hypotensive effect in men taking nitrates or NO donors, including nitrites (e.g., amyl nitrite or 'poppers' for recreational use)" to reflect the fact that not all use of nitrites are for recreational use. The MAH is proposing to remove the important potential risks of "Vision loss due to eye haemorrhage," "Use in in patients with severe renal impairment" [for sildenafil (ED) OTC 50 mg], "Use in in patients with hepatic impairment" [for sildenafil (ED) OTC 50 mg] and "Use in patients with severe hepatic impairment" [for sildenafil (ED) OTC 25 mg] as well as "Use in men with CV contraindications" and "Use in men with hereditary retinal disorders" as missing information in accordance with the guidance in GVP Module V (Rev 2). The MAH is proposing to upgrade "Use in patients with hypotension" from missing information to an important potential risk of "Symptomatic hypotension in men with pre-existing hypotension" based on the known hypotensive effects of sildenafil (ED).
3.1	Not yet approved	Minor RMP updates were made following the Norwegian Health authority assessment of the sildenafil (ED) OTC RMP version

	Procedure number in Norway: NO/H/0307/001/E/001	3.0. The updates included clarification that Part II SIII Clinical Trial Exposure section was updated in line with GVP Module V (Rev 2), updates to text in Part II SVII with regard to the Impact on Risk-Benefit Blance of the Product section for the safety concerns, and update in Part V to indicate that the MAH plans to provide an evaluation of the effectiveness of routine pharmacovigilance activities in the next 5-year Periodic Safety Update Report scheduled to be submitted on 31 March 2022.
3.2	Not yet approved Procedure number in Norway: NO/H/0307/001/E/001	RMP updates were made following the Norwegian Health authority assessment of the sildenafil (ED) OTC RMP version 3.1including: - Removal of "Serious cardiovascular (CV) events associated with sexual activity in men with pre-existing or undiagnosed cardiovascular disease (CVD) and/or other risk factors" as an important potential risk - Addition of rationale as to why concomitant use of sildenafil (ED) OTC with riociguat is not considered a safety concern to Part II SVII.2