NOVARTIS

Chief Medical Office & Patient Safety

Lapatinib

LAP016

EU Safety Risk Management Plan

Active substance(s) (INN or common name)	Lapatinib ditosylate monohydrate
Product(s) concerned (brand name(s))	Tyverb®, Tykerb®
Document status:	Final
Version number:	36.0
Data lock point for this RMP	05-Dec-2013
Date of final sign off	19-Mar-2019

Rationale for submitting an updated RMP:

This European Union Risk Management Plan (RMP) version 36.0 is prepared to reflect the responses to Pharmacovigilance Risk Assessment Committee (PRAC) assessment report from Procedure no.: EMEA/H/C/PSUSA/00001829/201803 based on the 14th Periodic Safety Update Report for lapatinib covering the reporting period of 13-Mar-2017 to 12-Mar-2018.

Additionally, the RMP has been updated to:

- Update the status of Study EGF117165 (CLAP016A2206), a Category 1 commitment under additional pharmacovigilance activities.
- Remove missing information topics in accordance with the PRAC recommendation: 'Children'; 'Patients with moderate and severe hepatic disease'; 'Patients with severe renal disease'; 'Patients with low cardiac ejection fraction' and 'Patients of different racial and / or ethnic origin'.

Summary of significant changes in this RMP:

Part	Major changes compared to RMP v35.1
Part I	Updated to reflect the current Summary of Product Characteristics.
Part II	• Updated the 'Rationale' for the following topics in Section 5.1 (Table 5-1; Populations not studied in clinical trials): 'Children'; 'Patients with moderate to severe hepatic disease'; Patients with severe renal disease' and 'Patients with low cardiac ejection fraction'. • Updated Section 8.2 (New safety concerns and reclassification with a submission of an updated RMP) with the rationale for removal of the following missing information topics: 'Children'; 'Patients with moderate and severe hepatic disease'; 'Patients with severe renal disease'; 'Patients with low cardiac ejection fraction' and 'Patients of different racial and / or ethnic origin'. • Removed the following missing information topics from Section 8.3.3. (Presentation of the missing information) and Section 9 (Table 9-1; Summary of safety concerns): 'Children'; 'Patients with moderate and severe hepatic disease'; 'Patients with severe renal disease'; 'Patients with low cardiac ejection fraction' and 'Patients of different racial and / or ethnic origin'.
Part III	Updated the status of Study EGF117165 (CLAP016A2206) - a Category 1 commitment under additional pharmacovigilance activities and removed it from Section 10.2 (Additional pharmacovigilance activities) and Section 10.3. (Table 10-1; Summary Table of additional pharmacovigilance activities).
Part IV	Study EGF117165 (CLAP016A2206) is removed from Section 11 (Plans for post-authorization efficacy studies).
Part V	Removed the following missing information from Section 12.1 (Routine risk minimization measures) and Section 12.3 (Table 12-10; Summary of pharmacovigilance activities and risk minimization activities by safety concerns): 'Children'; 'Patients with moderate and severe hepatic disease'; 'Patients with severe renal disease'; 'Patients with low cardiac ejection fraction' and 'Patients of different racial and / or ethnic origin'.
Part VI	• Removed the following missing information from Section 13.2.1 (Table 13-1; List of important risks and missing information) and Section 13.2.2. (Summary of important risks): 'Children'; 'Patients with moderate and severe hepatic disease'; 'Patients with severe renal disease'; 'Patients with low cardiac ejection fraction' and 'Patients of different racial and / or ethnic origin'.

	• Study EGF117165 (CLAP016A2206) is removed from Section 13.2.3.1. (Studies which are conditions of the marketing authorization).
Part VII	• Updated the status of Study EGF117165 (CLAP016A2206) in the corresponding annexes (i.e. Annex 2 [Tabulated summary of planned, ongoing and completed pharmacovigilance study program] and Annex 5 [Protocols for proposed and ongoing studies in RMP part IV]). • Updated Novartis internal references list. • Updated Annex 8 (Summary of changes to the risk management plan over time).

Other RMP versions under evaluation

None

Details of the currently approved RMP:

Version number: 35.1

Approved with procedure: EMEA/H/C/00795/II/0051

Date of approval (opinion date): 28-Jun-2018

QPPV name: [redacted]

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

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List of abbreviations

AE	Adverse event
AI	Aromatase inhibitor
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under curve
BCRP	Breast cancer resistance protein
Cmax	Maximum serum/plasma concentration
CHF	Congestive heart failure
CNS	Central nervous system
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DDI	Drug-drug Interactions
EEA	European Economic Area
EGFR	Epidermal growth factor receptor (also ErbB1 receptor)
EM	Erythema multiforme
ER	Estrogen receptor
ErbB1	Epidermal growth factor receptor 1/EGFR/HER-1
GI	Gastrointestine
HER2 (ErbB2)	HER2 (ErbB2: Epidermal Growth Factor Receptor 2/HER2) Human EGF receptor-2
hERG	Human ether-à-go-go
HLA	Human leukocyte antigen
IC	Inhibitory concentration
ILD	Interstitial lung disease
INR	International normalized ratio
LFT	Liver function tests
LVEF	Left ventricular ejection fraction
MAH	Marketing authorisation holder
MBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
PD	Pharmacodynamics
Pgp	P-glycoprotein
PhV	Pharmacovigilance
PK	Pharmacokinetics
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
QTcF	QT interval corrected with Fredericia's formula
RMP	Risk management plan

SAE	Serious adverse event
SJS	Stevens–Johnson syndrome
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA query
TdP	Torsade de Pointes
TEN	Toxic epidermal necrolysis
TKI	Tyrosine kinase inhibitor
ULN	Upper limit of normal
USA	United States of America

1 Part I: Product(s) Overview

Table 1-1 Part I.1 - Product Overview

Active substance (INN or common name)	Lapatinib
Pharmacotherapeutic group (ATC Code)	L01XE07
Marketing Authorization Holder	Novartis Europharm Limited
Medicinal products to which this Risk Management Plan (RMP) refers	01
Invented name in the European Economic Area (EEA)	Tyverb®
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class**: Lapatinib is an orally administered small molecule reversible tyrosine kinase inhibitor (TKI) that targets both ErbB1 (Epidermal Growth Factor Receptor [EGFR]) and Human EGF receptor-2 [HER2]/ (ErbB2) receptors.
	Summary of mode of action: Lapatinib works intracellularly and directly targets the tyrosine kinase (TK) domain of ErbB1 and HER2. Lapatinib binds reversibly to the cytoplasmic adenosine triphosphate (ATP)-binding site of the kinase and blocks receptor phosphorylation and activation, thereby preventing subsequent downstream signaling events leading to tumor growth inhibition and apoptosis.
	Important information about its composition: Each film-coated tablet contains lapatinib ditosylate monohydrate, equivalent to 250 mg lapatinib.
Hyperlink to the Product Information	[Current approved SmPC] [Proposed SmPC]: Not applicable
Indications in the EEA	**Current:** Tyverb is indicated for the treatment of adult patients with breast cancer, whose tumours overexpress HER2 (ErbB2); • In combination with capecitabine for patients with advanced or metastatic disease with progression following prior therapy, which must have included anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting. • In combination with trastuzumab for patients with hormone receptor-negative metastatic disease that has progressed on prior trastuzumab therapy(ies) in combination with chemotherapy. • In combination with an aromatase inhibitor for postmenopausal women with hormone receptor positive metastatic disease, not currently intended for chemotherapy. The patients in the registration study were not previously treated with trastuzumab or an

	aromatase inhibitor. No data are available on the efficacy of this combination relative to trastuzumab in combination with an aromatase inhibitor in this patient population.
	Proposed: Not applicable
Dosage in the EEA	**Current:** When taken in combination with capecitabine, the recommended dose of lapatinib is 1250 mg (5 tablets) given once daily (continuously). The recommended dose of capecitabine is 2000 mg/m^2/day taken in 2 doses 12 hours apart on days 1-14 of a 21-day treatment cycle. Capecitabine should be taken with food or within 30 minutes after food. When taken in combination with an aromatase inhibitor, the recommended dose of lapatinib is 1500 mg (6 tablets) given once daily continuously. Please refer to the full prescribing information of the co-administered aromatase inhibitor for dosing details of these medicinal products. The recommended dose of lapatinib is 1000 mg (i.e. 4 tablets) once daily continuously when taken in combination with trastuzumab. The recommended dose of trastuzumab is 4 mg/kg administered as an intravenous (iv) loading dose, followed by 2 mg/kg iv weekly. Please refer to the full prescribing information of trastuzumab.
	Proposed: Not applicable
Pharmaceutical form and strength	**Current:** Film-coated tablet, 250 mg
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

2 Part II Safety specification Module SI: Epidemiology of the indication(s) and target population

2.1 Indication: Breast Cancer

Incidence:

In 2012, it was estimated that 1677000 women would be diagnosed with breast cancer worldwide, and of these, approximately 464000 women would be diagnosed in Europe (Ferlay et al 2013). Geographically, breast cancer age-adjusted incidence rates are high in North America and Europe and much lower in Asia.

Table 2-1 Female breast cancer: age-adjusted incidence rate (IR, per 100000)[1,2] in 12 major markets, 2012

North America	Europe	Asia	South America
United States 92.9	United Kingdom 95.0	Japan 51.5	Brazil 59.5
Canada 79.8	France 104.5	China 22.1	Peru 28.0
	Spain 67.3	India 25.8	
	Italy 91.3		
	Germany 91.6		

[1] Source: Ferlay et al 2013. NB: Breast cancer was defined as ICD-10 C50: “malignant neoplasm of breast”.
[2] Age-adjustment is to the Standard World Population. Age-adjusted incidence rates are most appropriate for between-country comparisons.

Prevalence:

Breast cancer is the most prevalent cancer globally. In the United States (US), there were approximately 2.6 million breast cancer survivors in 2007 (Howlader et al 2014). Data from population based cancer registries in 38 European countries demonstrated that breast cancer accounted for over 30% of all prevalent cancers in women (Ferlay et al 2013). Burden of breast cancer ranked the highest in Belgium followed by Denmark and France (Ferlay et al 2013).

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

Male breast cancer is rare. Most breast cancer is diagnosed in post-menopausal women with incidence rates peaking in the 80-84 years age group (Howlader et al 2014). Data from the SEER program (below) show that the incidence is the highest among whites and lower among Asia/Pacific Islanders, American Indian/Alaska Native Hispanic women; black women had the highest mortality rate (Howlader et al 2014).

Table 2-2 Female breast cancer: US SEER age-adjusted incidence (IR, per 100000) and mortality rates (MR, per 100000) by race, 2003-2008

Race/Ethnicity	IR (2007-2011)	MR (2006-2010)
All Races	124.5	22.6
White	127.9	22.1
Black	122.8	30.8

Race/Ethnicity	IR (2007-2011)	MR (2006-2010)
Asian/Pacific Islander	93.6	11.5
American Indian/Alaska Native	79.3	15.5

Source: Howlader et al 2014.

Risk factors for the disease

Established risk factors for breast cancer include older age, family history of breast cancer in mother, sister or daughter, inherited germline mutations in high penetrance genes (e.g. BRCA1, BRCA2, ATM, PTEN and p53), reproductive characteristics (i.e. early menarche before age 12, late menopause after age 50, nulliparous or low parity, late age at first birth), obesity among postmenopausal women, history of benign breast disease, radiation exposure to chest as child or young adult, exposure to diethylstilbestrol while in utero, hormone-replacement therapy among postmenopausal women, mammographic breast density, and high socio-economic status (Dumitrescu and Cotarla 2005, Travis and Key 2003, Veronesi et al 2005, Mitrunen and Hirvonen 2003, Key et al 2003, Van Loon et al 1995).

The main existing treatment options:

Metastatic Breast Cancer Overview

The systemic treatment of breast cancer recurrence or stage IV disease prolongs survival and enhances quality of life but is not curative. Therefore, treatments associated with minimal toxicity are preferred; thus, endocrine therapies are preferred over the use of cytotoxic therapy whenever possible. However, for subjects who are estrogen receptor (ER)/ Progesterone Receptor (PR) negative, or have already progressed through endocrine therapy, cytotoxic chemotherapy has been an essential component of systemic palliative treatment. Combination chemotherapy generally provides higher rates of objective response and longer time to progression, in comparison to single-agent chemotherapy. However, multi-agent chemotherapy generally has greater toxicity than single agent chemotherapy. Therefore, single agent sequential cytotoxic chemotherapy allows for greater drug exposure secondary to fewer dose reductions. Among chemotherapy agents, anthracyclines (doxorubicin, epirubicin, and pegylated liposomal doxorubicin); taxanes (paclitaxel, docetaxel, and albumin-bound paclitaxel); anti-metabolites (capecitabine and gemcitabine); and non-taxane microtubule inhibitors (eribulin and vinorelbine) are preferred.

For HER2+ patients the addition of an anti-HER2 agent to cytotoxic chemotherapy provides greater benefit than cytotoxic or endocrine therapy alone. This benefit over cytotoxic chemotherapy alone was shown in several studies which also demonstrated cytotoxic therapy has decreased efficacy in the absence of anti-HER2 targeted therapy (Cancello et al 2008, Fabi et al 2008, Park et al 2009, Seidman et al 2008, Study EGF30001, GlaxoSmithKline Document UM2004/00098/00, von Minckwitz et al 2009). Therefore the use of anti-HER2 therapy has been recommended as the standard of care in HER2+ Metastatic Breast Cancer (MBC) (NCCN 2011, Cardoso et al 2011, Taira et al 2015).

Chemotherapy:

Chemotherapy is administered to women with hormone receptor-negative disease not localized to the bone or soft tissue, that are associated with symptomatic visceral metastasis, or who have

hormone receptor-positive tumors which have become refractory to endocrine therapy. Anthracyclines, taxanes, and capecitabine are some of the most commonly used agents.

Anthracyclines have limited usefulness due to the relationship between cardiac toxicity and cumulative dose. Therefore, anthracyclines are often only administered in the metastatic setting to patients who did not receive anthracyclines in the adjuvant treatment setting.

The taxanes paclitaxel and docetaxel have an important role in the treatment of breast cancer, and numerous randomized trials have evaluated their efficacy for this indication. Survival was improved when 4 cycles of paclitaxel were given after 4 cycles of conventional doxorubicin and cyclophosphamide in axillary node-positive operable breast cancer, when trastuzumab was added to paclitaxel as first-line therapy for HER2+ metastatic breast cancer, and when docetaxel was used as second-line therapy for anthracycline-resistant disease (Sparano 2000).

Capecitabine monotherapy is approved for both paclitaxel and anthracycline-containing chemotherapy resistant metastatic breast cancer. In the setting of HER2+ metastatic breast cancer, capecitabine is commonly used after anthracyclines, taxanes and trastuzumab and thus, capecitabine is an appropriate agent for combination with anti-HER2 agents such as lapatinib.

Trastuzumab:

Trastuzumab, a recombinant humanized monoclonal antibody against the extracellular domain of the HER2 protein, is a key component of therapies used to treat both metastatic and early-stage HER2+ breast cancers (Slamon et al 2001). Trastuzumab is currently registered for use in first line HER2+ metastatic breast cancer in combination with paclitaxel, where it increased time to disease progression by approximately 3 months compared with paclitaxel alone (Slamon et al 2001). Trastuzumab has also demonstrated clinical benefit in the HER2+ adjuvant breast cancer setting (Romond et al 2005, Piccart-Gebhart et al 2005). The addition of another anti-HER2 monoclonal antibody pertuzumab, to the combination of trastuzumab and docetaxel for the first-line treatment of MBC, demonstrated an additional 6 months of progression-free survival compared to trastuzumab and docetaxel only (Baselga et al 2012). This combination of pertuzumab, trastuzumab and docetaxel has recently been approved for first line treatment of HER2+ MBC.

Resistance to trastuzumab eventually occurs and some patients develop recurrence following adjuvant therapy with trastuzumab. There remains a need for alternative therapies to block HER2 signaling pathways when this occurs (Tripathy et al 2004, Montemurro et al 2006). Due to this lack of alternatives, it is common clinical practice, after progression on a trastuzumab-containing regimen, to change the cytotoxic component of the regimen while maintaining trastuzumab; although, trastuzumab is not indicated for use following disease progression after adjuvant trastuzumab therapy (Montemurro et al 2005, Pegram and Liao 2012). In response to the dilemma of trastuzumab resistance, novel modifications of trastuzumab have been evaluated for the treatment of MBC after progression on a trastuzumab based anti-cancer regimen. Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate of trastuzumab covalently coupled to a derivative of maytansine, a microtubule destabilizing agent. Recent results have shown T-DM1 improves progression-free and overall survival by nearly 6 months compared to lapatinib and capecitabine in patients with MBC that had previously received a trastuzumab- and taxane-containing regimen (Pegram et al 2012). Trastuzumab emtansine has recently been approved in several countries including Europe, Japan and the USA.

Aromatase Inhibitor and HER2/ErbB2-Directed Therapy

Endocrine therapies include aromatase inhibitors (AI) either non-steroidal (anastrozole and letrozole) or steroidal (exemestane); serum ER modulators (tamoxifen or toremifene); ER down-regulators (fulvestrant); progestin (megestrol acetate); androgens (fluoxymesterone); and high-dose estrogen (ethinyl estradiol).

Aromatase inhibitors have generally replaced serum ER modulators since AIs produce significantly lower recurrence rates compared with tamoxifen, either as initial monotherapy or after 2 to 3 years of tamoxifen (Dowsett et al 2010). Also, AIs are more effective and better tolerated than tamoxifen as first-line therapies for MBC (Smith and Dowsett 2003). Therefore, since the late 1990s, AIs such as letrozole, anastrozole (Arimidex) and exemestane (Aromasin) have become the "gold-standard" for first-line therapy for hormone receptor positive MBC in post-menopausal women (Smith and Dowsett 2003).

Epidermal growth factor receptor (EGFR) and ErbB2 receptors are frequently over-expressed or altered in human cancers (Hung and Lau 1999, Woodburn 1999) with data showing approximately 50% of the HER2-positive population are hormonally responsive (Romond et al 2005, Piccart-Gebhart et al 2005, Vaz-Luis et al 2013). However, HER2 over-expression and/or amplification confers intrinsic resistance to endocrine therapy via the activation of downstream pathways (Slamon et al 2001, Lipton et al 2003, Shin et al 2006, Prat and Baselga 2008), and an increased risk for disease progression and death (Nicholson et al 2004). Clinical evidence supports the hypothesis that ErbB2 amplification results in a hormone independent phenotype in women with ER-positive breast cancer such that postmenopausal patients with HR-positive, HER2-positive breast cancer treated with hormonal therapy alone experience a short duration of disease control. Based on preclinical data on the role of crosstalk between HER2 and HR signaling, simultaneous inhibition of both HER2 and HR pathways was postulated to be more effective than HR inhibition alone.

Current European clinical practice guidelines include the option of utilizing the combination of anti-HER2 targeted therapy in combination with hormonal therapy (Cardoso et al 2011). It is useful to note that this practice is supported by the favorable data reported from 2 large randomized Phase III studies:

- the TAnDEM study, which compared trastuzumab plus anastrozole to anastrozole monotherapy (Kaufman et al 2009),
- EGF30008 (m5.3.5.1), which compared lapatinib plus letrozole to letrozole monotherapy in HER2-positive hormonally-sensitive MBC (Johnston et al 2009).

Prior to the results of these studies, patients with HER2-positive hormonally-sensitive disease were treated with trastuzumab with or without chemotherapy, but not in combination with anti-oestrogen therapy.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Mortality in target indication

Breast cancer is the leading cause of cancer death among women worldwide, with an age-adjusted mortality rate of 12.5 per 100000 (Ferlay et al 2013).

It is estimated that 40000 women in the US will die of breast cancer in 2014, making breast cancer the second most common cancer death among US women (Howlader et al 2014). Corresponding data for Europe are available for 2012 when an estimated 131169 breast cancer deaths occurred in women (Ferlay et al 2013).

The 5-year relative survival rate varies by stage at diagnosis, from 98.6% for local disease to 23.3% for those diagnosed at distant or metastatic stage (Howlader et al 2014). Age-adjusted mortality rates for breast cancer are highest in Europe and North America while lowest in Asian countries:

Table 2-3 Female breast cancer: age-adjusted mortality rate (MR, per 100000)[1,2] in 12 major markets, 2012

North America	Europe	Asia	South America
United States 14.9	United Kingdom 17.1	Japan 9.8	Brazil 14.3
Canada 13.9	France 16.4	China 5.4	Peru 8.5
	Spain 11.8	India 12.7	
	Italy 15.8		
	Germany 15.5		

[1] Source: Ferlay et al 2013. NB: Breast cancer was defined as ICD-10 C50: "malignant neoplasm of breast".

[2] Age-adjustment is to the Standard World Population. Age-adjusted mortality rates are most appropriate for between-country comparisons.

Morbidity

Up to 40% of breast cancer patients will eventually develop refractory or resistant disease (Ring and Dowsett 2003). Metastatic breast cancer is incurable.

Important co-morbidities:

The Integrated Healthcare Information Services (IHCIS), a US medical claims database was utilized to evaluate prevalent co-morbidities in a newly diagnosed breast cancer population. Incident invasive breast cancer patients diagnosed from 1997 to mid-2005 (N = 43558) were included. The mean age of these patients was 56 years. Comparable European databases are not available; thus, U.S. estimates of important co-morbidities are presented as a surrogate for the European Union (EU).

The most prevalent co-morbidities included lump/mass in breast (46.8%), cancer in situ breast (31.8%), unspecified essential hypertension (22.5%), other disorders breast (17.9) and diffuse cystic mastopathy (15.2%). Others on the list include conditions common in an aging female population, such as benign essential hypertension (14.2%), hypercholesterolemia (12.5%), osteoporosis (8.6%), and breast cancer-related diagnoses and treatment-related side effects such as anaemia (10.6%), neutropenia (8.5%) and fatigue (9.1%).

The prevalence rates of pre-specified co-morbidities of interest that occurred post-cancer diagnosis was calculated for breast cancer patients and compared to those for a set of controls matched on age at enrolment, year of enrolment, gender, insurance plan and type of insurance plan. Conditions that occurred at least 3 times more frequently in breast cancer patients compared to controls include neutropenia, thrombocytopenia, cachexia, hepatic dysfunction, and pulmonary thrombosis.

3 Part II Safety specification Module SII: Non-clinical part of the safety specification

Table 3-1 Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non- clinical studies)	Relevance to human usage
Toxicity including:	
Single and repeat-dose toxicity: A single oral dose of 2000 mg/kg was well tolerated in both the rat and mouse. Lapatinib was well tolerated for up to 3 months in mice at doses ≤200 mg/kg/day, 6 months in rats at doses ≤60 mg/kg/day and 9 months in dogs at doses ≤40 mg/kg/day. Principal treatment-related effects in rats and dogs (inflammation and atrophy of skin and adnexal structures, and degeneration and inflammation of gastrointestinal (GI) and accessory digestive organs, mammary gland and prostate) were either directly associated with or resulted secondary to the pharmacologic action (inhibition of ErbB1 and ErbB2) of lapatinib, and showed differences in species responsiveness relative to systemic exposure and duration of treatment.	See Section 4.8 of Summary of Product Characteristics (SmPC).
Reproductive toxicity: There were no effects on male or female rat gonadal function, mating, fertility or pregnancy at doses of 120 mg/kg/day in females and 180 mg/kg/day in males (8-fold and 3-fold clinical exposure in females and males, respectively).	See Section 4.6 and Section 5.3 of SmPC.
Developmental toxicity: No increase in the number or incidence of malformations occurred when rats or rabbits were administered lapatinib during the period of major organogenesis at maximum oral doses of 120 mg/kg/day. At maternally toxic doses (120 mg/kg/day in rats and ≥60 mg/kg/day in rabbits), lapatinib treatment was associated with growth retardation and developmental variations in rats at 8-fold the efficacious clinical exposure and in rabbits at 8% to 23% of the clinical exposure. In a pre- and post-natal development study, F1 post-natal survival as well as F1 pre-weaning body weights and body weight gains were decreased at 60 (5-fold clinical exposure based upon exposures from the rat 14-day repeat dose study) and/or 120 mg/kg/day. This decrease in post-natal survival was not associated with HER2-related effects on mammary function as reduced post-natal survival was repeated in a cross-fostering study where pups born from treated dams were fostered to untreated dams. There was no evidence of F1 reproductive, F1 parental or F2 developmental toxicity at ≤60 mg/kg/day. It is not known if lapatinib is excreted in the milk.	See Section 4.6 and Section 5.3 of SmPC.
Nephrotoxicity: Lapatinib was not nephrotoxic in nonclinical toxicology studies.	Renal failure is not an identified adverse reaction for lapatinib.
Hepatotoxicity: In rats, liver inflammation was observed at ≥240 mg/kg/day in a 14-day study and hepatocellular hypertrophy and hyperplasia of	See Section 4.4 and Section 4.8 of SmPC.

Key Safety findings (from non- clinical studies)	Relevance to human usage
the Kupffer cells occurred at ≥60 mg/kg/day in a 3-month study. Generally, mild increases in liver transaminases (<2-fold above control) and bile acids (approximately 2-fold above control) were seen at non-lethal doses but did not consistently correlate with the liver inflammation. There were no treatment-related histopathological findings in the liver in the 6-month rat toxicity study at ≤120 mg/kg/day. In dogs, no liver changes were seen after 14 days of dosing at ≤360 mg/kg/day; however, chronic inflammation was noted at ≥40 mg/kg/day after 3 months. After 9 months of dosing, reactive sinusoidal lining cells, inflammation, hepatocellular degeneration/necrosis and cholestasis were seen at 100 mg/kg/day as well as liver weight increases at ≥40 mg/kg/day. These changes were believed to be associated with higher levels of alanine transaminase (ALT), alkaline phosphatase (ALP), total bilirubin, bile acids and globulin at ≥40 mg/kg/day, and lower albumin levels at 100 mg/kg/day. Improvement occurred during the 4-week recovery period. The hepatic inflammation seen in both rats and dogs was believed to be either directly associated with inhibition of the pharmacologic targets or secondary to the degenerative and inflammatory epithelial changes in the GI tract, possibly resulting in a reduction in the gut barrier function and passage of bacteria and endotoxin into the portal circulation. An additional non-clinical mechanistic study (09DMR017 'Lapatinib Metabolite Identification in Dog Plasma, Bile and Liver') was completed to evaluate the metabolism of lapatinib in plasma, liver, and bile samples from beagle dogs, to characterize the metabolites, to estimate the relative abundance of lapatinib and its metabolites in the selected tissues, and to investigate the distribution in dog liver tissue. A relationship between lapatinib-associated hepatoxicity and specific metabolite distribution could not be established. However, the metabolites observed with the major biotransformation pathways (O-, N-dealkylation and oxidation) were similar between humans and dogs.	
Genotoxicity: Lapatinib was found to be non-mutagenic and non-clastogenic in a battery of bacterial and mammalian cell assays which included the Ames test, Chinese hamster ovary (CHO) chromosome aberration assay, human peripheral lymphocyte chromosome aberration assay and an in vivo rat bone marrow chromosome aberration assay.	Lapatinib is considered not to pose a genetic toxicity risk to humans.

Key Safety findings (from non- clinical studies)	Relevance to human usage
Carcinogenicity: In oral carcinogenicity studies with lapatinib, severe skin lesions were seen at the highest doses tested which produced exposures based on Area Under Curve (AUC) up to 2-fold in mice and male rats, and up to 15-fold in female rats, compared to humans given 1250 mg of lapatinib once daily. There was no evidence of carcinogenicity in mice. In rats, the incidence of benign haemangioma of the mesenteric lymph nodes was higher in some groups than in concurrent controls. There was also an increase in renal infarcts and papillary necrosis in female rats at exposures 7- and 10-fold compared to humans given 1250 mg of lapatinib once daily.	The relevance of these findings for humans is uncertain. These findings are not considered to significantly impact the benefit-risk assessment for the intended cancer patient populations and no additional monitoring beyond that considered appropriate for the intended cancer patient populations is currently proposed.
General safety pharmacology:	
Cardiovascular (including potential for QT interval prolongation): No treatment-related effects were noted on action potential parameters in isolated canine cardiac Purkinje fibers following treatment with lapatinib at concentrations up to 2560 ng/mL, slightly in excess of the expected human maximum serum/plasma concentration (Cmax) of 2430 ng/mL. In addition, no direct chronotropic effects were noted in isolated guinea pig field stimulated atria, and there were no treatment-related electrocardiographic effects in conscious telemetered dogs at doses up to 500 mg/kg (approximately 2-fold the human Cmax) or in repeat dose studies of up to 9 months duration in the dog at Cmax and AUCs that were up to 2-fold the expected human exposure. The results of a human ether-a-go-go related gene (hERG) analysis provided the following information: The effect of a series of lapatinib (free base) concentrations (0.0262, 0.0785, 0.2616, 0.7848, and 2.6159 µM; 0.0152, 0.0456, 0.1520, 0.4560 and 1.520 µg/mL, respectively) on human ether-a-go-go-related gene (hERG) tail current was studied in the human embryonic kidney cell (HEK-293) which had been stably transfected with hERG cDNA. The inhibitory concentration (IC) 25 and IC50 values were reliably estimated to be 0.181 and 1.11µM (0.1052 and 0.6450 µg/mL), respectively. The IC25 and IC50 are, respectively, 4.3-fold and 26.5-fold higher than the predicted unbound concentration (0.0243 µg/mL, assuming 99% binding) of lapatinib associated with a Cmax of 2.43µg/mL observed in cancer patients after a 1250 mg/day oral dose (Study EGF10005).	See Section 4.2, Section 4.4, Section 4.8 and Section 5.1 of SmPC.
Nervous system: No treatment-related behavioural or overt pharmacological effects were noted in conscious female Wistar Han rats or conscious male beagle dogs (Irwin studies) at systemic exposures that were 20-fold and 2.4-fold, respectively, of the expected human Cmax of lapatinib administered in combination with capecitabine at 1250 mg/day (3203 ng/mL) (Clinical Study EGF10005).	See Section 4.8 of SmPC.
Mechanisms for drug interactions: Lapatinib is predominantly metabolized by cytochrome P450 (CYP3A). Therefore, inhibitors or inducers of these enzymes may	See Section 4.4 and Section 4.5 of SmPC.

Key Safety findings (from non- clinical studies)	Relevance to human usage
alter the pharmacokinetics (PK) of lapatinib. Clinical drug-drug interaction (DDI) studies with ketoconazole and carbamazepine resulted in an approximately 3-fold increase and decrease in plasma concentration, respectively. Lapatinib inhibits CYP3A4 and CYP2C8 in vitro at clinically relevant concentrations. The effect of lapatinib on CYP3A4 in vivo has been assessed in a clinical DDI study with the probe substrate midazolam (EGF10015). Lapatinib 1500 mg daily produced weak inhibition of CYP3A4-mediated hepatic metabolism of midazolam, resulting in 14% higher AUC following iv administration, and moderate inhibition of first pass intestinal metabolism resulting in 45% higher AUC following oral administration. These data indicate that lapatinib is a moderate inhibitor of intestinal CYP3A4 and a weak inhibitor of hepatic CYP3A4. Concomitant use of lapatinib with orally administered drugs that are strongly dependent on CYP3A4 metabolism and exhibit narrow therapeutic indices should be undertaken with caution and may require dose adjustment. Consistent with these data, a clinical DDI study with the CYP3A4 substrate docetaxel (EGF10021) showed no effect of 1250 mg lapatinib on the clearance of docetaxel which is administered intravenously. The effect of lapatinib on CYP2C8 has been assessed in a clinical DDI study with iv doses of paclitaxel, which is a substrate of CYP2C8 (EGF10009). Lapatinib 1500 mg daily increased the AUC of iv paclitaxel 23% and decreased clearance (19%) and volume of distribution (22%). These effects are consistent with lapatinib inhibition of ABCB1 (P-glycoprotein [Pgp]). However, inhibition of CYP2C8 cannot be ruled out. Therefore, concomitant use of lapatinib with medications that exhibit narrow therapeutic indices and are substrates of CYP2C8 should be avoided. The potential for an interaction in patients receiving capecitabine and lapatinib at the doses administered in the Phase III trial was examined (in Study EGF10005). There was no meaningful change in the PK of either lapatinib or capecitabine and its metabolites. The potential for an interaction in patients receiving letrozole and lapatinib at the doses administered in the Phase III trial was examined (in Study EGF10030, m5.3.3.2, patients with solid tumours). There was no meaningful change in the PK of either lapatinib or letrozole. The potential for an interaction in patients receiving trastuzumab and lapatinib at the doses administered in the Phase III trial was examined (in Study EGF10023, patients with solid tumours). There was no meaningful change in the PK of either lapatinib or trastuzumab. The effect of lapatinib on drug transporters has been evaluated in vitro and in animal models. Lapatinib is a substrate for Breast Cancer Resistance Protein (BCRP) and p-glycoprotein, and has also been shown to inhibit these transporters at concentrations achieved in vivo. Lapatinib also was found to inhibit the hepatic uptake transporter, OATP1B1, although it displayed no effect in	

Key Safety findings (from non- clinical studies)	Relevance to human usage
vitro on the renal OAT and OCT transporters. The clinical significance of these effects has not been investigated. Study EGF110557 examined the effect of lapatinib on the bioavailability of the Pgp substrate digoxin. Lapatinib had no meaningful effect on renal excretion of digoxin, but increased digoxin AUC nearly 2-fold due to inhibition of intestinal efflux.	
Other toxicity-related information or data: In response to the epithelial degeneration and general inflammatory effects (GI tract, skin, mammary gland, liver, etc.), increases in total WBC and alterations of leukograms occurred in the rat and dog. In addition, inflammatory cell infiltration was noted in multiple tissues in all toxicity studies. Alveolar histiocytosis and/or interstitial inflammation were seen in the 14-day and 3-month rat studies at doses ≥180 mg/kg/day and in a 3-month dog study at 160 mg/kg/day. However, no treatment-related lung changes were observed when lapatinib was given chronically for 6 months at 1.6- to 9.1-fold the efficacious clinical exposure to rats (180 and 120 mg/kg/day to male and female rats) and for 9 months at 1.6- to 1.7-fold the clinical exposure in dogs (100 mg/kg/day).	See Section 4.8 of SmPC.

Conclusions:

- Important identified risks from non-clinical studies, which have been confirmed by clinical data, include: Decreased left ventricular ejection fraction (LVEF), Interactions with other drugs and QTc prolongation. These risks are discussed in Section 8.3.1 SVII.3.1.
- No important potential risks were identified from pre-clinical safety studies.
- There is no missing information identified from pre-clinical safety studies.

4 Part II Safety specification Module SIII Clinical trial exposure

4.1 Part II Module SIII Clinical trial exposure

As of Dec-2013, lapatinib has been investigated in over 120 completed or ongoing Phase I, II, and III clinical studies conducted by Marketing Authorization Holder (MAH) as monotherapy or in various combination regimens. Approximately 28373 subjects have been enrolled in these studies, of which it is estimated 21318 have received lapatinib.

In addition to the MAH sponsored studies, lapatinib has been evaluated in over 90 ongoing or completed Investigator initiated trials (IIT).

The registration studies presented for lapatinib in combination with trastuzumab in the treatment of HER2+ metastatic breast cancer are the pivotal phase III study EGF104900, supporting Phase I combination study, EGF10023 and supporting studies, EGF106903 and LPT109096.

Cumulative lapatinib exposure across both treatment arms in pivotal study, EGF104900 is presented by duration, dose and age.

Exposure data is presented for pivotal lapatinib plus letrozole combination study EGF30008. Cumulative lapatinib exposure in the lapatinib plus letrozole treatment arm of study, EGF30008 is presented by duration, dose and age.

Cumulative lapatinib exposure in the lapatinib plus capecitabine treatment arm of study, EGF100151 is presented by duration, dose and age. Note: this data includes subjects who took lapatinib 1250 mg during the crossover period.

Table 4-1 Duration of Exposure, by Treatment Combination: EGF104900 Cumulative Lapatinib plus Trastuzumab

Duration of exposure	Persons	Person time (months)
0<1 month	50	38.3
≥1 month	245	1329.3
≥3 months	132	1112.3
≥6 months	66	833.5
≥9 months	35	604.9
≥12 months	20	448.8
≥15 months	13	352.3
≥18 months	7	251.5
≥21 months	7	251.5
≥24 months	7	251.5
≥27 months	6	225.1
≥30 months	5	197
≥33 months	4	165.3
≥36 months	4	165.3
≥39 months	2	88.6
≥42 months	1	48.6

Duration of exposure	Persons	Person time (months)
≥45 months	1	48.6
≥48 months	1	48.6

Table 4-2 Duration of Exposure, by Treatment Combination: EGF30008 Cumulative Lapatinib plus Letrozole

Duration of exposure	Persons	Person time (months)
0<1 month	38	21.8
≥1 month	616	10741.7
≥3 months	519	10518.8
≥6 months	417	10062.6
≥9 months	335	9444.1
≥12 months	271	8773.1
≥15 months	225	8146.1
≥18 months	179	7383.8
≥21 months	151	6844.5
≥24 months	127	6304.5
≥27 months	117	6051.3
≥30 months	108	5796.8
≥33 months	101	5579.8
≥36 months	78	4789.6
≥39 months	71	4529
≥42 months	62	4162.5
≥45 months	52	3725.4
≥48 Months	43	3305.8
≥60 months	32	2710.6
≥72 months	21	1977.9
≥84 months	15	1512.3
≥96 months	10	1061.4
≥108 months	4	448.7

Table 4-3 Duration of Exposure, by Treatment Combination: EGF100151 Cumulative Lapatinib plus Capecitabine

Duration of exposure	Persons	Person time (months)
0<1 month	14	5.6
≥1 month	232	1604.9
≥3 months	169	1485
≥6 months	92	1122.4
≥9 months	54	838.4
≥12 months	31	599.8
≥15 months	18	430

Duration of exposure	Persons	Person time (months)
≥18 months	13	347.8
≥21 months	8	249.7
≥24 months	7	226.2
≥27 months	3	126.7
≥30 months	3	126.7
≥33 months	3	126.7
≥36 months	2	92.2
≥39 months	2	92.2
≥42 months	2	92.2
≥45 months	1	47.7

Table 4-4 Clinical Trial Exposure: Duration of Exposure (totals)

Duration of exposure	Persons	Person time (months)
0-<1 month	102	65.7
≥1 month	1093	13676.0
≥3 months	820	13116.1
≥6 months	575	12018.5
≥9 months	424	10887.5
≥12 months	322	9821.7
≥15 months	256	8928.5
≥18 months	199	7983.1
≥21 months	166	7345.7
≥24 months	141	6782.3
≥27 months	126	6403.2
≥30 months	116	6120.5
≥33 months	108	5871.8
≥36 months	84	5047.0
≥39 months	75	4709.8
≥42 months	65	4303.2
≥45 months	54	3821.6
≥48 months	44	3354.3
≥60 months	32	2710.6
≥72 months	21	1977.9
≥84 months	15	1512.3
≥96 months	10	1061.4
≥108 months	4	448.7
Total	1195	13741.6
Combined Data from Studies: EGF104900/EGF100151/EGF30008.		

Table 4-5 Clinical Trial Exposure by Dose, by Treatment Combination: EGF104900 Cumulative Lapatinib plus Trastuzumab

Dose of exposure	Persons	Person time (months)
Lapatinib 1000 mg	226	921.1
Lapatinib 1500 mg	146	444

Table 4-6 Clinical Trial Exposure by Dose, by Treatment Combination: EGF30008 Cumulative Lapatinib plus Letrozole

Dose of exposure	Persons	Person time (months)
Letrozole 2.5mg + Lapatinib 1500mg	654	10763.5

Table 4-7 Clinical Trial Exposure by Dose, by Treatment Combination: EGF100151 Cumulative Lapatinib plus Capecitabine

Dose of exposure	Persons	Person time (months)
Lapatinib 1250mg + Capecitabine 2000mg/m^2	246	1610.5

Table 4-8 Clinical Trial Exposure by Dose (totals)

Dose of exposure	Persons	Person time (months)
1000mg	226	921.1
1250mg	246	1610.5
1500mg	800	11207.5
Lapatinib Total	1272	13739.1
Combined Data from Studies: EGF104900/EGF100151/EGF30008 Note: EGF104900 has subject's crossover from Lapatin b 1500mg to Lapatinib 1000mg. Their exposure data are summarized in respective dose level from different phases. The total persons are counted twice due to two different dose levels.		

Table 4-9 Clinical Trial Exposure, by Age Group, by Treatment Combination: EGF104900 Cumulative Lapatinib

Age group	Persons	Person time (months)
Age <65 Years	258	1222.8
Age ≥65 Years	37	144.8

Table 4-10 Clinical Trial Exposure, by Age Group, by Treatment Combination: EGF30008 Cumulative Lapatinib

Age group	Persons	Person time (months)
Age <65 Years	359	5602.8
Age ≥65 Years	295	5160.7

Table 4-11 Clinical Trial Exposure, by Age Group, by Treatment Combination: EGF100151 Cumulative Lapatinib

Age group	Persons	Person time (months)
Age <65 Years	209	1420.3
Age ≥65 Years	37	190.2

Table 4-12 Clinical Trial Exposure: By Age Group (totals)

Age Group	Persons	Person time (months)
<65 Years	826	8245.9
≥65 Years	369	5495.7
Total	1195	13741.6
Combined Data from Studies: EGF104900/EGF100151/EGF30008 Note: The Studies recruited only female patients		

Table 4-13 Clinical Trial Exposure, by Ethnic or Racial Origin, by Treatment Combination: EGF104900 Exposure to Lapatinib

Ethnic/Race origin	Persons	Person time (months)
Asian	5	24.3
Black	11	53.4
Hispanic	20	93.8
White	257	1191.9
Other	2	4.3
Total	295	1367.6

Table 4-14 Clinical Trial Exposure, by Ethnic or Racial Origin, by Treatment Combination: EGF30008 Exposure to Lapatinib

Ethnic/Race origin	Persons	Person time (months)
Asian	30	298.3
Black	17	235.2
Hispanic	55	712.1
White	543	9398.2
Other	9	119.7
Total	654	10763.5

Table 4-15 Clinical Trial Exposure, by Ethnic or Racial Origin, by Treatment Combination: EGF100151 Exposure to Lapatinib

Ethnic/Race origin	Persons	Person time (months)
Asian	8	56.6
Black	6	17.2
Hispanic	5	20.6
White	225	1510.5
Other	2	5.5
Total	246	1610.5

Table 4-16 Clinical Trial Exposure: By Ethnic or Racial Origin (totals)

Ethnic/Race origin	Persons	Person time (months)
Asian	43	379.2
Black	34	305.8
Hispanic	80	826.5

Ethnic/Race origin	Persons	Person time (months)
White	1025	12100.6
Other	13	129.5
Total	1195	13741.6
Combined Data from Studies: EGF104900/EGF100151/EGF30008		

Table 4-17 Clinical Trial Exposure: Special Populations (totals)

Population	Persons	Person time
Pregnant women	-	-
Lactating women	-	-
Renal impairment (specify or categorise)	-	-
Hepatic impairment (moderate)	8	NA*
Hepatic impairment (severe)	4	NA*
Cardiac impairment (specify or categorise)	-	-
Sub populations with genetic polymorphism (specify)	-	-
Immuno-compromised	-	-
* Each subject received a single oral 100mg dose of lapatin b in Study EGF10014.		

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

5.1 Part II SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 5-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Malabsorption syndrome, any disease significantly affecting GI function, or resection of the stomach or small bowel, or persons unable to swallow oral medication. Subjects with ulcerative colitis are also excluded.	Study participation in the lapatinib clinical trial program excluded subjects with malabsorption or diseases affecting the GI tract as lapatinib is an oral medication and has a known adverse drug reaction (ADR) of diarrhoea which could impact absorption of lapatinib and thus affect the efficacy of lapatinib.	No	Patients with malabsorption syndrome or any other diseases potentially affecting GI function are not expected to have a different safety profile. Patients are monitored carefully for diarrhoea. Section 4.2 and Section 4.4 of the SmPC, provide detailed recommendations on the management of diarrhea as part of standard clinical practice.
Patients with a history of other malignancy. However, subjects who had been disease free for 5 years, or subjects with a history of completely resected non-melanoma skin cancer or successfully treated in situ carcinoma were eligible.	Patients with malignancies are having worse prognosis with shorter survival time in general; including them in clinical trials may confound the assessment of the data on safety and efficacy.	No	No different lapatinib safety profile is expected in breast cancer patients, with concomitant other malignancies.
Patients with moderate to severe hepatic disease	Lapatinib is metabolized in the liver. Moderate and severe hepatic impairment have been associated, respectively, with 56% and 85% increases in systemic exposure.	No	Safety data from well-controlled studies in these patient populations are very limited and the interpretation of post marketing safety data may be hampered by the lack of available (un-confounded) data. In addition, due to the declining use of lapatinib both in clinical studies and in the post marketing setting, it is agreed that the likelihood of gaining any valuable safety

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
			information in these populations are limited.
Patients with severe renal disease	Patients with severe renal disease are having worse prognosis with shorter survival time in general; including them in clinical trials may confound the assessment of the data on safety and efficacy.	No	Safety data from well-controlled studies in these patient populations are very limited and the interpretation of post marketing safety data may be hampered by the lack of available (un-confounded) data. In addition, due to the declining use of lapatinib both in clinical studies and in the post marketing setting, it is agreed that the likelihood of gaining any valuable safety information in these populations are limited.
Patients with low cardiac ejection fraction	Lapatinib is associated with low ejection fraction, as ADR, therefore patients with abnormal baseline LVEF were excluded in order to minimize the risk of severe cardiac outcomes.	No	No new safety concern regarding the use in patients with low cardiac ejection fraction has been identified from the post marketing study cumulative data. No additional pharmacovigilance (PhV) activities are planned to further characterize this missing information and the available data so far do not suggest a change in the safety profile. The lapatinib associated risk of cardiac toxicity is well known to oncologists and considered adequately addressed in the SmPC including recommendations on risk minimization measures (Section 4.2, Section 4.4 and Section 4.8).
Pregnant or lactating females	Lapatinib was studied in pregnant rats and rabbits given oral doses of 30, 60, and 120 mg/kg/day. There were no teratogenic effects; however, minor anomalies (left-sided	Yes	Limited number of patients in this category exposed to lapatinib.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	umbilical artery, cervical rib and precocious ossification) occurred in rats at ≥60 mg/kg/day (4 times the expected human clinical exposure)		
Children	The target indication for lapatinib is the treatment of patients with advanced and metastatic breast cancer which overexpresses the HER2 (ErbB2) receptor. The approved indications for lapatinib in metastatic breast cancer have extremely limited applicability to pediatric patients because the pathophysiology of this disease occurs, for the most part in the adult population.	No	As lapatinib is licensed only in breast cancer which occurs extremely rarely in children, removal from the safety specification is supported. Pediatric studies with lapatinib in other types of cancer have been performed and have not been indicative of any safety signal pertaining specifically to children.

5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 5-2 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	Not included in the clinical development program.
Patients with relevant comorbidities: • Patients with moderate to severe hepatic impairment • Patients with severe renal impairment	Patients with moderate to severe hepatic impairment were not included in the clinical development program. Patients with severe renal impairment were not included in the clinical development program.

Type of special population	Exposure
Population with relevant different ethnic origin	Patients of different racial and/or ethnic origins were included in the clinical development program.
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Other	
Elderly patients (≥65 years)	Included in the clinical development program.
Pediatric patients (<18 years of age)	Not included in the clinical development program.

6 Part II Safety specification Module SV: Post-authorization experience

6.1 Part II Module SV.1. Post-authorization exposure

6.1.1 Part II Module SV.1.1 Method used to calculate exposure

Lapatinib in combination with capecitabine was first approved on 13-Mar-2007 in USA and is now available in the USA, all EU Member States, and Japan as well as over 100 countries. Based on Intercontinental Medical Statistics (IMS) Health data till 31-Dec-2015, cumulative post-marketing exposure to lapatinib is estimated to be 59976 patient-years as of 31-Dec-2015. The algorithm used to derive post-marketing exposure data from IMS is based on a daily dose of 1250 mg. Cumulative post-marketing exposure from launch to 31-Dec-2015 is presented in Table 6-1 where 1 person year = 5 x 250 mg tablets per day for 365 days, assumed in accordance with the calculation of patient exposure in previous years (Periodic Safety Update Report-1 [PSUR 1]- reporting period: 13-Sep-2014 to 12-Mar-2015).

6.1.2 Part II Module SV.1.2. Exposure

Table 6-1 Cumulative exposure from marketing experience

Formulation	EU (Person Years)	Non-EU (Person Years)
Lapatinib 250 mg Film-coated tablets	23937.8	36038.8
Source: PSUR 1- Reporting period: 13-Sep-2014 to 12-Mar-2015.		

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

A possible risk of misuse or dependence on lapatinib is not anticipated on the basis of its mechanism of action and lack of psychopharmacologic effects. While no clinical studies have been carried out to specifically investigate abuse potential, no evidence has emerged from clinical trials which would suggest a potential for abuse or dependence with lapatinib. A review of all complete and incomplete spontaneous reports of abuse and misuse, with or without associated adverse reactions, did not reveal any use patterns or other safety information relevant to the benefit-risk assessment for lapatinib.

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II SVII.1: Identification of safety concerns in the initial RMP submission

This section is not applicable, the RMP was already approved.

8.2 Part II SVII.2: New safety concerns and reclassification with a submission of an updated RMP

In accordance with the Pharmacovigilance Risk Assessment Committee's (PRAC's) recommendation from the Periodic Safety Update Report (PSUR) review (reporting period: 13-Mar-2017 to 12-Mar-2018; Procedure no.: EMEA/H/C/PSUSA/00001829/201803), the following missing information topics are removed from the RMP: 'Children'; 'Patients with moderate and severe hepatic disease'; 'Patients with severe renal disease'; 'Patients with low cardiac ejection fraction' and 'Patients of different racial and / or ethnic origin'.

Pharmacovigilance Risk Assessment Committee's assessment conclusions from the Periodic Safety Update Report:

Children:

As lapatinib is licensed only in breast cancer which occurs extremely rarely in children, removal from the safety specification is supported. Paediatric studies with lapatinib in other types of cancer have been performed and have not been indicative of any safety signal pertaining specifically to children. There are no indications in children under evaluation. Considering that no additional PhV activities are ongoing to further characterize this missing information and no change in the safety profile have been identified in children so far, PRAC agreed and recommended to remove this missing information from the RMP.

Patients with moderate and severe hepatic disease and Patients with severe renal disease:

Patients with moderate/ severe hepatic disease as well as patients with severe renal disease were excluded from clinical studies. Safety data from well-controlled studies in these patient populations are thus very limited and the interpretation of post marketing safety data may be hampered by the lack of available (un-confounded) data. In addition, due to the declining use of lapatinib both in clinical studies and in the post marketing setting, it is agreed that the likelihood of gaining any valuable safety information in these populations are limited. No new safety concern regarding the use in patients with moderate and severe hepatic disease has been identified from post marketing safety data.

Considering that no additional PhV activities are planned to further characterize this missing information and the SmPC contains appropriate information on this safety concern, it is endorsed to remove this missing information from the RMP. The MAH will continue monitoring safety in this category of patients with routine PhV and inform through appropriate procedure in case of new safety aspects.

Patients with low cardiac ejection fraction:

Patients with low cardiac ejection fraction at base-line were also excluded from clinical studies. The lapatinib associated risk of cardiac toxicity is well known to oncologists and considered adequately addressed in the SmPC including recommendations on risk minimization measures (Section 4.2, Section 4.4 and Section 4.8). It is recognized that there has been no safety concerns identified to date in continuous PSUR monitoring. Therefore, removal of this item is also supported.

Considering that no additional PhV activities are planned to further characterize this missing information, that the available data so far do not suggest a change in safety profile and that the SmPC contains appropriate information on this safety concern, removing this missing information from RMP is endorsed.

Patients of different racial and / or ethnic origin:

To date the majority of patients enrolled in the lapatinib program are Caucasians and safety data of lapatinib thus remains limited for non-Caucasian patients. The MAH justification to remove this item from the RMP i.e. more patients (basically Asians) have been exposed to lapatinib over time and the safety profile is essentially comparable with Caucasians, is acceptable. Again, considering the declining use of lapatinib, it is not likely that enough patients of other ethnicities (e.g. Black, Hispanic) will be exposed to fully characterize the safety profile in these patient populations.

Considering that no additional PhV activities are planned to further characterize this missing information and that the available data so far do not suggest a change in safety profile of lapatinib, removing this missing information from RMP is endorsed.

8.3 Part II SVII.3: Details of important identified risks, important potential risks and missing information

8.3.1 SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk: Hepatobiliary events

Table 8-1 Important identified risk: Hepatobiliary events

Identified Risk - Hepatobiliary Events	
Clinical trial data	
Frequency with 95% CI	EGF104900: On review of serious adverse event (SAE) data, there was a 2% incidence of hepatobiliary events on the dual blockade arm, regardless of causality or confoundedness, and 3.4% on the lapatinib monotherapy arm. The table below provides several relevant liver test abnormalities reflecting varying degrees of hepatic dysfunction. The data demonstrates the percentage of subjects who experience elevated liver function tests (LFTs) was relatively similar between the lapatinib plus trastuzumab and lapatinib monotherapy treatment arms:

Identified Risk - Hepatobiliary Events

	Lapatinib 1000mg + Trastuzumab (N=149)	Lapatinib 1500mg (N=146)
ANY EVENT	37 (25%)	34 (23%)
Possible Hy's Law		
>= 3 X ULN AST and/or ALT & >2 X ULN total bilirubin and ALP < 2 X ULN	0	0
>= 3 X ULN AST and/or ALT & >2 X ULN total bilirubin and ALP missing	0	0
ALT, AST & Total Bilirubin elevations		
>= 3 X ULN AST and/or ALT & >1.5 X ULN total bilirubin	5 (3%)	5 (3%)
>= 3 X ULN AST and/or ALT & >2 X ULN total bilirubin	4 (3%)	4 (3%)
ALT & AST elevations		
>=3x ULN	4 (3%)	5 (3%)
>=5x ULN	2 (1%)	1 (<1%)
>=10x ULN	1 (<1%)	0
>=20x ULN	1 (<1%)	0
ALT elevations		
>=3x ULN	6 (4%)	6 (4%)
>=5x ULN	2 (1%)	2 (1%)
>=10x ULN	1 (<1%)	1 (<1%)
>=20x ULN	1 (<1%)	0
AST elevations		
>=3x ULN	13 (9%)	13 (9%)
>=5x ULN	6 (4%)	7 (5%)
>=10x ULN	1 (<1%)	1 (<1%)
>=20x ULN	1 (<1%)	0

EGF30008: On review of SAE data, there was a 3.5% incidence of hepatobiliary events on the lapatinib plus letrozole treatment arm, regardless of causality or confoundedness, or 1.4% based on cases with a possible association to study medication. The overall incidence of hepatobiliary events in the letrozole plus placebo arm was 1.2%. The table below provides several relevant liver test abnormalities reflecting varying degrees of hepatic dysfunction. The data demonstrates the percentage of subjects who experience elevated LFTs was relatively similar between the lapatinib plus letrozole and lapatinib monotherapy treatment arms:

	Lapatinib 1500mg + Letrozole		Letrozole	
	N	%	N	%
Total Patients	656	100.00	622	100.00
Possible HYs Law: >3x ULN AT & < 2x ULN ALP & > 2x ULN BIL	1	0.15	0	0.00
Possible HYs Law: >3x ULN AT & ALP missing > 2x ULN BIL	0	0.00	0	0.00
>3x ULN AT & >1.5x ULN BIL	19	2.90	6	0.96
>3x ULN AT & >2x ULN BIL	7	1.07	5	0.80
>= 3x ULN ALT & AST	39	5.95	21	3.38
>= 5x ULN ALT & AST	21	3.20	5	0.80
>= 10x ULN ALT & AST	4	0.61	1	0.16
>= 20x ULN ALT & AST	0	0.00	0	0.00
>= 3x ULN ALT	64	9.76	29	4.66
>= 5x ULN ALT	36	5.49	10	1.61
>= 10x ULN ALT	10	1.52	2	0.32
>= 20x ULN ALT	1	0.15	0	0.00
>= 3x ULN AST	70	10.67	44	7.07
>= 5x ULN AST	37	5.64	16	2.57
>= 10x ULN AST	7	1.07	5	0.80
>= 20x ULN AST	1	0.15	2	0.32
>1.5x ULN BIL	52	7.93	32	5.14
>2x ULN BIL	22	3.35	18	2.89
>1.5x ULN ALP	185	28.20	152	24.44

EGF100151: Examination of shift tables revealed that 92% of subjects in the lapatinib plus capecitabine combination arm had normal total bilirubin levels at Baseline; of these subjects, 25% developed grade 1, 13% grade 2, and

Identified Risk - Hepatobiliary Events

1% grade 3 abnormalities at any post-baseline time point. Of subjects in the capecitabine monotherapy arm, 92% had normal total bilirubin at Baseline; of these, 15%, 8%, and 2% developed grade 1, 2, 3 abnormalities, respectively, at any post-baseline time point (see Annex 12 of EU RMP for definitions of Common Terminology Criteria for Adverse Events (CTCAE) v3.0 grades used in this study). The incidence of known liver metastases (45% in the lapatinib plus capecitabine arm and 46% in the capecitabine alone arm) was similar in subjects who had normal bilirubin levels at Baseline and elevations to any grade at Week 6. There were no apparent differences in the liver enzymes, aspartate transaminase (AST) and alanine transaminase (ALT), between treatment arms. On review of SAE data, there was a 2% incidence of serious hepatobiliary events on the lapatinib plus capecitabine treatment arm, regardless of causality or confoundedness, or 0.5% based on cases with a possible association to study medication. The overall incidence of serious hepatobiliary events in the capecitabine alone arm was 1.5%. The table below provides several relevant liver test abnormalities reflecting varying degrees of hepatic dysfunction. The data demonstrates that with the exception of bilirubin increases, the percentage of subjects who experience elevated LFTs was relatively similar between the capecitabine monotherapy and the lapatinib plus capecitabine treatment arms:

	Capecitabine		Lapatinib + Capecitabine	
	N	%	N	%
Total Patients	194	100.00	243	100.00
Possible HYs Law: >3x ULN AT & < 2x ULN ALP & > 2x ULN BIL	0	0.00	1	0.41
Possible HYs Law: >3x ULN AT & ALP missing > 2x ULN BIL	0	0.00	1	0.41
>3x ULN AT & >1.5x ULN BIL	5	2.58	4	1.65
>3x ULN AT & >2x ULN BIL	4	2.06	4	1.65
>= 3x ULN ALT & AST	4	2.06	8	3.29
>= 5x ULN ALT & AST	1	0.52	0	0.00
>= 10x ULN ALT & AST	0	0.00	0	0.00
>= 20x ULN ALT & AST	0	0.00	0	0.00
>= 3x ULN ALT	9	4.64	9	3.70
>= 5x ULN ALT	3	1.55	3	1.23
>= 10x ULN ALT	1	0.52	0	0.00
>= 20x ULN ALT	0	0.00	0	0.00
>= 3x ULN AST	8	4.12	22	9.05
>= 5x ULN AST	5	2.58	6	2.47
>= 10x ULN AST	1	0.52	2	0.82
>= 20x ULN AST	0	0.00	1	0.41
>1.5x ULN BIL	25	12.89	47	19.34
>2x ULN BIL	17	8.76	23	9.47
>1.5x ULN ALP	43	22.16	46	18.93

Overall: As of 05-Dec-2013, cumulative SAE data from clinical trials demonstrates the incidence of hepatobiliary events is 1.5%. There was a higher incidence of serious hepatobiliary events in both the neo-adjuvant (6.5%), and the adjuvant (2.4%) breast cancer settings, when compared with the metastatic breast cancer setting (0.8%). This difference is attributed to the more stringent SAE reporting/stopping criteria applied to hepatobiliary events in the adjuvant and neo-adjuvant studies (all grade 2 hepatic events and laboratory values were reported as SAEs), and possibly to the wider range of concomitant chemotherapies used in these studies. The events reported from the adjuvant/neo-adjuvant studies are consistent in nature with those reported from lapatinib studies in the metastatic setting. No additional risk factors have been

<table>
<tr><th colspan="2">Identified Risk - Hepatobiliary Events</th></tr>
<tr><td></td><td>identified which could explain the increased incidence of hepatobiliary events in the ongoing neo-adjuvant studies.
The estimated incidences for hepatobiliary events associated with a fatal outcome (0.1%), hepatic failure (0.05%), and possible Hy's law events (0.2%) arising from the clinical program are unchanged. The data were reviewed using the Food and Drug Administration's (FDA's) guidance on drug-induced liver injury (DILI) defining Hy's law as: AST or ALT >3xUpper limit of normal (ULN) and total bilirubin ≥2xULN, with no initial findings of cholestasis (ALP activity ≤2xULN). Since the majority of reports were in the setting of metastatic cancer, some cases had alkaline phosphatase values higher than 2xULN, and information on fractionated bilirubin was rarely available. These reports were included in the category "possible Hy's law cases" for completeness. The incidence of possible Hy's law cases from the metastatic cancer program (predominantly metastatic breast cancer patients) was 0.2% (19/11407). The incidence of possible Hy's law cases from studies in the adjuvant/neo-adjuvant breast cancer program was comparable, at 0.3% (24/8583).
The incidence and nature of hepatobiliary events from active/post-marketing surveillance (0.9%) and marketed use of lapatinib (0.3% per patient year) are comparable to those reported from the clinical trial program.
The MAH notes the incidences of serious hepatobiliary events are relatively unchanged, and a stable pattern consistent with the chemotherapy-induced sinusoidal injury (CSI) and global labeling for lapatinib, appears to have been established.</td></tr>
<tr><td>Seriousness/outcomes</td><td>Severe hepatobiliary events can be life-threatening, and lead to a fatal outcome. Following identification of the hepatic signal for lapatinib, a specific hepatic event definition was added to the SAE criteria included in lapatinib clinical trial protocols:
"ALT >3xULN and total bilirubin >2.0xULN (>35% direct; bilirubin fractionation required)" later protocols also include "... or ALT>3xULN and International Normalized Ratio (INR)>1.5, if INR measured (INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants)"
The outcome of patients with serious hepatobiliary events (regardless of causality or confoundedness):
<table><tr><th colspan="3">EGF104900</th></tr><tr><th>Outcome</th><th>Lapatinib plus Trastuzumab (N=149)</th><th>Lapatinib Monotherapy (N=146)</th></tr><tr><td>Any Hepatobiliary SAE</td><td>3 (2%)</td><td>5 (3.4%)</td></tr><tr><td>Fatal</td><td>0</td><td>1 (0.7%)</td></tr><tr><td>Improved</td><td>1 (0.7%)</td><td>1 (0.7%)</td></tr><tr><td>Resolved with Sequelae</td><td>0</td><td>0</td></tr><tr><td>Resolved</td><td>2 (1.3%)</td><td>3 (2%)</td></tr><tr><td>Unresolved</td><td>0</td><td>0</td></tr><tr><td colspan="3">EGF30008:</td></tr></table></td></tr>
</table>

Identified Risk - Hepatobiliary Events

Outcome	Lapatinib plus Letrozole (N=656)	Placebo plus Letrozole (N=622)
Any Hepatobiliary SAE	20 (3%)	5 (0.8%)
Fatal	4 (0.6%)	1 (0.2%)
Improved	0	0
Resolved with Sequelae	3 (0.5%)	1 (0.2%)
Resolved	9 (1.4%)	2 (0.3%)
Unresolved	4 (0.6%)	1 (0.2%)

EGF100151:

Outcome	Lapatinib plus Capecitabine (N=243)	Capecitabine (N=194)
Any Hepatobiliary SAE	5 (2%)	3 (1.5%)
Fatal	2 (0.8%)	3 (1.5%)
Improved	1 (0.4%)	0
Resolved with Sequelae	0	0
Resolved	1 (0.4%)	0
Unresolved	1 (0.4%)	0

Severity and nature of risk

Data from EGF104900 (05-May-2011) showed that aside from ALP elevations (22% >1.5xULN in each study arm), the most common hepatobiliary laboratory event in the dual blockade combination treatment arm was AST elevations >3xULN = 8% and 9% in the lapatinib monotherapy arm, the majority of which were grade 1 or 2 elevations. There were no possible Hy's law cases* in this study. One combination arm case of abnormal LFTs was adjudicated as probable drug induced cholestatis liver injury by MAHs hepatotoxicity board. The subject also had febrile neutropenia (unrelated) and was receiving ativan and oxycodone. The event resolved on discontinuation of lapatinib due to disease progression. One lapatinib subject who had liver metastases at Screening had fatal hepatic and renal failure 27 days after treatment onset.

Data from EGF30008 indicated that mean values for total bilirubin remained relatively constant over the course of the study in both treatment groups, although mean values were slightly lower in the letrozole plus placebo group compared with the lapatinib plus letrozole group. Elevations in AST, and ALT were amongst the most frequently reported grade 3 or 4 clinical chemistry assessments in the lapatinib plus letrozole group: AST – 6% grade 3, no grade 4; ALT 5% grade 3, <1% grade 4, and total bilirubin - <1% grade 3, <1% grade 4. One possible Hy's law case* was reported from this study. The subject received lapatinib plus letrozole and resolved/improved on lapatinib discontinuation. The MAH hepatotoxicity board adjudicated the event as probable DILI.

* Defined as ALT or AST ≥3xULN and bilirubin ≤2xULN, with ALP <2xULN or unknown.

Data from Study EGF100151 (03-Apr-2006) revealed that most clinical chemistry assessments were Common Terminology Criteria (CTC) grades 0 to 2 during treatment; no differences were observed between treatment groups or on the basis of age or race with the possible exception of a low-grade increase in total bilirubin levels at study visits at weeks 6 and 12 as compared

Identified Risk - Hepatobiliary Events	
	to Baseline in subjects in the lapatinib plus capecitabine arm vs. capecitabine alone arm. One possible Hy's law case* was reported from this study. The subject received lapatinib plus capecitabine; however, the event was confounded by progressive disease, liver metastases/cirrhosis, and ascites. Studies EGF104900, EGF30008 and EGF100151 utilized CTCAE v3.0.
Other Details	
Potential mechanisms	The mechanism for lapatinib associated hepatobiliary events is not fully clear. It is being discussed that reactive metabolites are contributing to the liver injury (Hardy et al 2014) and the induction of CYP3A4 has enhanced lapatinib-induced cytotoxicity in an in vitro human hepatic cell line experiment (Hardy et al 2014). Pharmacogenetic evaluations suggest a mechanism of lapatinib-specific, Class II Human leucocyte antigen (HLA) and immune-mediated cell damage, targeted to the liver (Spraggs et al 2011, Schaid et al 2014).
Evidence source(s) and strength of evidence	Tyrosine kinase inhibitors have been associated with hepatotoxicity, and has been observed in clinical studies during the clinical development and in the post-marketing use.
Risk groups or risk factors	Patients who carry the HLA alleles DQA1*02:01 and DRB1*07:01 have increased risk of Tyverb-associated hepatotoxicity. In a large, randomised clinical trial (Study EGF105485 [Teach], n=1194), the cumulative frequency of severe liver injury (ALT >5 times the ULN, National Cancer Institute (NCI) CTCAE grade 3) at 1 year of treatment was 2.8% overall. The cumulative frequency in DQA1*02:01 and DRB1*07:01 allele carriers was 10.3% and in non-carriers was 0.5%. Carriage of the HLA risk alleles is common (15 to 25%) in Caucasian, Asian, African and Hispanic populations but lower (1%) in Japanese populations.
Preventability	Current text in the SmPC (Section 4.2, Section 4.4, Section 4.8 and Section 5.2) addresses the risk in the patient population. Patients receiving lapatinib are informed about the risk of hepatic events in the patient information leaflet, and are instructed to contact their physician if they experience any side effects, which become severe or troublesome.
Impact on individual patient	Hepatotoxicity is common and requires dose discontinuation if severe. These events could potentially lead to more severe outcomes, e.g. hepatic failure requiring hospitalization and liver transplant.
Public health impact	Severe hepatotoxicity may in rare cases be fatal, thus the public health impact is expected to be low.

Important Identified Risk: Decreased left ventricular ejection fraction

Table 8-2 Important Identified risk: Decreased left ventricular ejection fraction

Important Identified Risk - Decreased left ventricular ejection fraction	
Clinical Trial Data	
Frequency with 95% CI	These figures are based on cases which meet the protocol defined reporting requirement for serious LVEF events. Subjects participating in lapatinib studies are required to have a normal LVEF at Baseline.

<table>
<tr><th colspan="2">Important Identified Risk - Decreased left ventricular ejection fraction</th></tr>
<tr><td></td><td>Data from across the whole lapatinib program indicates that lapatinib-associated decreased LVEF occurs at a low incidence, approximately 1.2%. Data from individual pivotal studies is presented below.

<table>
<tr><th>Study</th><th>Frequency</th></tr>
<tr><td>EGF104900 / Lapatinib plus trastuzumab (N=149)</td><td>6.7%</td></tr>
<tr><td>EGF100151 / Lapatinib plus capecitabine (N=243)</td><td>2.1%</td></tr>
<tr><td>EGF30008 / Lapatinib plus letrozole (N=656)</td><td>3.4%</td></tr>
</table>

Data from Study EGF104900 (as of Sep-2011), showed decreases in LVEF were reported at 6.7% (10/149) in the dual blockade arm, as compared to 2.1% (3/146) in the lapatinib-monotherapy arm. Three of these subjects experienced symptomatic cardiac events, including 1 fatal outcome which occurred in conjunction with a pulmonary embolism. Although the overall incidence of cardiac events was higher in the combination arm, the events were consistent in severity with the current labelled cardiac toxicity profile of lapatinib and were mostly transient and asymptomatic. In addition, many of these subjects recovered while continuing to receive lapatinib. A possible explanation for the increased incidence observed in this study is that both lapatinib and trastuzumab are associated with cardiotoxicity, and trastuzumab has a different mode of action to lapatinib. Also, subjects on the combination arm spent longer on treatment (20 weeks vs. 13 weeks with lapatinib monotherapy) due to prolonged time to disease progression.

Data from Study EGF100151 (as of 15-Mar-2007) demonstrate that decreased LVEF was reported at an equal incidence (2.1%) in each treatment arm (lapatinib plus capecitabine, capecitabine monotherapy).

Data from Study EGF30008 (as of 05-Dec-2009), demonstrate that decreased LVEF was reported at an incidence of 3.4% in the lapatinib plus letrozole treatment arm, and 1.4% in the placebo plus letrozole treatment arm.
A possible explanation for this difference in incidences between Study EGF30008 and Study EGF100151 may be that Study EGF30008 was carried out in post-menopausal women who are older and likely to be more susceptible to cardiac events due to a reduction in estrogen levels. In addition, the majority of cases for EGF30008 subjects (61%, 14/23) with LVEF events who received lapatinib plus letrozole had concurrent and/or previous medical history which may have contributed. Examples included Congestive Heart Failure (CHF), previous episodes of decreased LVEF, diabetes, hypertension, smoker, atherosclerosis, bradycardia, hypercholesterolemia, and ventricular arrhythmia. Subjects in EGF30008 had a median age of 63 years (range 31-95) as compared to the subjects in Study EGF100151 who had a median age of 53 years (range 26-83). The MAH therefore considers the higher incidence of cardiac events in EGF30008 may be attributable to the differences in the study population (older, with more previous or concurrent cardiac conditions).</td></tr>
<tr><td>Seriousness/outcomes</td><td>The ErbB receptor TKI has been associated with reports of CHF and asymptomatic decreases in ejection fraction. Therefore, decreased LVEF was</td></tr>
</table>

Important Identified Risk - Decreased left ventricular ejection fraction

used to monitor for cardiac toxicity in lapatinib clinical trials, and was defined as "any signs or symptoms of deterioration in left ventricular cardiac function that are grade 3 (NCI CTCAE) or a ≥20% decrease in left ventricular cardiac ejection fraction relative to Baseline which is below the institution's lower limit of normal." Studies EGF104900, EGF30008 and EGF100151 all utilized CTCAE v3, see Annex 12 of EU RMP for Adverse event (AE) definitions.

During clinical trials, events meeting these requirements were reported as SAEs and targeted Follow-up was requested to ensure the cases were fully documented. During initial lapatinib clinical trials, LVEF was monitored at Baseline, approximately every 8 weeks, and at study end. Currently, LVEF is monitored at Baseline, 12 weekly intervals while on treatment, and at study end. The definition for cardiac events was agreed in conjunction with MAH's Global Safety Board and Internal Cardiac Safety Panel. It is recognized that there is inherent variability in LVEF measurements due to factors including the hydration status of the patient, catecholamine levels, whether the patient is frightened or in pain etc. Therefore, it was determined the threshold level for asymptomatic cardiac events would be set at ≥20% decrease in LVEF relative to Baseline. The aim was to focus monitoring activities on those events most likely to represent a drug-induced effect, rather than a variation in LVEF measurement. A combination of Medical Dictionary for Regulatory Activities (MedDRA) preferred terms are used to search for cardiac events therefore the figures presented in the RMP incorporate both symptomatic and asymptomatic cardiac events.

The outcome of patients with serious cardiac events (regardless of causality or confoundedness):

EGF104900		
Outcome	**Lapatinib plus Trastuzumab (N=149)**	**Lapatinib monotherapy (N=146)**
Any serious cardiac event	10 (6.7%)	3 (2%)
Fatal	1 (0.7%)	0
Improved	0	0
Resolved with Sequelae	0	0
Resolved	6 (4%)	3 (2%)
Unresolved	3 (2%)	0
EGF30008		
Outcome	**Lapatinib plus Letrozole (N=656)**	**Placebo plus Letrozole (N=622)**
Any serious cardiac event	22 (3.4%)	9 (1.4%)
Fatal	0	0
Improved	1 (0.2%)	0
Resolved with Sequelae	0	0
Resolved	17 (2.6%)	9 (1.4%)
Unresolved	4 (0.6%)	0

<table>
<tr><td colspan="2">Important Identified Risk - Decreased left ventricular ejection fraction</td></tr>
<tr><td></td><td>
<table>
<tr><td colspan="3">EGF100151</td></tr>
<tr><td>Outcome</td><td>Lapatinib plus Capecitabine (N=243)</td><td>Capecitabine (N=194)</td></tr>
<tr><td>Any serious cardiac event</td><td>5 (2.1%)</td><td>4 (2.1%)</td></tr>
<tr><td>Fatal</td><td>0</td><td>0</td></tr>
<tr><td>Improved</td><td>0</td><td>0</td></tr>
<tr><td>Resolved with Sequelae</td><td>0</td><td>0</td></tr>
<tr><td>Resolved</td><td>5 (2.1%)</td><td>3 (1.5%)</td></tr>
<tr><td>Unresolved</td><td>0</td><td>1 (0.5%)</td></tr>
</table>
</td></tr>
<tr><td>Severity and nature of risk</td><td>Across the lapatinib clinical program as a whole, the majority (69%) of lapatinib-associated LVEF decreases are asymptomatic. Overall, 77% of these asymptomatic subjects recovered or improved. There was a 0.3% incidence of symptomatic LVEF decreases. Amongst subjects with symptomatic LVEF decreases, 63% recovered or improved. Seven symptomatic LVEF decreases were ongoing at the time of the subject’s death due to disease progression. Three symptomatic subjects died due to cardiac failure, all 3 reports were confounded by factors such as hypertension/pulmonary thromboembolism, history of decreased LVEF whilst receiving trastuzumab, and history of cardiac valve disease, diabetes and hypertension. The remaining subjects had ongoing symptomatic LVEF events after study medication was discontinued.</td></tr>
<tr><td colspan="2">Other Details:</td></tr>
<tr><td>Potential mechanisms</td><td>Lapatinib is a dual inhibitor of ErbB1 (EGFR) and ErbB2 (HER2). ErbB2 plays a role in cardiomyocyte proliferation during development and cardiomyocyte survival during adulthood. Inhibitors of the HER2 pathway can cause cardiac dysfunction because this pathway is involved in cardiac function and is also disrupted by disease (Azim et al 2009).</td></tr>
<tr><td>Evidence source(s) and strength of evidence</td><td>Data from clinical studies across the clinical development program revealed a decrease in LVEF in approximately 1% of patients receiving lapatinib and was asymptomatic in more than 70% of cases. Symptomatic LVEF decreases were observed in approximately 0.3% of patients who received lapatinib monotherapy or in combination with other anti-cancer medicinal products. (SmPC).</td></tr>
<tr><td>Risk groups or risk factors</td><td>Patients with history of cardiac disorders are at a risk.</td></tr>
<tr><td>Preventability</td><td>Evaluation of cardiac function, including LVEF determination, should be conducted for all patients prior to initiation of treatment with lapatinib to ensure that the patient has a baseline LVEF that is within the institutions normal limits. Left Ventricular Ejection Fraction should continue to be evaluated during treatment with Tyverb to ensure that LVEF does not decline to an unacceptable level.

Current text in the SmPC (Section 4.2, Section 4.4, Section 4.8 and Section 5.1) addresses the risk in the patient population.</td></tr>
</table>

Important Identified Risk - Decreased left ventricular ejection fraction	
Impact on individual patient	In studies across the clinical development program for lapatinib, cardiac events including LVEF decreases were reported in approximately 1% of patients. Symptomatic LVEF decreases were observed in approximately 0.3% of patients who received lapatinib. While the incidence is low, cardiac dysfunction and CHF may lead to death.
Potential public health impact of safety concern	Symptomatic LVEF decrease were rare across the lapatinib clinical development program, thus a significant impact on public health is not expected.

Important Identified Risk: Pneumonitis/Interstitial lung disease

Table 8-3 Important identified risk: Pneumonitis / Interstitial lung disease

<table>
<tr><th colspan="3">Important Identified Risk – Pneumonitis / Interstitial lung disease</th></tr>
<tr><td colspan="3">Clinical trial data</td></tr>
<tr><td>Frequency with 95% CI</td><td colspan="2">The safety database was searched using the comprehensive version of the standard MedDRA query (SMQ) for ‘interstitial lung disease’ to identify potential cases. From the total 84 cases retrieved, 62 subjects on the lapatinib clinical program have experienced serious pulmonary events suggestive of pneumonitis: 48 of these subjects received lapatinib, 12 subjects received comparator (trastuzumab, paclitaxel, or radiotherapy), and 2 subjects received placebo. This gives an approximate incidence of 0.2% (48/19642) for serious pulmonary events in lapatinib subjects from the program as a whole.
Data for serious pulmonary events from individual pivotal studies is presented below.</td></tr>
<tr><td></td><td>Study</td><td>Frequency</td></tr>
<tr><td></td><td>EGF104900 / Lapatinib plus trastuzumab (N=149)</td><td>NA</td></tr>
<tr><td></td><td>EGF100151 / Lapatinib plus capecitabine (N=243)</td><td>NA</td></tr>
<tr><td></td><td>EGF30008 / Lapatinib plus letrozole (N=656)</td><td>0.50%</td></tr>
<tr><td></td><td colspan="2">During Study EGF104900, 1 subject who received lapatinib monotherapy then crossed over to the lapatinib-trastuzumab combination experienced a non-serious (grade 2) event of pneumonitis which resolved on study treatment. There were no serious reports of ILD/pneumonitis from Study EGF104900.
There were no reports of pneumonitis/ILD from Study EGF100151.
There were 4 reports of pulmonary events suggestive of pneumonitis from Study EGF30008: Three subjects received lapatinib plus letrozole, this gives an approximate incidence of 0.5% (3/642). The remaining subject received placebo plus letrozole.
The majority of these ILD/pneumonitis reports were complicated by pre-existing conditions, or previous/concurrent medications. Examples included: conventional chemotherapy (including irinotecan), radiotherapy, underlying infection and disease progression.</td></tr>
</table>

<table>
<tr><th colspan="2">Important Identified Risk – Pneumonitis / Interstitial lung disease</th></tr>
<tr><td>Seriousness/outcomes</td><td>Drug-induced ILD/pneumonitis has been associated with cytotoxic chemotherapies, and can lead to respiratory failure. Lapatinib clinical trial protocols include a specific definition for pulmonary (ILD/pneumonitis) SAEs:
“Any signs or symptoms of pneumonitis that are grade 3 (NCI CTCAE) (defined as radiographic changes and requiring oxygen). Refer to NCI CTCAE grading of pneumonitis/pulmonary infiltrates”.
Subjects with an NCI CTCAE grade 3 or 4 interstitial pneumonitis must be withdrawn from study medication and must be reported as a SAE to GlaxoSmithKline.
Studies EGF104900, EGF30008 and EGF100151 all utilized CTCAE v3, see Annex 12 of EU RMP for AE definitions.
There were no serious reports of ILD/pneumonitis from studies EGF104900 or EGF100151. The outcome of pulmonary (pneumonitis/ILD) SAEs (regardless of causality or confoundedness):
<table>
<tr><th colspan="3">EGF30008</th></tr>
<tr><th>Outcome</th><th>Lapatinib plus letrozole (N=656)</th><th>Placebo plus letrozole (N=622)</th></tr>
<tr><td>Any serious pulmonary event</td><td>3 (0.5%)</td><td>1 (0.2%)</td></tr>
<tr><td>Fatal</td><td>0</td><td>0</td></tr>
<tr><td>Improved</td><td>0</td><td>0</td></tr>
<tr><td>Resolved with Sequelae</td><td>0</td><td>0</td></tr>
<tr><td>Resolved</td><td>1 (0.2%)</td><td>1 (0.2%)</td></tr>
<tr><td>Unresolved</td><td>2 (0.3%)</td><td>0</td></tr>
</table>
</td></tr>
<tr><td>Severity and nature of risk</td><td>Drug-induced pneumonitis can be progressive and fatal.</td></tr>
<tr><th colspan="2">Other Details</th></tr>
<tr><td>Potential mechanisms</td><td>Interstitial lung disease /pneumonitis have been observed with the TKI class of drugs (gefitinib, erlotinib), conventional cytotoxic chemotherapy and other drugs that effect the EGFR site (trastuzumab). The mechanism for TKI associated pneumonitis has not been elucidated, however it may be due to an effect on the EGF receptor pathway involved with alveolar epithelial proliferation.</td></tr>
<tr><td>Evidence source(s) and strength of evidence</td><td>Cases of ILD have been reported in clinical trials and in post marketing setting.</td></tr>
<tr><td>Risk groups or risk factors</td><td>Gefitinib, a small molecule TKI that targets ErbB1, has been associated with reports of interstitial pneumonitis, and data indicated that this event was more common in Japanese patients.</td></tr>
<tr><td>Preventability</td><td>Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis.
Current text in the SmPC (Section 4.2, Section 4.4 and Section 4.8) addresses the risk in the patient population.</td></tr>
<tr><td>Impact on individual patient</td><td>Patients should be monitored for symptoms of pulmonary toxicity (dyspnea, cough, fever) and treatment discontinued in patients who experience symptoms</td></tr>
</table>

Important Identified Risk – Pneumonitis / Interstitial lung disease	
	which are NCI CTCAE grade 3 or greater. Drug-induced pneumonitis can lead to respiratory failure requiring hospitalization, and can be fatal.
Public health impact	Cases of pneumonitis were rare across the lapatinib clinical trial program, thus a significant impact on public health is not expected.

Important identified risks: Interactions with other drugs

Table 8-4 Important identified risks: Interactions with other drugs

Interacting substance(s)	**CYP2C8 substrates (e.g. paclitaxel)**
Effect of interaction	Lapatinib moderately increased (23%) systemic exposure to paclitaxel.
Evidence source	Study EGF10009 examined the effect of 1500 mg lapatinib on iv doses of paclitaxel, which is a substrate of CYP2C8.
Possible mechanisms	In vitro data indicate that lapatinib inhibits CYP2C8 more potently than it inhibits CYP3A4 or Pgp, which also modulate paclitaxel PK. However, CYP2C8 is expressed only in the liver, and as described with midazolam and docetaxel above, first-pass elimination of lapatinib would limit its effect on CYP2C8. It is therefore possible that the in vivo increase in paclitaxel exposure does not reflect CYP2C8 inhibition.
Potential health risk	Concomitant use of lapatinib with medications that exhibit narrow therapeutic indices and are substrates of CYP2C8 should be avoided.
Discussion	Lapatinib produced a 23% increase in systemic exposure to the CYP2C8-substrate paclitaxel. This increased exposure may result in severe neutropenia, which may coincide with diarrhoea. Current text in the SmPC (Section 4.4 and Section 4.5) addresses the risk in the patient population.
Interacting substance(s)	**CYP3A4 inducers (e.g. rifampin, carbamazepine, or phenytoin)**
Effect of interaction	Decreased lapatinib systemic exposure. Carbamazepine induction of CYP3A4 resulted in a 72% decrease in lapatinib concentrations.
Evidence source	Study EGF10018 examined the effect of carbamazepine on lapatinib PK in healthy subjects. Study LAP113130 (LANTERN): A randomized Phase II Screening trial with functional imaging and patient reported toxicity sub-studies comparing Lapatinib plus capecitabine versus continued Trastuzumab plus capecitabine after local therapy in patients with ErbB2-positive metastatic breast cancer developing brain metastasis/es.
Possible mechanisms	Enzyme induction, increasing the CYP3A4-mediated metabolism of lapatinib. Carbamazepine induces synthesis of intestinal and hepatic CYP3A4 and intestinal Pgp (ABCB1).
Potential health risk	Decreased systemic exposure to lapatinib may result in inadequate efficacy and disease progression.

Discussion	Co administration of lapatinib with strong inducers of CYP3A4 should proceed with caution and clinical response should be carefully monitored. Inducers of CYP3A4 can decrease systemic exposure to lapatinib. Current text in the SmPC (Section 4.4 and Section 4.5) addresses the risk in the patient population.
Interacting substance(s)	**CYP3A4 inhibitors (e.g. ketoconazole)**
Effect of interaction	Ketoconazole inhibition of CYP3A4 resulted in a 3.6-fold increase in lapatinib plasma concentrations.
Evidence source	Study EGF10013 examined the effect of ketoconazole on lapatinib PK in healthy subjects.
Possible mechanisms	Inhibition of intestinal and hepatic CYP3A4 and intestinal Pgp (ABCB1).
Potential health risk	Increased systemic exposure to lapatinib may result in toxicity.
Discussion	Co administration of lapatinib with strong inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole or grapefruit juice) should proceed with caution and clinical response and AEs should be carefully monitored. Current text in the SmPC (Section 4.4 and Section 4.5) addresses the risk in the patient population.
Interacting substance(s)	**CYP3A4 substrates (e.g. midazolam)**
Effect of interaction	Lapatinib 1500 mg daily produced weak inhibition of CYP3A4-mediated hepatic metabolism of midazolam, resulting in 14% higher AUC following iv administration, and moderate inhibition of first pass intestinal metabolism of midazolam resulting in 45% higher AUC of midazolam following oral administration. Consistent with this effect, lapatinib 1500 mg daily produced no inhibition of the CYP3A4 substrate docetaxel after iv administration.
Evidence source	Study EGF10015 examined the effect of lapatinib on midazolam metabolism after iv and PO administration in cancer patients. The results of this study were consistent with the results of EGF10021, which examined the effect of lapatinib on docetaxel after iv administration.
Possible mechanisms	Lapatinib inhibition of CYP3A4 is moderate in the intestine and weak in the liver. This difference in the extent of inhibition may reflect first pass metabolism of lapatinib in the intestine, which diminishes exposure of the liver relative to exposure of the intestine to lapatinib.
Potential health risk	Increased systemic exposure to oral drugs highly dependent on CYP3A4 for elimination that have narrow therapeutic indices.
Discussion	Orally administered drugs with narrow therapeutic indices that are highly metabolized by CYP3A4 may require dose reductions to avoid toxicity from increased systemic exposure. Current text in the SmPC (Section 4.4 and Section 4.5) addresses the risk in the patient population.
Interacting substance(s)	**Substrates, inhibitors and inducers of BCRP, p-glycoprotein and OATP1B1**

Effect of interaction	Lapatinib inhibits Pgp-mediated absorption resulting in an 80% increase in digoxin systemic exposure. The clinical impact of these effects is unknown. Evaluation is ongoing.
Evidence source	Pre-clinical data and Study EGF110557 which examined the effect of lapatinib on the Pgp substrate digoxin.
Possible mechanisms	Lapatinib inhibits Pgp, BCRP and OATP1B1, and is a substrate of Pgp and BCRP.
Potential health risk	Studies are ongoing which should provide evidence for potential interactions involving these transporters.
Discussion	The effect of lapatinib on drug transporters has been evaluated in vitro and in animal models. Lapatinib is a substrate for Pgp and BCRP. Lapatinib also inhibits the hepatic uptake transporter OATP1B1, although it displayed no effect in vitro on the renal OAT and OCT transporters. The clinical significance of these effects has not been investigated. Study EGF110557 examined the effect of lapatinib on the Pgp substrate digoxin. Lapatinib had no meaningful effect on renal excretion of digoxin, but increased digoxin AUC nearly 2-fold due to inhibition of intestinal efflux. Current text in the SmPC (Section 4.4 and Section4.5) addresses the risk in the patient population.
Interacting substance(s)	**Gastric Acid Secretion Inhibitors**
Effect of interaction	Administration of lapatinib with esomeprazole resulted in a geometric mean (range) 27% (6-49%) decrease in lapatinib AUC that was related to age, and may be mitigated by concurrent dosing.
Evidence source	Study EGF109275 demonstrated that esomeprazole decreased systemic exposure to lapatinib.
Possible mechanisms	In vitro data indicate decreased solubility of lapatinib above pH 4. Proton pump inhibitors raise gastric pH above 4 in vivo, which would decrease solubility and presumably decrease absorption.
Potential health risk	Decreased systemic exposure to lapatinib which could result in inadequate treatment and disease progression.
Discussion	Study EGF109275 evaluated the maximal effect of oesomeprazole on gastric pH by dosing the evening prior to dosing lapatinib. The time between doses allowed maximal pH elevation to be achieved. This was done because the effect of acid reducing agents is delayed. It is therefore reasonable to infer that concurrent dosing would mitigate this interaction. Current text in the SmPC (Section 4.4 and Section 4.5) addresses the risk in the patient population.

Important identified risk: QTc prolongation

Table 8-5 Important identified risk: QTc prolongation

Important Identified Risk - QTc Prolongation	
Clinical trial data	
Frequency with 95% CI	In studies with healthy volunteers (n=43) receiving single doses of 10 to 250 mg of lapatinib or repeated daily dosing of 25 mg to 175 mg for 8 days (studies EGF10001 and EGF10002), no clinically significant changes in electrocardiogram (ECG) were observed with continuous ECG monitoring and

	12-lead ECGs. Based on automated machine readings, mean changes from pre-dose assessments tended to be small, with no consistent patterns noted across treatment groups. In several Phase I studies of patients with advanced cancer, repeated dosing of lapatinib as single agent (studies EGF10003 and EGF10004) and in combination with trastuzumab (study EGF10023) was not associated with any clinically significant changes in ECG. In Study EGF10004 (n=67), subjects received lapatinib doses of 500-1600 mg once daily; ECGs were measured at Screening, after the first dose, and after treatment had ended. Based on automated machine readings, there was no observed QTcF greater than 480 msec at any time, 2 patients had increases in QTcF from Baseline greater than 30 msec, and no patients had increases in QTcF from Baseline greater than 60 msec. In Study EGF10023 (n=54) subjects received lapatinib doses of 750-1500 mg once daily with trastuzumab 2 mg/kg weekly; ECGs were measured at Screening and at 3-4 weekly intervals during treatment. Based on automated machine readings, there was 1 patient with a QTcF greater than 480 msec at Baseline, and no subject had an increase in QTcF from Baseline greater than 30 msec. Study EGF10032 also examined the effect of food on single 1500 mg doses of lapatinib in subjects with cancer. Serum concentrations of lapatinib were on average 3-fold higher in the presence of food. Based on automated machine readings, no subject had a QTcF greater than 480 msec, 5 subjects had an increase in QTcF from Baseline greater than 30 msec, and no subject had increases in QTcF from Baseline greater than 60 msec. In Study EGF10003 (n=81), heavily pre-treated subjects with advanced cancer received lapatinib in repeated daily doses ranging from 175 mg to 1800 mg once daily (QD) and 500 mg to 900 mg twice daily, to determine the maximum tolerated dose. In a subset of 32 subjects that received once daily lapatinib (175 to 1800 mg) and 6 subjects that received twice daily lapatinib (900 mg twice daily), serial ECGs were obtained prior to dosing (in triplicate), and at 2, 4, 6, 8, 12, 16, and 24 hours post-dose on Day 1 and Day 14 (steady-state) of dosing. Blood samples for lapatinib analysis were obtained on days 1 and 14 at the same time as the ECG measurements noted above. This subset of the study population (n=38) included subjects who had received prior doxorubicin, trastuzumab, and/or radiation therapy (including mediastinal radiation therapy) for their malignancy. In addition, some subjects had a history of cardiac abnormalities (e.g. prior myocardial infarction, atrial fibrillation) prior to treatment with lapatinib. Manually over-read ECGs interval data by an external central validated ECG laboratory remains the “gold standard” for ECG interpretation. Therefore, both machine-read and manually over-read ECG data by a central validated ECG laboratory were obtained. Based on threshold values of particular concern defined by ICH E14 (EMEA 2005), a categorical analysis of the manually over-read data along with the original machine-read data are provided in the table for the 38 subjects included in the EGF10003 sub study. For both machine-read and manual over-read analyses, the average of the Day 1 pre-dose ECG interval values (in triplicate) was defined as the Baseline when interpreting post-dose observations. **Data from EGF10003 sub study:**

Category	Number of Subjects (Machine-read QTcF Values)	Number of Subjects (Manually-read QTcF Values)
450<QTcF≤480	4	7
480<QTcF≤500	4	0
QTcF>500	5	0
30<change in QTcF from Baseline≤60	10	11
change in QTcF from Baseline >60	8	0
QTcF>480 and change in QTcF>30	9	0
QTcF>500 and change in QTcF>60	5	0
QTcF>480 or change in QTcF>60	11	0

The number of subjects with threshold values of particular concern was significantly lower when comparing results from manually-read to machine-read ECGs. Specifically, based upon manually over-read data, no subject had a QTcF of >480 msec. Eleven subjects had a change in QTcF from Baseline of >30 msec but ≤60 msec (maximum value = 49 msec).

In addition, using a linear mixed effects modeling approach, the potential for a relationship between QT or QTcF duration and lapatinib serum concentrations was examined. These analyses were performed using the manually over-read ECGs from 38 subjects included in the EGF10003 sub study. The analysis indicated no statistically significant relationship between QT interval duration and lapatinib serum concentrations. However, the model predicted a small but, statistically significant population mean effect of lapatinib serum concentration on QT interval prolongation. At the median observed Cmax value associated with the 1200 mg daily dose of lapatinib, the model predicted a QTcF interval prolongation of approximately 3 msec. At the maximum observed Cmax value associated with the 1200 mg daily dose of lapatinib, the model predicted a QTcF interval prolongation of approximately 6 msec. Predicted QTcF prolongation was estimated to be greater than 10 msec for extreme exposures to lapatinib (i.e. ketoconazole inhibition, or ingestion with high-fat meal). However, the true mean effect of lapatinib on QTcF duration is not known due to the lack of a placebo comparison.

Study EGF114271 (CLAP016A2403), was conducted as part of the PhV plan to estimate the effect of lapatinib on cardiac repolarization (QTc interval duration) in subjects with advanced solid tumors. Patients (n=58) with metastatic breast cancer or recurrent, advanced, or metastatic solid tumor malignancy refractory to standard therapies, were included in the study and received 3 doses of placebo followed by lapatinib 2000 mg (8 x 250 mg) administered 12 hours apart in a single-blind, placebo-controlled, single sequence (placebo and active treatment) crossover study.

In the Evaluable Population (n=37), the maximum mean ΔΔQTcF (90% CI) of 8.75 ms (4.08, 13.42) was observed 10 hours after ingestion of the third dose of lapatinib. The results for the pharmacodynamic (PD) population (n=52) were consistent with those from the Evaluable population (maximum ΔΔQTcF (90% CI) of 7.91 ms (4.13, 11.68) at 10 hours after ingestion of the third dose of lapatinib of 2000 mg). In both populations, the increase of ΔΔQTcF exceeded 5 ms and the 90% CIs exceeded 10ms at multiple time points.

	Placebo (N=51)	**Lapatinib (N=52)**
QTcF Interval, Aggregate (msec)	n%	n%
N	51	52
Increase of <31 msec	49 (96%)	47 (90%)
Increase of 31 - 60 msec	2 (4%)	5 (10%)
Increase of >60 msec	0	0
New <450 msec	44 (86%)	41 (79%)
New 450 - <481 msec	6 (12%)	10 (19%)
New 481 - <501 msec	1 (2%)	0
≥501 msec	0	1 (2%)
Source: Novartis internal references		

Administration of 3 doses of 2000 mg lapatinib given 12 hours apart resulted in a median Cmax of 3830 ng/mL observed at a median Tmax of 3.55 hours and a geometric mean AUC0-24 of 59.2 µg*hr/mL. The median lapatinib plasma concentration was 3039.76 ng/mL prior to administration of the third lapatinib dose. The median concentration observed at 4 hours post-dose was 3716.51 ng/mL.

Lapatinib geometric mean (95% CI) Cmax, i.e. 3920 (3450-4460) ng/mL, was higher than the upper 95% CI of the Cmax values after the approved dosing regimens, listed below:

- Lapatinib 1250 mg once daily with capecitabine: 3200ng/mL (2390 to 4280 ng/mL);
- Lapatinib 1500 mg once daily with letrozole: 1940 ng/mL (1130 to 3340 ng/mL);
- Lapatinib 1000 mg once daily with trastuzumab: 1500 ng/mL (1180 to 1910 ng/mL).

The PK/PD analyses confirmed the presence of a positive relationship between lapatinib plasma concentrations and ΔΔQTcF.

The AE profile observed in Study EGF114271 (CLAP016A2403) was consistent with past experience with lapatinib; and no clinically relevant cardiac arrhythmias were seen following administration of 3 doses of 2000 mg lapatinib given within 24 hours (Clinical overview).

Seriousness/outcomes

Abnormal QTc prolongation can result in a specific form of polymorphic ventricular tachycardia, known as Torsade de Pointes (TdP). The sequelae from this arrhythmia include palpitations, pre-syncope, syncope, and potentially sudden cardiac death.

Severity and nature of risk	Manually over-read ECGs from a subset of 38 cancer subjects in EGF10003 (i.e. those with time-matched ECG and lapatinib serum concentration data) indicated that no subject had a QTcF interval duration >480 msec or an increase in QTcF from Baseline of >60 msec, both thresholds for concern specified in ICH-E14. There was no clinically significant effect of lapatinib serum concentration on individually corrected or Fridericia corrected QT interval duration based on a linear mixed effects model using manually over-read ECG data from the subset of 38 subjects in EGF10003. In Study EGF114271 (CLAP016A2403), most of the increases of the QTcF-interval were below 31 msec, 2 (4%) and 5 (10%) of the patients on placebo and lapatinib respectively had an increase between 31 and 60 msec and none had an increase of more than 60 msec. New increases of the QTcF-interval to 450 to 481 msec were seen in 6 (12%) and 10 (19%) of the patients on placebo and lapatinib, respectively. One patient had an increase of 481 to 500 msec on placebo and 1 subject had an increase of more than 500 msec on lapatinib (Study EGF114271 [CLAP016A2403] -Listing 30.0212).
Other details	
Potential mechanisms	Lapatinib showed an inhibition of the hERG tail current with IC25 and IC50 values of 0.181 and 1.11 µM (0.1052 and 0.6450 µg/mL), respectively. The IC25 and IC50 are, respectively, 4.3-fold and 26.5-fold higher than the predicted unbound concentration (0.0243 µg/mL, assuming 99% binding) of lapatinib associated with a Cmax of 2.43 µg/mL observed in cancer patients after a 1250 mg/day oral dose (Study EGF10005). Accordingly, hERG inhibition provides an explanation for the prolongation of the QT-interval.
Evidence source(s) and strength of evidence	The effect of lapatinib on the QTc-interval was investigated in a thorough QT-study in cancer patients (Study EGF114271). The maximum mean ΔΔQTcF increase following three doses of lapatinib of 2000 mg administered 12 hours apart exceeded 5 msec, and the 90% CI exceeded 10 msec in the by-time-point analysis. The PK/PD analyses confirmed the presence of a positive relationship between lapatinib plasma concentrations and ΔΔQTcF.
Risk groups or risk factors	Patients with hypokalemia or hypomagnesemia, congenital long QT syndrome, patients taking anti-arrhythmic medicines or other medicinal products that lead to QT prolongation are at a risk.
Preventability	Caution should be taken if Tyverb is administered to patients with conditions that could result in prolongation of QTc (including hypokalemia, hypomagnesemia, congenital long QT syndrome), co-administration of other medicinal product known to cause QT prolongation, or conditions that increase the exposure of lapatinib, such as co-administration of strong CYP3A4 inhibitors. Hypokalemia or hypomagnesemia should be corrected prior to treatment. Electrocardiograms with QT measurement should be performed prior to and 1 to 2 weeks after the start of Tyverb therapy. When clinically indicated, e.g. after initiation of a concomitant treatment that might affect QT or that may interact with lapatinib, ECG measurement should also be considered. Current text in the SmPC (Section 4.4, Section 4.8 and Section 5.1) addresses the risk in the patient population.

Impact on individual patient	QT prolongation can lead to TdP; the sequelae from this arrhythmia include palpitations, pre-syncope, and potentially sudden cardiac death.
Public health impact	QTc prolongation may predispose patients to arrhythmias. This could have significant impact if associated with hemodynamic effects and can lead to fatal outcome.

Important identified risk: Severe cutaneous reactions

Table 8-6 Important identified risk: Severe cutaneous reactions

Important Identified Risk: Severe cutaneous reactions	
Clinical trial data	
Frequency with 95% CI	Incidence of severe cutaneous reactions from 8 completed trials (EGF20002, EGF20003, EGF20008, EGF20004, EGF100151, EGF104535, EGF104900 and EGF30008) was reviewed. Data showed the incidence of severe cutaneous adverse reactions, including erythema multiforme (EM), Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), on the lapatinib clinical program is low and comparable with the incidences seen in placebo/comparator treatment groups. Exfoliative rash incidence 1% (2 cases) on each treatment arm (LAP+capecitabine and capecitabine only) in Study EGF100151, and <1% (1 case) vs no cases in Study EGF30008 (LAP+letrozole, vs placebo+letrozole, respectively). Erythema multiforme incidence - <1% (1 case) in the LAP+capecitabine treatment arm, vs no cases in the capecitabine treatment arm of study EGF100151, and <1% (1 case) vs no cases in study EGF30008 (LAP+letrozole, vs placebo+letrozole respectively). There were no reports of SJS or TEN in these studies. A search of the safety database using MedDRA (version 18.1) SMQ (narrow) “Severe cutaneous adverse reactions" retrieved 47 reports (45 health care provider (HCP) and 2 non-HCP) including 18 cases from spontaneous reports, 16 cases from post-marketing surveillance, 10 cases from clinical trials, and three literature cases related to search terms of the SMQ. The review of the cases led to the identification of seven cases describing serious cutaneous reactions for which a causal relationship with lapatinib cannot be excluded, albeit the time to onset varies significantly for the seven cases. Of these cases, 1 was reporting EM, 4 SJS, 1 TEN and one toxic skin eruption. Based on the results from this search of the safety database, Severe Cutaneous Reaction has now been upgraded to an important identified risk.
Seriousness/outcomes	The mortality rate for TEN is between 25-35% (Foster 2013).
Severity and nature of risk	The majority of reports of severe cutaneous reactions from the lapatinib program in the safety database were mild in nature and did not appear to represent widespread exfoliation events such as EM, SJS and TEN. In addition many cases were confounded by concurrent medications (capecitabine, docetaxel, and phenytoin) which have been associated with SJS/TEN.
Other details	

Important Identified Risk: Severe cutaneous reactions	
Potential mechanisms	Stevens-Johnson Syndrome and TEN are part of a single disease spectrum and differ only in severity. Albeit the exact pathophysiologic mechanism of SJS and TEN remains still unknown, the prevailing evidence suggests primary involvement of an immunologic response, in particular mediated by memory cytotoxic T cells.
Evidence source(s) and strength of evidence	Clinical study data showed the incidence of severe cutaneous adverse reactions, including EM, SJS and TEN, in the lapatinib clinical program is low and comparable with the incidences seen in placebo/comparator treatment groups. However, given the seriousness of SJS and TEN, severe cutaneous reactions have been added as an identified risk.
Risk groups or risk factors	Various etiologic factors (e.g. infection, drugs, and malignancies) have been implicated as causes of SJS; however, as many as half of them are idiopathic. There is strong evidence for a genetic predisposition to SJS provoked by certain drugs (Foster 2013).
Preventability	Detection of severe skin reactions at an early stage could mitigate seriousness by preventing progression to SJS/TEN. Most patients present early and prior to obvious signs of hemodynamic compromise. The single most important role for the physician is to detect SJS/TEN early and initiate the appropriate patient management. If EM or life-threatening reactions such as SJS/TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are suspected, discontinue treatment with Tyverb. Underlying diseases and secondary infections must be identified and treated. Current text in the SmPC (Section 4.4 and Section 4.8) addresses the risk in the patient population.
Impact on individual patient	Stevens-Johnson Syndrome/TEN are potentially life threatening, medical emergencies which usually require hospitalization. Treatment focuses on eliminating the underlying cause, controlling symptoms and minimizing complications. Recovery can take weeks to months, depending on the severity of the condition. Stevens-Johnson Syndrome patients may experience numerous long-term sequelae; the most disabling are those of the eye, including photophobia, burning sensation in the eyes, or corneal and conjunctival neovascularization. As many as 40% of TEN patients have residual potentially disabling lesions that may cause blindness (Foster 2013).
Public health impact	Potentially life-threatening, usually requires hospitalization and may be associated with significant morbidity and mortality. The mortality rate for TEN is between 25-35% due to complicating factors (Foster 2013).

Important identified risk: Food effect

Table 8-7 Important identified risk: Food effect

Interacting substance(s)	**Food effect**
Effect of interaction	Administration of lapatinib with food results in an increase in systemic exposure, averaging 3-fold with a low-fat meal (studies EGF10003 and EGF10032), and 4-fold with a high-fat meal (Study EGF 10032). However, increases of 6-fold and 20-fold, respectively, have been observed in individual patients. These data were obtained after a single dose of lapatinib, but it is likely that the magnitude of this effect would be similar with repeated dosing at steady state.

	Bioavailability of a once daily 1250 mg dose (Study EGF111582) was approximately 2-fold higher when lapatinib was administered 1 hour after a low-fat meal (15% fat, 283-300 calories) and approximately 3-fold higher 1 hour after a high fat meal (50%, 800-1000 calories) in subjects with cancer. Given the effects of meals on bioavailability, it is recommended that patients take their doses in the fasted state at least 1 hour before or after a meal. The effect of specific foods on lapatinib metabolism has not been examined, although it is known that certain food constituents inhibit CYP3A4 and might therefore diminish lapatinib first-pass metabolism and increase bioavailability. Specifically, grapefruit juice has been shown to inhibit intestinal CYP3A4, although this effect may vary up to 5-fold depending on the source of the juice. The effect of most foods or beverages containing CYP3A4 inhibitors is unlikely to exceed the 3.6-fold increase observed with the highly potent inhibitor ketoconazole.
Evidence source	Studies EGF10008, EGF10003 and EGF10032 demonstrated that high and low fat meals produced significant increases in systemic exposure to lapatinib.
Possible mechanisms	Actual mechanism(s) unknown. Increased solubility and permeability or inhibition of intestinal efflux or metabolism may be involved.
Potential health risk	Increased systemic exposure to lapatinib which could result in increased toxicity.
Discussion	Study EGF111583, to evaluate the effect of grapefruit on the bioavailability of lapatinib, was under discussion with the Swiss Authority. The agency cancelled the requirement for this study as it was inappropriate to use healthy volunteers due to the risk of hepatotoxicity, and using patients on therapeutic doses would risk toxicity due to increased lapatinib exposure resulting from inhibition of lapatinib metabolism. Current text in the SmPC (Section 4.2, Section 4.5, Section 5.1 and Section 5.2) addresses the risk in the patient population.

8.3.2 Important potential risks:

None

8.3.3 SVII.3.2. Presentation of the missing information

Table 8-8 Elderly

Name of missing information	**Elderly**
Evidence source	**<u>Population in need of further characterization</u>**: There is limited information on the safety of lapatinib in the elderly (patients ≥65 years). In Study EGF104900, 15% (23 subjects) in the dual blockade arm, and 10% (14 subjects) in the lapatinib monotherapy arm were 65 years and over. In Study EGF104535, 7% (16 subjects) in the lapatinib plus paclitaxel treatment arm were 65 years and over. In the lapatinib plus letrozole treatment arm of Study EGF30008, 45% (295 subjects) were 65 years and over. Of the total number of metastatic breast cancer patients in the Phase III clinical study, EGF100151 who were treated with lapatinib in combination with capecitabine (N=198 as of 03-Apr-2006), 17% were 65 years and over. For single agent lapatinib (N=307, EGF20002 and EGF20008), 15% were 65 years and over. No overall differences in safety were observed between these subjects and younger subjects. Other reported

Name of missing information	Elderly
	clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Similarly, no differences in effectiveness on the basis of age have been observed.
Anticipated risk/ consequence of the missing information:	Current information suggests there is no difference in the safety of lapatinib in older patients (SmPC).

Table 8-9 Pregnant or lactating females

Name of missing information	Pregnant or lactating females
Evidence source	**Population in need of further characterization**: There is limited data available on the safety of lapatinib in pregnant or lactating females due to exclusion from clinical trials. Few pregnancy reports were received and the majority of these cases were from long-term follow up studies (ALTTO-study and NeoALTTO-study), and in these cases treatment with lapatinib was stopped several years before the pregnancy.
Anticipated risk/ consequence of the missing information:	There is no adequate data from the use of lapatinib in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is not known. Lapatinib should not be used during pregnancy unless clearly necessary. Women of childbearing potential should be advised to use adequate contraception and avoid becoming pregnant while receiving treatment with lapatinib. The safe use of lapatinib during lactation has not been established. It is not known whether lapatinib is excreted in human milk. In rats, growth retardation was observed in pups which were exposed to lapatinib via breast milk. Breast feeding must be discontinued in women who are receiving therapy with lapatinib (SmPC).

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Table Part II SVIII.1: Summary of safety concerns

Important identified risks	• Hepatobiliary events • Decreased LVEF • Pneumonitis/ILD • Interactions with other drugs • QTc prolongation • Severe cutaneous reactions • Food effect
Important potential risks	None
Missing information	• Elderly • Pregnant or lactating females

10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

10.1 Part III.1. Routine pharmacovigilance activities

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific adverse reaction follow-up questionnaires for risks:

Specific adverse event follow-up checklists are being used to collect further data to help further characterize and/or closely monitor each of the respective risks.

The following adverse event follow-up checklists are used to collect additional data for lapatinib.

- Hepatobiliary Events (Important identified risk)
- Decreased Left Ventricular Ejection Fraction (Important identified risk)
- Pneumonitis/ Interstitial Lung Disease (Important identified risk)

These checklists are provided in Annex 4 of the RMP.

Other forms of routine pharmacovigilance activities for risks

Not applicable.

10.2 Part III.2. Additional pharmacovigilance activities

None

10.3 Part III.3 Summary Table of additional pharmacovigilance activities

Table 10-1 Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

11 Part IV: Plans for post-authorization efficacy studies

There are currently no commitments for any post-authorization efficacy studies.

12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

12.1 Part V.1. Routine risk minimization measures

Table 12-1 Table Part V.1: Risk minimization measures for Hepatobiliary events

Safety concern	Hepatobiliary events
	Routine risk communication Section 4.2, Section 4.4, Section 4.8 and Section 5.2 of the SmPC **Routine risk minimization activities recommending specific clinical measures to address the risk** Liver function (transaminases, bilirubin and alkaline phosphatase) should be monitored before the initiation of treatment and monthly thereafter, or as clinically indicated. **Other routine risk minimization measures beyond the Product Information** None

Table 12-2 Table Part V.1: Risk minimization measures for Decreased left ventricular ejection fraction

Safety concern	Decreased left ventricular ejection fraction
	Routine risk communication Section 4.2, Section 4.4, Section 4.8 and Section 5.1 of the SmPC **Routine risk minimization activities recommending specific clinical measures to address the risk** Evaluation of cardiac function, including LVEF determination, should be conducted for all patients prior to initiation of treatment with lapatinib to ensure that the patient has a Baseline LVEF that is within the institutions normal limits. Left ventricular ejection fractionshould continue to be evaluated during treatment with lapatinib to ensure that LVEF does not decline to an unacceptable level. **Other routine risk minimization measures beyond the Product Information** None

Table 12-3 Table Part V.1: Risk minimization measures for Pneumonitis/ Interstitial lung disease

Safety concern	Pneumonitis/ Interstitial lung disease
	Routine risk communication Section 4.2, Section 4.4 and Section 4.8 of the SmPC

	Routine risk minimization activities recommending specific clinical measures to address the risk Patients should be monitored for symptoms of pulmonary toxicity (dyspnoea, cough, fever) and treatment should be discontinued in patients who experience symptoms which are NCI CTCAE grade 3 or greater. **Other routine risk minimization measures beyond the Product Information** None

Table 12-4 Table Part V.1: Risk minimization measures for Interactions with other drugs

Safety concern	Interactions with other drugs
	Routine risk communication Section 4.4 and Section 4.5 of the SmPC **Routine risk minimization activities recommending specific clinical measures to address the risk** Coadministration of lapatinib with orally administered medicinal products with narrow therapeutic windows that are substrates of CYP3A4 and CYP2C8 should be avoided. Concomitant treatment with substances that increase gastric pH should be avoided, as lapatinib solubility and absorption may decrease. **Other routine risk minimization measures beyond the Product Information** None

Table 12-5 Table Part V.1: Risk minimization measures for QTc prolongation

Safety concern	QTc prolongation
	Routine risk communication Section 4.4, Section 4.8 and Section 5.1 of the SmPC **Routine risk minimization activities recommending specific clinical measures to address the risk** Electrocardiograms with QT measurement should be performed prior to and 1 to 2 weeks after the start of lapatinib therapy. **Other routine risk minimization measures beyond the Product Information** None

Table 12-6 Table Part V.1: Risk minimization measures for Severe cutaneous reactions

Safety concern	Severe cutaneous reactions
	Routine risk communication Section 4.4 and Section 4.8 of the SmPC

	Routine risk minimization activities recommending specific clinical measures to address the risk Treatment with lapatinib should be discontinued, if EM or life-threatening reactions such as SJS/TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are suspected. **Other routine risk minimization measures beyond the Product Information** None

Table 12-7 Table Part V.1: Risk minimization measures for Food effect

Safety concern	Food effect
	Routine risk communication Section 4.2, Section 4.5, Section 5.1 and Section 5.2 of the SmPC **Routine risk minimization activities recommending specific clinical measures to address the risk** Lapatinib should always to be taken 1 hour before a meal. **Other routine risk minimization measures beyond the Product Information** None

Table 12-8 Table Part V.1: Risk minimization measures for Elderly

Safety concern	Elderly
	Routine risk communication Section 4.2 of the SmPC **Routine risk minimization activities recommending specific clinical measures to address the risk** None **Other routine risk minimization measures beyond the Product Information** None

Table 12-9 Table Part V.1: Risk minimization measures for Pregnant or lactating females

Safety concern	Pregnant or lactating females
	Routine risk communication Section 4.6 of the SmPC **Routine risk minimization activities recommending specific clinical measures to address the risk** None

	Other routine risk minimization measures beyond the Product Information None

12.2 Part V.2. Additional Risk minimization measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

12.3 Part V.3 Summary of risk minimization measures

Table 12-10 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Routine risk minimization measures	Pharmacovigilance activities
Hepatobiliary events	Section 4.2, Section 4.4, Section 4.8 and Section 5.2 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific AE follow-up checklists will be used to collect further data to help further characterize and/or closely monitor this risk. Additional pharmacovigilance activities: None
Decreased LVEF	Section 4.2, Section 4.4, Section 4.8 and Section 5.1 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific AE follow-up checklists will be used to collect further data to help further characterize and/or closely monitor this risk. Additional pharmacovigilance activities: None
Pneumonitis/ ILD	Section 4.2, Section 4.4 and Section 4.8 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific AE follow-up checklists will be used to collect further data to help further characterize and/or closely monitor this risk. Additional pharmacovigilance activities: None
Interactions with other drugs	Section 4.4 and Section 4.5 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Routine risk minimization measures	Pharmacovigilance activities
QTc prolongation	Section 4.4, Section 4.8 and Section 5.1 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Severe cutaneous reactions	Section 4.4 and Section 4.8 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Food effect	Section 4.2, Section 4.5, Section 5.1 and Section 5.2 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Elderly	Section 4.2 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Pregnant or lactating females	Section 4.6 of the SmPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

13 Part VI: Summary of the risk management plan: Tyverb (Lapatinib)

This is a summary of the RMP for lapatinib. The RMP details important risks of lapatinib, how these risks can be minimized, and how more information will be obtained about lapatinib's risks and uncertainties (missing information).

Lapatinib's SmPC and its package leaflet give essential information to healthcare professionals and patients on how lapatinib should be used.

This summary of the RMP for lapatinib should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of lapatinib's RMP.

13.1 Part VI: I. The medicine and what it is used for

Tyverb® contains lapatinib as the active substance and it is used for in the following indications:

Tyverb is indicated for the treatment of adult patients with breast cancer, whose tumours overexpress HER2 (ErbB2);

- In combination with capecitabine for patients with advanced or metastatic disease with progression following prior therapy, which must have included anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting.
- In combination with trastuzumab for patients with hormone receptor-negative metastatic disease that has progressed on prior trastuzumab therapy (ies) in combination with chemotherapy.
- In combination with an aromatase inhibitor for postmenopausal women with hormone receptor positive metastatic disease, not currently intended for chemotherapy.

Additional details on the approved indications are available in the SmPC.

Route of administration, pharmaceutical forms and strengths:

Tyverb is available as 250 mg film-coated tablets

Additional details are available in the SmPC.

Further information about the evaluation of lapatinib's benefits can be found in lapatinib's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage*:* link to product's EPAR summary landing page on the EMA webpage: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000795/WC500044957.pdf (last accessed: 04-05-2018).

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet 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 patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR, so that immediate action can be taken as necessary. These measures constitute routine PhV activities.

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

13.2.1 Part VI – II.A: List of important risks and missing information

Important risks of lapatinib are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. 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 lapatinib. 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 13-1 List of important risks and missing information

Important identified risks	• Hepatobiliary events • Decreased LVEF • Pneumonitis/ILD • Interactions with other drugs • QTc prolongation • Severe cutaneous reactions • Food effect
Important potential risks	None
Missing information	• Elderly • Pregnant or lactating females

13.2.2 Part VI - II B: Summary of important risks

Table 13-2 Important identified risk: Hepatobiliary events

Evidence for linking the risk to the medicine	Tyrosine kinase inhibitors have been associated with hepatotoxicity, and has been observed in clinical studies during the clinical development and also in the post-marketing use. It is known that hepatotoxicity shown as increase of transaminases accompanied by bilirubin, and can be observed within days after drug administration. Hepatotoxicity can have a severe outcome and in rare cases can be fatal.
Risk factors and risk groups	Patients who carry the HLA alleles DQA1*02:01 and DRB1*07:01 have increased risk of Tyverb-associated hepatotoxicity. Carriage of the HLA risk alleles is common (15 to 25%) in Caucasian, Asian, African and Hispanic populations but lower (1%) in Japanese populations.
Risk minimization measures	**Routine risk minimization measures** Section 4.2, Section 4.4, Section 4.8 and Section 5.2 of the SmPC. **Additional risk minimization measures** None

Table 13-3 Important identified risk: Decreased left ventricular ejection fraction

Evidence for linking the risk to the medicine	Data from clinical studies across the clinical development program revealed a decrease in LVEF in approximately 1% of patients receiving lapatinib and was asymptomatic in more than 70% of cases.

Risk factors and risk groups	Patients with history of cardiac disorders are at a risk.
Risk minimization measures	**Routine risk minimization measures** Section 4.2, Section 4.4, Section 4.8 and Section 5.1 of the SmPC **Additional risk minimization measures** None

Table 13-4 Important identified risk: Pneumonitis/ Interstitial lung disease

Evidence for linking the risk to the medicine	Cases of interstitial lung disease have been reported in clinical trials and in post marketing setting.
Risk factors and risk groups	Gefitinib, a small molecule TKI that targets ErbB1, has been associated with reports of interstitial pneumonitis, and data indicated that this event was more common in Japanese patients.
Risk minimization measures	**Routine risk minimization measures** Section 4.2, Section 4.4 and Section 4.8 of the SmPC. **Additional risk minimization measures** None

Table 13-5 Important identified risk: Interactions with other drugs

Evidence for linking the risk to the medicine	Lapatinib inhibits CYP3A4 and CYP2C8 in vitro at clinically relevant concentrations.
Risk factors and risk groups	Co-administration of Tyverb with medicinal products with narrow therapeutic windows that are substrates of CYP2C8 should be avoided. Concomitant treatment with inducers of CYP3A4 should be avoided due to risk of decreased exposure to lapatinib. Concomitant treatment with strong inhibitors of CYP3A4 should be avoided due to risk of increased exposure to lapatinib.
Risk minimization measures	**Routine risk minimization measures** Sections 4.4 and 4.5 of the SmPC. **Additional risk minimization measures** None

Table 13-6 Important identified risk: QTc prolongation

Evidence for linking the risk to the medicine	The effect of lapatinib on the QTc-interval was investigated in a thorough QT-study in cancer patients (Study EGF114271). The PK/PD analyses confirmed the presence of a positive relationship between lapatinib plasma concentrations and ΔΔQTcF.
Risk factors and risk groups	Risk groups include, patients with hypokalemia or hypomagnesemia, congenital long QT syndrome, patients taking anti-arrhythmic medicines or other medicinal products that lead to QT prolongation.
Risk minimization measures	**Routine risk minimization measures** Section 4.4, Section 4.8 and Section 5.1 of the SmPC. **Additional risk minimization measures**

	None

Table 13-7 Important identified risk: Severe cutaneous reactions

Evidence for linking the risk to the medicine	Clinical study data showed the incidence of severe cutaneous adverse reactions, including EM, SJS and TEN, in the lapatinib clinical program is low and comparable with the incidences seen in placebo/comparator treatment groups. However given the seriousness of SJS and TEN, severe cutaneous reactions have been added as an identified risk.
Risk factors and risk groups	Various etiologic factors (e.g. infection, drugs, and malignancies) have been implicated as causes of SJS. However, as many as half of cases are idiopathic. There is strong evidence for a genetic predisposition to SJS provoked by certain drugs (Foster 2013).
Risk minimization measures	**Routine risk minimization measures** Section 4.4 and Section 4.8 of the SmPC. **Additional risk minimization measures** None

Table 13-8 Important identified risk: Food effect

Evidence for linking the risk to the medicine	The bioavailability of lapatinib is increased up to about 4 times by food, depending on e.g. the fat content in the meal. Furthermore, depending on type of food the bioavailability is approximately 2-3 times higher when lapatinib is taken 1 hour after food compared with 1 hour before the first meal of the day.
Risk factors and risk groups	Not applicable
Risk minimization measures	**Routine risk minimization measures** Section 4.2, Section 4.5, Section 5.1 and Section 5.2 of the SmPC. **Additional risk minimization measures** None

Table 13-9 Important missing information: Elderly

Risk minimization measures	**Routine risk minimization measures** Section 4.2 of the SmPC. **Additional risk minimization measures** None

Table 13-10 Important missing information: Pregnant or lactating females

Risk minimization measures	**Routine risk minimization measures** Section 4.6 of the SmPC. **Additional risk minimization measures** None

13.2.3 Part VI – II C: Post-authorization development plan

13.2.3.1 II.C.1 Studies which are conditions of the marketing authorization

None

13.2.3.2 II.C.2. Other studies in post-authorization development plan

None

14 Part VII: Annexes

Table of contents

Annex 1 – EudraVigilance Interface

Available in electronic format only.

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study program

Table 14-1 Planned and ongoing studies

Study	Summary of objectives	Safety concerns addressed	Milestones
None	-	-	-

Table 14-2 Completed studies

Study	Summary of objectives	Safety concerns addressed	Date of submission of final study report
EGF109275 An Open-Label, Two-Part, Single Sequence Study to Examine the Effects of Esomeprazole on the Pharmacokinetics of Orally Administered Lapatinib in Subjects with Metastatic ErbB2	Characterize the effect of elevated gastric pH mediated by the proton-pump inhibitor, esomeprazole, on the relative bioavailability of lapatinib	Interactions with other drugs	Sep-2010
EGF110557 Effect of lapatinib on the bioavailability of the Pgp substrate digoxin	Part 1: Effect of lapatinib on PK of digoxin (DDI); Part 2: Safety and clinical benefit of lapatinib alone or lapatinib in combination with selected anticancer agents	Interactions with other drugs	Mar-2010
EGF111582 An Open-Label, Two-Part Study to Examine the Effects of High-Fat and Low-Fat Meals on the Pharmacokinetics of Orally Administered Lapatinib in Cancer Patients	PK, bioavailability, safety, tolerability	Food effect	Dec-2011
EGF113892 (PGX240) Exploratory pharmacogenetic study of subjects who experienced hepatic events.	Retrospective exploratory pharmacogenetic investigation of Associations between Genetic Markers and Elevated Alanine Aminotransferase Levels and/or Total Bilirubin Concentration in Patients treated with lapatinib.	Hepatobiliary events	Mar-2010 (synopsis in RMPv8)
EGF113893 (PGX132) Exploratory pharmacogenetic Investigation of Associations between Genetic Markers and Diarrhoea Events in Patients Treated with lapatinib.	Exploratory pharmacogenetic analysis of lapatinib patients who experienced diarrhoea	Diarrhoea	Mar-2010 (synopsis in RMPv8)
EGF113894 (PGX123) Exploratory pharmacogenetics study of subjects who experienced decreased LVEF	Exploratory pharmacogenetic analysis of lapatinib patients who experienced decreased LVEF	Decreased LVEF	Mar-2009 (synopsis in RMPv5)

Study	Summary of objectives	Safety concerns addressed	Date of submission of final study report
EGF113895 (PGX272) Exploratory pharmacogenetic investigation of lapatinib associated hepatobiliary safety signals using Whole Genome Screen methods	Retrospective exploratory pharmacogenetics analysis.	Hepatobiliary events	Mar-2010 (synopsis in RMPv8)
EGF113896 (PGX275) Pharmacogenetic investigation of lapatinib associated hepatobiliary safety signals in EGF30008	Confirmatory retrospective, PGx analysis	Hepatobiliary events	Mar-2010 (synopsis in RMPv8)
EGF114471 (PGX320) Tykerb TEACH EGF105485 liver safety pharmacogenetics	Prospectively defined, retrospectively conducted PGx analysis	Hepatobiliary events	Jul-2012 (Type II/26 FUM)
LAP114369 NCI PBTC 016 A Phase I Trial of Lapatinib in Children with Refractory CNS malignancies	To estimate the maximum tolerated dose (MTD), dose-limiting toxicities (DLT), and pharmacokinetic properties of lapatinib, a selective epidermal growth factor receptor (EGFR) and ERBB2 inhibitor, in children with refractory or recurrent CNS malignancies.	Children	Mar-2008 (synopsis in RMPv4a)
WEUK191 Occurrence of cardiac adverse events in breast cancer patients with advanced disease.	Influence of cardiovascular risk factors before start of treatment and Influence of different cardiotoxic treatment regimens	Decreased LVEF	Apr-2007 (synopsis in RMPv2)
WEUKBRE975 Background LFT elevations in oncology patients contained in pooled MAH clinical trials data (INET)	Feasibility of using clinical trial datasets (INET) to evaluate Baseline liver function of cancer patients	Hepatobiliary events	Aug-2009 (synopsis in RMPv6)
WEUKSTV668 Occurrence of Interstitial Pneumonitis in Advanced and Metastatic Breast Cancer Patients	Retrospective study on the occurrence of interstitial pneumonitis in advanced and metastatic breast cancer patients	Pneumonitis/ILD	Apr-2007 (synopsis in RMPv2)
WEUSKOP3177 FDA label review (Part A) and clinical trial literature review (Part B) of liver enzyme elevations reported in clinical trials of marketed tyrosine kinase-inhibiting drugs (TKIs)	Quantify background rates of LFT elevations among cancer patients who received various TKIs, including lapatinib	Hepatobiliary events	Mar-2009 (synopsis in RMPv5)
WWE112883 WEUKBRE3262 Cohort study to document background rates of hypertension and Liver Function Test (LFT) elevations in users of tyrosine kinase	Obtain estimates of incident LFT elevations among cancer patients in general and those receiving TKI drugs. Describe the time to the first elevated LFT, time to return to normal after an elevated LFT, as well	Hepatobiliary events	Mar-2010 (synopsis in RMPv8)

Study	Summary of objectives	Safety concerns addressed	Date of submission of final study report
inhibiting drugs - Varian Oncology Database	as predictors of any LFT elevation.		
WWE113153 WEUKSTV3635 Liver Function Test (LFT) elevations in cancer patients and users of tyrosine kinase inhibitor (TKI) drugs using the LabRx Database. Full study and including Tykerb	Explore the feasibility of utilizing the LabRx claims database to examine LFT elevations among cancer patients in general and those treated with one or more EGFR targeted small molecule TKI	Hepatobiliary events	31-Aug-2010 21-Jul-2012
WWE115270 WEUKSTV4275 Assessment of physician compliance to recommended liver function test monitoring for Tykerb patients	Determine if physicians conduct liver function testing (LFT) prior to prescribing lapatinib (Baseline) and at regular intervals during lapatinib exposure; describe the prevalence of LFT elevations at Baseline and incidence during lapatinib exposure	Hepatobiliary events	04-Aug-2012 (synopsis in RMPv15)
EGF115159 (PGx349): Exploratory pharmacogenetic analysis of GWAS data for liver safety in EGF30008	To use available genetic data from all studies to refine the previously identified genetic marker, HLA-DQA1*02:01/DRB1*07:01	Hepatobiliary events	27-Mar-2013 (synopsis in RMPv17)
EGF116294 (PGx419): Pharmacogenetic Evaluation	Pharmacogenetic Evaluation of Decrease in Left Ventricular Ejection Fraction (LVEF) in Lapatinib Treated Metastatic Breast Cancer (MBC) patients	Decreased LVEF	27-Mar-2013 (synopsis in RMPv17)
110858 (GERICO): Phase II Study Evaluating the Activity of the Combination Lapatinib plus Capecitabine in Elderly Patients Aged 70 and Older with Locally Advanced or Metastatic Breast Cancer (MBC) Over-expressing HER2+	To assess clinical benefit (defined at 4 months as complete response, partial response or stable disease), safety and preserved geriatric independence.	Use in the Elderly	Not applicable
Development of an animal model to study tyrosine kinase inhibitor-induced mucosal injury and diarrhoea (NCS/Keefe)	Investigation of mechanisms of TKI monotherapy-induced diarrhoea in the rat, and dose-finding for long course chemotherapy-induced diarrhoea.	Mechanism of diarrhoea	October 2014 (synopsis in RMPv24)
201486 (PGX6475)	To determine if HLA genetic variants predict lapatinib-induced severe rash, allowing identification of a high-risk subpopulation for focused management.	Risk factors for rash	31-Oct-2014

Study	Summary of objectives	Safety concerns addressed	Date of submission of final study report
EGF115152 (PGX397): Whole genome sequencing of lapatinib concurrent ALT/TBL elevation and extreme ALT elevation cases	This interim objective is to provide DRB1*07:01, DQA1*02:01 and UGT1A1*28 genotype results in selected hepatic SAE cases who presented in lapatinib clinical trials.	Risk factors for hepatotoxicity	15-Jun-2015
LAP112539 (CERN 08-01): A Phase II Study of Lapatinib and Bevacizumab in Children with Recurrent or Refractory Ependymoma	To estimate the sustained objective response rates (CR plus PR) to lapatinib 700 mg/m2/dose bid, bevacizumab 10 mg/kg iv q 2 weeks to children with recurrent or refractory ependymoma.	Use in children	15-Jun-2015
LAP113130 (LANTERN): A randomised phase II Screening trial with functional imaging and patient reported toxicity sub-studies comparing LApatiNib plus capecitabine versus continued Trastuzumab plus capecitabine after local therapy in patients with ERb B2 positive metastatic breast cancer developing braiN metastasis/es	To investigate the effect of lapatinib plus capecitabine compared with trastuzumab plus capecitabine on time to progression of CNS metastases as measured by Response Evaluation Criteria In Solid Tumors (RECIST). Secondary objectives include: Total days of steroid use for palliation of CNS symptoms.	Concomitant use of corticosteroids with lapatinib	26-Jan-2015
EGF117394 (PGX6622)	To identify genetic markers to refine association with HLA- DRB1*07:01/-DQA1*02:01 in the lapatinib-treated patients. To identify genetic markers associated with ALT elevations in the lapatinib-treated patients.	Hepatobiliary events	NA
09DMR017 Lapatinib Metabolite Identification in Dog Plasma, Bile and Liver	To identify lapatinib metabolites in dog plasma, bile and liver.	Mechanism of hepatotoxicity	Q4-2017
112477	An open label, multi-centre, non-interventional post-marketing surveillance (PMS) to monitor the safety and effectiveness of Tykerb™ administered in Korean patients	Patients of different racial and / or ethnic origin	Mar-2015

Study	Summary of objectives	Safety concerns addressed	Date of submission of final study report
EGF114498	A Post Marketing Surveillance Study of Lapatinib ditosylate (Tykerb) among Filipinos diagnosed with Advanced or Metastatic Breast Cancer	Not applicable	Not applicable
EGF113780	Clinical Outcomes of ErbB2+ MBC patients treated with Lapatinib plus capecitabine after Trastuzumab progression: Role of early versus late switch to Lapatinib plus capecitabine (TYCO1).	Not applicable	Oct-2014
EGF114271 (CLAP016A2403): A study to evaluate the effect of lapatinib on QT interval in patients with cancer	To estimate the effect of lapatinib on QTcF interval as compared to placebo in patients with advanced cancer.	Potential for QTc prolongation	Sep-2016
EGF114299 (ALTERNATIVE/ CLAP016A2307): A Phase III trial to compare the safety and efficacy of lapatinib plus trastuzumab plus an aromatase inhibitor (AI) versus trastuzumab plus an AI versus lapatinib plus an AI as first- or second-line therapy in postmenopausal subjects with hormone receptor positive, HER2-positive metastatic breast cancer (MBC) who have received prior trastuzumab and endocrine therapies	To present data in patients with hormone receptor-positive metastatic breast cancer, not currently intended for chemotherapy, and previously treated with trastuzumab.	Not applicable	Nov-2017
EGF117165 (CLAP016A2206): A two-arm study to evaluate biomarkers of drug resistance in patients with HER2+ metastatic breast cancer whilst on treatment with trastuzumab in combination with either lapatinib or chemotherapy	The primary objective was to evaluate changes in biomarkers associated with immunomodulation.	Biomarkers associated with immunomodulation	Apr-2019 (CSR EGF117165 [CLAP016A2206])

Annex 3 - Protocols for proposed, ongoing and completed studies in the pharmacovigilance plan

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

None

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.

None

Part C: Previously agreed protocols for ongoing studies and final protocols not reviewed by the competent authority.

None

Annex 4 - Specific adverse drug reaction follow-up forms

Standard Targeted Follow-up Checklist for Hepatobiliary Events

Event Description:

1. Diagnosis and date of diagnosis:
2. Did the patient present with any of the following signs or symptoms? **Check all that apply**

☐ Jaundice ☐ Ascites ☐ Asterixis (flapping tremor)
☐ Dark urine ☐ Fever ☐ Altered mental status
☐ Pale stool ☐ Fatigue ☐ Abdominal pain (specify location)
☐ Pruritus ☐ Bleeding (specify location) ☐ Anorexia
☐ Nausea ☐ None
☐ Other (specify)_____

Diagnostic tests

Were any of the following diagnostic tests performed?

►**If yes,** please specify the dates and results including reference range and pre- and post-treatment values.

☐ Liver function tests
☐ Serology & PCR testing for Hepatitis A, B, C &/or E virus
☐ Autoantibody test
☐ Abdominal or hepatobiliary ultrasound
☐ Abdominal CT scan
☐ Liver biopsy
☐ Liver transplant (planned or completed)
☐ None
☐ Other (specify) _____

Does the patient have a history of any of the following prior to the start of the suspect drug? Check all that apply and include date(s) of onset as well as status (i.e. active/inactive) and details

☐ Previously elevated liver enzymes☐ Tattoos
☐ Hepatitis☐ Transfusion or blood product administration
☐ Other hepatobiliary disease or dysfunction☐ Gilbert's disease
☐ Autoimmune disease☐ Alcohol intake
☐ Active pancreatitis☐ Drug abuse
☐ Diabetes mellitus (Type I or II)☐ Foreign travel
☐ Non-alcoholic steatohepatitis☐ Active gall bladder disease
☐ None
☐ Other (specify)_____

Has the patient recently (i.e. within the past 6 months) taken any of the following? Check all that apply

☐ Sulfonamides ☐ Furosemide☐ ACE Inhibitors☐ Valproic acid☐ NSAIDS (e.g. ibuprofen) ☐ Estrogens (oral contraceptives)
☐ Metronidazole ☐ Acetaminophen/Paracetamol☐ Amiodarone
☐ COX II inhibitors(e.g. celecoxib)☐ Tetracycline☐ Steroids
☐ Thiazide diuretics☐ 6-Mercaptopurine☐ Statins

☐ Nicotinic acid ☐ Methotrexate ☐ None
☐ Other (specify) _____

Lapatinib Standard Targeted Follow-up Checklist for Decreased Left Ventricular Ejection Fraction

Event Description

Was the subject's decreased ejection fraction

☐ symptomatic or ☐ asymptomatic?

If *symptomatic*, please describe symptoms:

_____

_____

_____

Did the patient respond to conventional heart failure therapy? **Yes** ☐ **No** ☐

If *yes*, please provide details of therapy_____

_____

Was the patient intubated and treated with artificial respiration? **Yes** ☐ **No** ☐

Did the symptoms resolve with diuretics/digoxin? **Yes** ☐ **No** ☐

Was the subject rechallenged with the suspect drug? **Yes** ☐ **No** ☐

If *yes*, what was the outcome?_____

Diagnostic tests

What was the subject's Baseline MUGA or echocardiogram result? **Attached** ☐

Please describe and attach the report if available: _____

_____

_____

Is repeat MUGA or echocardiographic data available to confirm the reduction in ejection fraction?

Yes ☐ **No** ☐

Please attach if available: **Attached** ☐

If an echocardiogram was carried out please provide cardiac end systolic and diastolic dimensions:

_____

Were serum peptides (troponin, BNP) measured? **Yes** ☐ **No** ☐

If *yes*, please provide the results:_____

Is repeat MUGA or echocardiographic data available to confirm the event resolved?

Yes ☐ **No** ☐

Please attach if available: **Attached** ☐

Patient History

Please provide details of metastatic disease: _____

_____

Were chest or heart involved? **Yes** ☐ **No** ☐

Did the subject have any relevant past medical history of cardiovascular disease or other risk factors?

Yes ☐ **No** ☐

If *yes*, please describe: _____

_____

Concomitant medications

Did the subject receive any of the following medications?

If *yes* please give dates / doses

Anthracycline (e.g. doxorubicin hydrochloride) **Yes** ☐ **No** ☐

Trastuzumab **Yes** ☐ **No** ☐

Mitoxantrone hydrochloride **Yes** ☐ **No** ☐

Please provide details of prior radiation therapy treatment (e.g. to left chest) with dates and total dose:

_____

Lapatinib Standard Targeted Follow-up Checklist for Pneumonitis/ILD

Event Description:

Did the patient present with any of the following signs or symptoms? **Check all that apply**

- ☐ Dyspnea/Rapid breathing/Shortness of breath
- ☐ Dry cough
- ☐ Chest pain
- ☐ Clubbing of the fingers
- ☐ Chest discomfort
- ☐ Fatigue/Malaise
- ☐ Arrhythmia
- ☐ Hypotension
- ☐ Other Cardio-Respiratory symptoms *(please specify)*
- ☐ Leg edema
- ☐ Wheezing, crackles
- ☐ Palpitations
- ☐ Cyanosis
- ☐ Fever/Pyrexia
- ☐ Pleural effusion
- ☐ Arthralgia
- ☐ None of the above

Were any of the following diagnostic tests performed? **Check all that apply and specify including dates and results**

- ☐ Chest x-ray/CT scan /MRI
- ☐ Arterial blood gases
- ☐ Lab tests (blood count, microbiology cultures, viral/bacterial serology, anti-DNA
- ☐ Pulmonary function tests
- ☐ Bronchoalveolar lavage (BAL)
- ☐ Bronchoscopy with lung biopsy
- ☐ Lung transplant (planned or completed)
- ☐ None of the above

Was there a final diagnosis (i.e. Obstructive lung disease, restrictive lung disease)?

☐ **Yes** *(please specify)* ☐ **No** ☐ **Unknown**

Patient History:

Does the patient have a history of any of the following risk factors? **Check all that apply and please specify**

- ☐ Cancer
- ☐ Asthma or Respiratory Allergies
- ☐ Occupational or environmental toxins exposure (e.g. silicosis, asbestos, hard metal dust)
- ☐ Other relevant history *(please specify)*
- ☐ Infections *(please specify)*
- ☐ Familial history of interstitial lung disease
- ☐ Smoking
- ☐ Hematological diseases (e.g. lupus, scleroderma, rheumatoid arthritis)
- ☐ None of the above

Was the patient taking any of the following drugs (immediately before the event)? **Check all that apply**

- ☐ Radiation therapy
- ☐ Chemotherapy (e.g. methotrexate, bleomycin)
- ☐ Antiarrhythmics (e.g. amiodarone)
- ☐ Antibiotics
- ☐ Psychiatric medications
- ☐ Chlorpromazine
- ☐ Methyldopa
- ☐ Procainamide
- ☐ Hydralazine
- ☐ None of the above

Annex 5 - Protocols for proposed and ongoing studies in RMP part IV

None

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Not applicable.

Annex 7 - Other supporting data (including referenced material)

Brief Statistical Description and Supportive Outputs

Not applicable

MedDRA Search terms for spontaneous post-marketing data

Not applicable

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Novartis internal reference

[CSR EGF117165 (CLAP016A2206)]

Annex 8 – Summary of changes to the risk management plan over time

Table 14-3 Summary of changes to the risk management plan over time

Version	Approval date and Procedure	Change
1.0	18-Sep-06	The first version of the initial EU-RMP; lapatinib plus capecitabine combination study EGF100151 (15-Nov-2005)
2.0	3-Apr-07	Changes to initial EU-RMP as a result of review by the EMA
3.0	31-Aug-07	Update due to new data from study EGF100151 (03-Apr-2006)
4a	21-May-08	Update due to addition of information on the potential risk of QTc prolongation
5.0	5-Mar-09	Addition of data from lapatinib plus letrozole combination study EGF30008 (03-Jun-2008)
6.0	11-Aug-09	Updates during review by the EMA
7.0	1-Dec-09	Additional updates during the EMA review process
8.0	8-Feb-10	Addition of QT study and approved SmPC
9.0	28-Apr-10	Addition of updated cum. safety review, EGF114471 (PGx320), and study results (EGF110557; WEUKBRE3262)
10.0	14-Jun-10	Added details of agreed QT study EGF114271
11.0	22-Mar-11	Update due to addition of data from lapatinib plus paclitaxel combination study EGF104535 (18-Jun-2010), study EGF115159 (PGx349), and results from EGF115152 (PGx397)
12.0	9-Feb-12	Update due to addition of data to support dual blockade, trastuzumab combination submission
13.0	23-Jan-12	Updated following EMA review of the renewal application
14.0	9-Feb-12	Updated following EMA review of the renewal application
15.0	6-Aug-12	Updated following EMA review of version 12, the dual blockade, trastuzumab combination submission.
16.0	23-Jul-12	Version 14 updated to include the outcome of the Hepatic Pharmacogenetic study EGF114471 (PGx320).
17.0	14-Mar-13	Migration to new GVP RMP format, combines v15 and v16
18.0	28-May-13	Correction of migration compilation misunderstanding of V15 and V16 into V17 and inclusion of EGF117165 biomarkers study

Version	Approval date and Procedure	Change
19.0	11-Jun-13	Updated following EMA review of version 18; Supersedes V18
20.0	30-Oct-13	Updated estimated completion dates for EGF114271 and LAP113130
21.0	08-Jan-14	Updated at the request of the EMA to add PV study categorisations (1 – Imposed; 2 – Specific Obligation; 3 – Required)
22.0	02-Jul-14	Amended estimated completion date for LAP113130
23.0	19-Sep-14	Updated to include outcome of CNS metastases Special Obligation (SOB)
24.0	27-Oct-14	General RMP update including study status, outcome, milestones.
25.0	10-Dec-14	Updated following EMA review of version 23, outcome of CNS metastases Special Obligation (SOB)
26.0	19-Jan-15	Update to include summarised outcome of study LAP113130 (LANTERN)
27.0	02-Feb-15	Base RMP version 24 updated to include EMA approved additions to RMPv25
28.0	09-Mar-15	Addition of 'severe cutaneous reactions' as a potential risk
28.1	21-Apr-15	Combined versions 26 and 28
29.0	06-May-15	Consolidated RMP version 27 and EMA approved RMPv28.1
30.0	12-May-15	RMP version 28.1 updated to include results for studies 201216 (PGx7521), EGF117393 (PGx6557), 110858 (GERICO), LAP112539, and final results from EGF115152 (PGx397)
31.0	28-Aug-15	Consolidates EMA approved RMP versions 29 and 30.
32.0	20-Jul-2017 EMEA/H/C/000795/II/48/G	RMP version 32.0 updated to include results from studies EGF114271 (LAP016A2403) <u>Safety concerns</u> • Based on the results from the QT study, the potential risk of 'QTc prolongation' is upgraded to an 'important identified risk' • Based on the results of the search of the safety database, Severe Cutaneous Reactions is upgraded to an 'important identified risk' • Based on review of Clinical Study Report EGF10003, EGF 10032 and EGF 111582 food effect is upgraded to an 'important identified risk' <u>Pharmacovigilance Plan</u> None

Version	Approval date and Procedure	Change
		Post-authorization efficacy plan None Risk minimization measures None
33.0	25-Jan-2018 EMEA/H/C/000795/II/0050/G	This RMP has been updated. Safety concerns • Important Identified risks 'rash' and 'diarrhoea' removed as per PRAC recommendation • Updated the name of Missing information: "Patients with hepatic disease" to "Patients with moderate to severe hepatic disease" and "Patients with renal disease" to "Patients with severe renal disease" as per PRAC recommendation. Pharmacovigilance Plan • Reflect the change in the due date for submission of CSR of Study EGF117165 (CLAP016A2206) from Q2-2018 to Q2-2019. • Reflect the completion of Non-clinical Study 09DMR017 - Lapatinib Metabolite Identification in Dog Plasma, Bile and Liver Post-authorization efficacy plan None Risk minimization measures None Annexes Updated to reflect the change in the due date for submission of CSR of Study EGF117165 (CLAP016A2206) from Q2-2018 to Q2-2019.
34.0	Not applicable EMEA/H/C/000795/II/0051	This RMP has been updated from v32. Safety concerns None Pharmacovigilance Plan Reflect the completion of Study EGF114299 (ALTERNATIVE/ CLAP016A2307), which was a PAM commitment for lapatinib.

Version	Approval date and Procedure	Change
		Post-authorization efficacy plan Reflect the completion of Study EGF114299 (ALTERNATIVE/ CLAP016A2307), which was a PAM commitment for lapatinib Risk minimization measures None Annexes Updated to reflect the completion of Study EGF114299 (ALTERNATIVE/ CLAP016A2307).
35.0	(Not applicable) 15-May-2018	This RMP is prepared in the new RMP template and integrates the information included in the RMP versions (v33.0 and v34.0). Safety concerns No updates Pharmacovigilance Plan Addition of EGF114299 (ALTERNATIVE/ CLAP016A2307) study results (Update of Progression free survival [PFS] and survival data) as Category 3 commitment. Post-authorization efficacy plan None Risk minimization measures No updates Annexes Updated information under the annexes to reflect the addition of EGF114299 (ALTERNATE/ CLAP016A2307) study (update of PFS and survival data) as Category 3 commitment.
35.1	28-Jun-2018 EMEA/H/C/000795/II/0051	Safety concerns No updates Pharmacovigilance Plan Removal of EGF114299 (ALTERNATIVE/ CLAP016A2307) study results (update of PFS and survival data) as Category 3 commitment. Post-authorization efficacy plan None

Version	Approval date and Procedure	Change
		Risk minimization measures No updates Annexes Removal of EGF114299 (ALTERNATIVE/ CLAP016A2307) study (update of PFS and survival data) as Category 3 commitment under Planned and Ongoing studies.
36.0	Not applicable	Safety concerns • Removed the following missing information from the RMP (as per PRAC recommendation): o Children o Patients with moderate and severe hepatic disease o Patients with severe renal disease o Patients with low cardiac ejection fraction o Patients of different racial and /or ethnic origin Pharmacovigilance Plan • Removed Study EGF117165 Post-authorization efficacy plan • Removed Study EGF117165 Risk minimization measures Following missing information (safety concerns) were removed from this section: o Children o Patients with moderate and severe hepatic disease o Patients with severe renal disease o Patients with low cardiac ejection fraction o Patients of different racial and /or ethnic origin