European Medicines Agency
Evaluation of Medicines for Human Use

Doc.Ref.: EMEA/302222/2008

ASSESSMENT REPORT FOR TYVERB

International Nonproprietary Name:
Lapatinib

Procedure No. EMEA/H/C/795

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Glaxo Group Limited submitted on 4 October 2006 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Tyverb, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 29 June 2006.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is a complete dossier:
composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies

Scientific Advice:
The applicant received Scientific Advice from the CHMP on 26 May 2005. The Scientific Advice pertained to clinical development aspects of the dossier.

Licensing status:
A new application was filed in the following countries: U.S.A.
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Tomas Salmonson Co-Rapporteur Beatriz Silva Lima

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 4 October 2006.
- The procedure started on 25 October 2006.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 January 2007. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 18 January 2007.
- During the meeting on 19 – 22 February 2007, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 February 2007.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 13 April 2007.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 25 May 2007.
- During the CHMP meeting on 18 – 21 June 2007, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP list of outstanding issues on 24 August 2007.
- During a meeting of a SAG Oncology on 5 September 2007, experts were convened to address questions raised by the CHMP.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 6 September 2007.
- During the CHMP meeting on 17 – 20 September 2007, the CHMP agreed on a second list of outstanding issues to be addressed in an oral explanation and/or in writing by the applicant.

- The applicant submitted the responses to the second list of outstanding issues on 11 October 2007.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the second list of outstanding issues to all CHMP members on 26 October 2007.
- During the CHMP meeting on 12 – 15 November 2007, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 10 – 13 December 2007, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion by majority decision for granting a conditional Marketing Authorisation to Tyverb on 13 December 2007. The applicant provided the letter of undertaking on the specific obligations and follow-up measures to be fulfilled post-authorisation on 11 December 2007.
- On 29 February 2008 the applicant informed Rapporteurs/EMEA of new safety analyses suggesting hepatotoxicity associated with Tyverb in the context of ongoing clinical trials.
- On 3 March 2008 the EMEA informed the European Commission about new safety information.
- On 5 March 2008 the applicant submitted full documentation on the new analyses and a revised risk/benefit evaluation for the current indication. On 11 March 2008 the applicant submitted a proposal to revise the product information annexes and on 12 March 2008 a proposal to revise the RMP.
- The Rapporteur's Preliminary Assessment Report was circulated to the CHMP on 12 March 2008.
- On 14 March 2008, the European Commission informed the EMEA that the preparation of a Commission decision on the basis of the CHMP opinion of 13 December 2007 had been suspended, and referred back the Opinion in view of the new safety data to the EMEA.
- During the CHMP meeting on 17 – 19 March 2008, the CHMP agreed on a List of Outstanding Issues on Hepatoxicity Findings to be addressed in an oral explanation and/or in writing by the applicant.
- The applicant submitted the responses to the list of outstanding issues on 2 April 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 11 April 2008.
- During the meeting of 21 – 24 April 2008, the CHMP, in the light of the information submitted and the proposed revisions of the Summary of Product Characteristics, Package Leaflet and Risk Management Plan the CHMP adopted a revised positive opinion by majority decision for granting a conditional Marketing Authorisation for Tyverb on 24 April 2008. The applicant provided the letter of undertaking on the specific obligations and follow-up measures to be fulfilled post-authorisation on 21 April 2008.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Breast cancer is the most common malignancy and the second most common cause of cancer-related death in Western Europe. The world-wide incidence of breast cancer in the year 2002 was estimated at 1,151,298 cases; mortality in the same year was estimated at 410,712 deaths [Parkin, 2005]. In the European Union, the incidence of breast cancer is increasing, although the mortality rate from breast cancer has decreased in some European countries since 1990. It is estimated that in the year 2000 there were 350,000 new breast cancer cases in Europe, while the number of deaths from breast cancer was estimated at 130,000. Breast cancer is responsible for 26.5% of all new cancer cases among women in Europe, and 17.5% of cancer deaths. Despite improvements in early diagnosis, almost all patients with metastatic disease, and up to 40% of patients receiving adjuvant therapy, eventually relapse and die from their disease [Ring, 2003]

Therapeutic approaches to patients with metastatic breast cancer (MBC) are based on endocrine therapy, biological therapy or chemotherapy, depending on the hormonal status of the tumour. The treatment goals in MBC are mainly to prolong survival, palliate symptoms and improve quality of life. Cure in MBC is rare and median survival extents between 18 and 36 months. In recent years, several new agents alone or in combination have contributed to the improvements in the treatment outcome, including taxanes, anthracyclines, antimetabolites, aromatase inhibitors, and antibodies.

About the product:

Lapatinib is a tyrosine kinase inhibitor which dually inhibits the growth factor receptors ErbB1 (epidermal growth factor receptor, EGFR) and ErbB2 (HER2). Lapatinib is a member of the 4-anilinoquinazoline class of kinase inhibitors. Members of this class of molecules have been shown to bind to the ATP binding site of protein kinases and compete with the ATP substrate [Denny, 1996; Shewchuk, 2000]. This blocks receptor phosphorylation and activation, preventing subsequent downstream signalling events.

ErbB2 is one of four members of a family of genes encoding transmembrane receptors for growth factors, the other three being ErbB1 (EGFR or HER1), ErbB3 (HER3) and ErbB4 (HER4). There is evidence in the literature that induced overexpression of ErbB1 or ErbB2 receptors in cells *in vitro* produces phenotypes associated with oncogenic transformation, such as the ability to grow in soft agar and formation of tumours in nude mice. *In vivo*, overexpression of ErbB1 or ErbB2 has been reported in a variety of human tumours and has been associated with poor prognosis and reduced overall survival in patients with cancer. Several therapeutic strategies have been employed to block the ErbB2 signalling pathways as a means to improve the therapeutic efficacy of hormonal and chemotherapy regimens. The rationale for lapatinib use as an anticancer entity is that the blockade of the tyrosine kinase activity of ErbB1 or ErbB2 is expected to block the transforming activity that results from overexpression of these receptors.

2.2 Quality aspects

Introduction

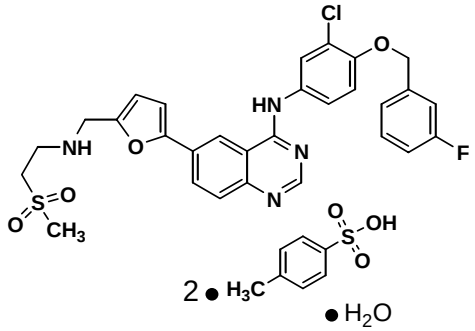
The applicant has submitted an application for Tyverb 250 mg film-coated tablets containing the new active substance, lapatinib ditosylate monohydrate.

Active Substance

The structure of the active substance lapatinib ditosylate monohydrate (INN: lapatinib) is shown below. It is a non-hygroscopic yellow crystalline solid. The molecule has no chiral centre and presents

no isomerism. It exists as the monohydrate, anhydrate and solvate crystal forms. The active substance is in the form of the monohydrate, and exists as a single polymorphic form.

Physico-chemical characterisation is adequately detailed including pH, partition coefficient, pKa values, UV characterisation, X-ray diffraction and solubility (practically insoluble in aqueous media).



- Manufacture

The synthesis of lapatinib ditosylate is a multi-stage process including a final crystallization purification step. The process has been sufficiently detailed including operating conditions and quantities.
No quality critical process parameters have been identified, but a number of quality process parameters are defined.
Adequate specification has been provided for all starting materials (reagents, solvents and auxiliary materials) and intermediates have been satisfactorily controlled.
Impurities and degradation products have been extensively investigated and fully justified by toxicological studies.
The chemical structure of lapatinib ditosylate is supported by the route of synthesis and fully elucidated by ^{1}H NMR, ^{13}C NMR, Mass Spectrometry, IR, elemental analysis and X-ray diffraction analysis.
No materials of human or animal origin have been used for the synthesis of lapatinib.

- Specification

Specification of the active substance includes parameters such as description, identification (IR), identification of p-toluenesulfonate (HPLC), assay of lapatinib ditosylate monohydrate (HPLC), related substances (HPLC), specific impurity (LC/MS/MS), water content (Karl-Fischer), residual solvents (GC), residue on ignition (PhEur sulfated ash), residual metals by inductively coupled plasma with optical emission (ICP-OES). Analytical methods have been described and validated in accordance with ICH requirements.
Specification is appropriate and in accordance with ICH requirements. In particular, the impurity limits have been justified by toxicology studies.
Analyses of batches manufactured according to the commercial synthesis have been presented. All the results were found within the specification in particular for the impurities and the residual solvents.

The active substance is stored in metal, plastic or fibreboard containers lined with low-density polyethylene (LDPE) bags, food-grade quality and sealed with metal or plastic ties. The packaging provides adequate protection against moisture and light during storage and transport.

- Stability

In line with ICH requirements, primary production scale batches of lapatinib ditosylate monohydrate have been manufactured and placed on stability. These primary batches were manufactured with a slightly different final purification process than the commercial one. Batches were kept in polyethylene bags, under ICH conditions (36 months at 30°C/65% RH and 6 months at 40°C/75% RH). Parameters tested were: appearance, content of lapatinib ditosylate, water content, impurities, X-

ray powder diffraction. Results showed that no significant changes could be observed and all the results remained within the specification.

Production scale batches of lapatinib ditosylate monohydrate, kept in the same packaging as for primary studies, and manufactured by the commercial process have been placed on confirmatory stability studies. Studies were carried out under ICH conditions (results available after 12 months at 25°C/60% RH and 30°C/65% RH, and 6 months at 40°C/75% RH). The parameters tested were the following: appearance, content of lapatinib ditosylate, water content, and related substances and X-ray powder diffraction. No significant change could be observed after storage and all the results remained within the specification.
Photostability studies according to ICH option 2 have been carried out on 1 batch. Lapatinib was found to be sensitive to light. In addition, forced degradation studies carried out on solid state and in solution have shown that lapatinib was sensitive to oxidation, and hydrolysis.
The analytical methods used during the stability studies are the same as those used for testing lapatinib ditosylate.
Stability data justify the proposed re-test period when the active substance is stored at not more than 25°C and protected from light.

Medicinal Product

Lapatinib 250 mg film-coated tablets contain 405 mg lapatinib ditosylate monohydrate, corresponding to 250 mg of lapatinib free base. The product is packaged in PA/Alu/PVC/Alu blisters.

- Pharmaceutical Development

The objective was to develop an immediate release tablet with high dissolution characteristics due to poor water solubility.
The pharmaceutical development has been adequately detailed. The choice of the salt (ditosylate) has been justified based on crystalline properties and good bioavailability. Since dissolution is considered a critical quality attribute because of its impact on bioavailability, the particle size was thoroughly discussed. It was convincingly demonstrated that it did not significantly impact dissolution.
Based on the active substance properties, the process retained was a fluid bed granulation. The manufacturing process development has been described in great detail and the main focus has been on the critical steps granulation and compression.
The formulations used in clinical trials included the same excipients as used in the final medicinal product.

The excipients selected are conventional for this dosage form. All the excipients are compendial except the film-coating colourants (which are in accordance with EC Directive 95/45/EC relating to colourants used in foodstuffs). The excipients of the core tablet are: microcrystalline cellulose as diluent, povidone as binder, sodium starch glycolate as disintegrant, and magnesium stearate as lubricant. Non-compendial analytical methods have been detailed and validated.
Certificates of analysis for each excipient have been provided.

- Adventitious Agents

None of the ingredients used in the manufacture or in the composition is of human or animal origin.

- Manufacture of the Product

The manufacturing process has been fully described. The process is a conventional fluid bed granulation process followed by compression of the tablet cores. Finally, the tablet cores are film-coated and packaged into blisters.
There are no intermediate products in the manufacture of Lapatinib film-coated tablets, 250 mg but there are critical steps. Granulation and compression have been identified as critical parameters and adequate in-process controls have been applied. No overage has been used.

The manufacturing process is considered standard and has been satisfactorily validated on production scale batches and a process validation scheme has been included. It should ensure the consistency and the reproducibility of the manufacture.

- Product Specification

Adequate release and shelf-life specifications are presented for the medicinal product and include parameters such as: appearance, identification of lapatinib (HPLC, UV), identification of colorants (colour reactions), assay of lapatinib (HPLC), related substances (HPLC and LC/MS/MS), uniformity of dosage units (PhEur), dissolution (PhEur) and microbiological quality (PhEur). Tablet hardness has not been included in the specification and this has been justified. Impurities have been appropriately controlled and their limits justified by toxicological studies.
Analytical methods have been sufficiently described and non-compendial methods validated in accordance with ICH guidelines.
Batch analysis data have been provided for-production-scale batches kept in the commercial packaging and results comply with the proposed specification demonstrating the consistency of the process.
The medicinal product is kept in blisters made of polyamide/aluminium/polyvinylchloride (PVC) laminate sealed with an aluminium foil lidding with a vinyl acrylic seal coating. Suitability of packaging material was demonstrated during pharmaceutical development and stability studies. The packaging materials (in compliance with Directive 2002/72/EC and section 3.1.11 of PhEur) have been suitably characterised and certificates of analysis provided.

- Stability of the Product

Primary stability studies have been carried out on laboratory and pilot batches kept in the commercial packaging under ICH conditions (24 months at 30°C/65% RH and 6 months at 40°C/75% RH).
Confirmatory stability studies have been started with 3 production batches (using lapatinib obtained by the commercial synthesis) and results are available after 12 months at 30°C/65% RH and 6 months 40°C/75% RH.
All results reported were within the proposed specification and no significant change could be observed.
Photostability studies indicated that the product was not light-sensitive.
Based on the stability data, the proposed shelf-life can be granted when the medicinal product is kept under the precautions as defined in the SPC.
Both primary and confirmatory stability studies will continue up to 60 months. Three production batches of Lapatinib film-coated tablets, 250 mg will be placed on long-term and accelerated stability studies.

Discussion on chemical and pharmaceutical aspects

Generally, satisfactory documentation has been provided. The active substance lapatinib is well characterised and the retained specification including the impurities levels have been justified by toxicological studies. Lapatinib is stable and stability data support the proposed re-test period of 18 months providing that it is kept in the commercial packaging protected from light and not above 25°C.

Regarding the finished product, the manufacturing process is a standard fluid bed granulation process. It is adequately described and controlled. It should ensure a consistent quality for the product. Appropriate specification has been selected for these film-coated tablets. Stability studies under ICH conditions have demonstrated the good stability of the finished product. Stability data support the proposed shelf life and storage conditions as defined in the SPC.

2.3 Non-clinical aspects

Introduction

General toxicity studies and range finding studies were declared by the applicant to have been conducted in accordance with accepted scientific practice and in general agreement with the principles of Good Laboratory Practice (GLP). All pivotal safety studies were stated to be carried out in full compliance with GLP regulations.

Pharmacology

The primary pharmacodynamic actions of lapatinib have been assessed *in vitro* and *in vivo* respect to treatment of various cancers.

- Primary pharmacodynamics

In vitro studies

Intracellular domains of human ErbB1 and ErbB2 were produced using the baculovirus expression system. Lapatinib was shown to inhibit phosphorylation of an exogenous peptide substrate with IC_{50} values of 9.2 nM (ErbB1) and 10.8 nM (ErbB2). Lapatinib acts as a reversible inhibitor with a slow dissociation rate (half-life ≥300 minutes). As a result of the slow dissociation rate, inhibition of receptor phosphorylation recovered only slowly after a 4 hour treatment of ErbB1 expressing tumour cells (15% of control levels at 96 hours post-washout). The crystal structure of the lapatinib/ErbB1 complex was elucidated. Lapatinib binds to the ATP binding cleft in a manner similar to that of other quinazoline TK inhibitors (such as erlotinib and gefitinib). Unlike the other agents, lapatinib has a bulky aniline substituent that reaches deep into an opened back pocket and the COOH terminal is shifted to a position that partially blocks the opening of the inhibitor binding site. Thus dissociation of lapatinib may require a conformational change in ErbB1 resulting in the slow dissociation rate for ErbB1 and ErbB2.

The specificity of lapatinib was studied by examining the effects on 18 other protein kinases. ErbB4 was inhibited with an IC_{50} of 0.36 μM (36-fold higher than for ErbB2) and c-Src, a non-receptor tyrosine kinase was inhibited with an IC_{50} of 3.5 μM (300-fold higher). IC_{50} values for all other tested enzymes were >1000-fold than for ErbB1/ErbB2.

A number of studies were performed to analyse the consequences of tyrosine kinase inhibition in cell lines, derived from both transformed and normal cells.

- Lapatinib inhibited the phosphorylation of ErbB1 and ErbB2 as well as the downstream mediators Akt, Erk1 and Erk2 in tumour cell lines overexpressing ErbB1 or ErbB2. IC_{50} values were between 0.1 μM and 3 μM.
- In S1 tumour cells, expressing high levels of phosphorylated ErbB2, inhibition of ErbB2 tyrosine phosphorylation by lapatinib was accompanied by an increase in the percentage of apoptotic cells. In the non-tumour cell line Hb4a, lapatinib reduced baseline phosphorylation of ErbB1 and ErbB2 and blocked the stimulatory effect of EGF on ErbB1 tyrosine phosphorylation. In the same cell line, EGF stimulated cell growth by 20% while treatment with lapatinib inhibited cell growth by 50%. Growth inhibition by lapatinib was not reversed by EGF.
- Increased expression of survivin, an inhibitor of apoptosis, is associated with poor prognosis in breast cancer patients. Lapatinib treatment of ErbB2-overexpressing breast cancer cell lines resulted in reduced levels of survivin and an increased frequency of apoptotic cells.
- Combining lapatinib with anti-ErbB2 antibodies (polyclonal antisera or the monoclonal antibody trastuzumab) resulted in an additive or synergistic effect on tumour cell apoptosis.
- Lapatinib retained significant activity in trastuzumab conditioned tumour cell lines, suggesting non-cross-resistance between lapatinib and trastuzumab.

- Chronic exposure of tumour cells to lapatinib resulted in resistance. Inhibition of estrogen receptor expression was associated with less resistance development.
- Lapatanib inhibited the phosphorylation of the NH_2-terminally truncated ErbB2 receptor ($p95^{ErbB2}$), the expression of which correlates with metastatic disease progression in breast cancer.
- The effects of lapatinib on cell growth were examined in four human transformed cell lines overexpressing ErbB1 and/or ErB2, one human transformed cell line overexpressing mutant Ras and in normal human foreskin fibroblasts. Marked inhibition of growth was noted in the four cell lines overexpressing ErbB1 and/or ErbB2 (BT474, HN5, N87 and Hb4a c5.2), while only minimal growth inhibition was observed in the Ras overexpressing cell line (Hb4a r4.2) and human foreskin fibroblasts. It was also shown that lapatinib dihydrochloride and lapatinib ditosylate monohydrate exhibited a similar growth inhibitory activity on a molar basis.
- A panel of 49 human normal or transformed cell lines was tested for sensitivity to lapatinib. The cell lines responded with IC50 values ranging from 0.025 to 11.5 μM. The most sensitive cell lines were derived form breast, gastric, lung and head/neck tumour tissue.
- Four human tumour cell lines with low levels of ErbB2 expression and a relatively weak response to lapatanib as a single agent were tested for their response to lapatinib in combination with 5-fluorouracil. The cell lines showed a response to the combination that was approximately additive.
- The two metabolites GW690006A and GSK342393A were compared to lapatinib for tumour cell growth inhibition. The potency of GW690006A was similar to lapatinib in one the ErbB1 dependent cell line (HN5) but was less potent on the ErbB2 dependent cell line BT474. GSK342393A had much lower potency in all cell lines tested.

In vivo studies

The in vivo pharmacodynamics of lapatinib was studied in mouse xenograft models. A summary of the findings in single agent studies is presented in Table 1:

Table 1 - Summary of the pharmacodynamic findings

Cell Line	Dose Regimen[1]	Measured Parameters	Summary of Results
BT474	0, 30, 100 mg/kg BID for 21 days	Tumour growth and receptor phosphorylation	Complete suppression of growth at 100 mg/kg. Tumour regression in 7/40 animals.
BT474	0, 30, 60, 100, 200 mg/kg SD 0, 30, 60, 100 mg/kg BID for 3 days 200 mg/kg for 3 days	Receptor phosphorylation	Complete inhibition of phosphorylation at ≥100 mg/kg/day
HN5	0, 30, 100 mg/kg BID for 21 days	Tumour growth and receptor phosphorylation	Complete suppression of growth at 100 mg/kg. Tumour regression in 18/40 animals. Up to 93% reduction in phosphorylation at 150 mg/kg for 3 days.
NCI-H322	0, 15, 30, 45, 60, 75, 100 mg/kg BID for 21 days	Tumour growth	≥90% inhibition of growth at >60 mg/kg. Regression in >80% of animals treated with ≥45 mg/kg. Continued sensitivity following 2nd cycle of therapy - complete inhibition of growth.

Key:
1 = Lapatinib was administered orally in all studies.
BT474 = Human breast ductal carcinoma overexpressing ErbB2.
HN5 = Head and neck carcinoma overexpressing ErbB1.
NCI-H322 = Human non-small cell lung carcinoma expressing moderate levels of ErbB1 and ErbB2.

Regression = >25% reduction in tumour mass.
BID = Twice daily dosing. SD = Single dose.

The compatibility with conventional anti-cancer therapy was investigated. Studies were conducted to examine potential favourable responses and over toxicity of lapatinib at high doses and with reduced doses in combination.

- Secondary pharmacodynamics

Lapatinib was examined in a standard battery of 38 various physiological receptors and ion channels. At 30 μM, lapatinib did not significantly (≥50%) alter the binding of any of the radioligands to their respective binding sites, with the exception of the sigma receptor, noradrenergic and dopamine transporters, and L-type calcium and sodium channel sites. At the catecholamine transporters and the calcium channel, the concentration-response curves of lapatinib displayed a weak binding profile with submaximal inhibition of radioligand binding (<70%) and IC_{50}values of 9-26 μM. At the sigma receptor and the sodium channel, the compound displayed typical concentration-response curves, with IC_{50} values of 1 and 3 μM, respectively. Functional activity of the compound at sigma receptors and sodium channels was evaluated using isolated field-stimulated guinea pig left atrial and vas deferens preparations, respectively. No functional activity was observed at a lapatinib concentration up to 100 μM.

- Safety pharmacology programme

Central Nervous System
No behavioural or overt effects were observed in rats (3 females) and dogs (2 males) following single oral doses of 50, 150 or 500mg/kg Lapatinib leading in rats to Cmax values of 6, 10 and 27 fold the Cmax at clinical dose of 1250mg/day, and in dogs to 1.6, 1.8 and 3.1 the Cmax at the same clinical dose.

Respiratory System
In guinea pigs (4 males) single oral doses of Lapatinib of 50, 150 or 500mg/Kg were well tolerated without effect on lung compliance, airway resistance, respiration rates or clinical observations. The mean Cmax values were only 0.14, 0.14 and 0.27 fold the Cmax to be obtained with the proposed clinical dose. With such a low exposure the value of the study is questionable.

Cardiovascular System

In vitro studies
Lapatinib inhibited hERG channels in stably transfected human embryonic kidney cells with IC25 and IC50 values of 0.181 and 1.11 μM, respectively. 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 C_{max} of 2430 ng/mL. In addition, no direct chronotropic effects were noted in isolated guinea pig field stimulated atria.

In vivo studies (Rat and Dog)
In conscious, telemetered rats and dogs, no treatment-related effects were noted on clinical observations, body temperature, body weights, heart rate, systemic blood pressure or tracheal inflation pressure following single oral doses of lapatinib at up to 500 mg/kg or 50 mg/kg, respectively. In addition, there were no treatment-related effects on electrocardiograms (ECG) at doses up to 500 mg/kg in rats or dogs (approximately 2-fold the human C_{max}). Very slight increases in mean systolic, mean diastolic and mean arterial pressure were noted in dogs at doses ≥150 mg/kg 6 to 14 hours after dosing while values for control and 50 mg/kg groups declined. All values remained within the historical control range for these parameters. Although these changes are considered very slight, their relationship to treatment cannot be ruled out. Maximum plasma concentrations at the 500 mg/kg and 50 mg/kg doses represent 2-fold and approximately 0.5-fold the expected human C_{max} of 2430 ng/mL. No significant blood pressure changes have occurred in patients receiving lapatinib.

- Pharmacodynamic drug interactions

No non-clinical studies on pharmacodynamic drug interactions have been performed that are relevant to the claimed indication.

Pharmacokinetics

The pharmacokinetics, absorption, distribution, metabolism and elimination of lapatinib were investigated through a series of oral, intravenous and in vitro studies in the mouse, rat, rabbit, dog and human using unlabelled and ^{14}C-labelled drug. The concentration of lapatinib in plasma and serum samples was determined using high performance liquid chromatography with tandem mass spectrometry (HPLC/MS/MS). Determination of the radiolabeled material in biological samples was carried out by liquid scintillation counting or autoradiography. The profiling and identification of metabolites of lapatinib were performed by HPLC with radiochemical and UV detection, liquid chromatography mass spectrometry (LC-MS) with in-line radiochemical detection, liquid chromatography with tandem mass spectrometry (LC-MSMS) and nuclear magnetic resonance (NMR) analysis.

- Absorption-Bioavailability

Pharmacokinetic parameters of lapatinib after a single dose are summarised in Table 2:

Table 2 - Summary of the pharmacokinetic parameters

PK parameters	Mouse		Rat		Dog		Human
Route	i.v.	oral	i.v.	oral	i.v.	oral	oral
Dose (mg/kg)	10	10	10	10	10	10	250 mg
AUC (ng·h/mL)	3469	1735	8275	2375	13111	8291	3668
Cmax (ng/ml)	942	504		535		1016	317
Cl (L/h/kg)	48.0		22.9		14.6		
Vss (L/kg)	9.55		1.82		5.16		
t1/2, (h)	5.69	1.99	3.11	1.45	4.63	2.92	8.78
F (%)		50.0		28.7		63.2	
Reference	RD2000/00063/00		RD2000/00327/00		RD2000/00321/00		EGF10001

- Distribution

Plasma protein binding of ^{14}C-lapatinib was very high (>99%) in all species tested and independent of the concentration used. Erythrocyte binding of ^{14}C-lapatinib was species dependent, being low in the mouse, rat and human (blood to plasma ratio <1) whereas in the rabbit and the dog blood to plasma ratio was close to 1.

In vitro studies using Madin-Darby canine kidney (MDCK) type II cells heterologously expressing different efflux transporters demonstrated that lapatinib was a substrate for the human P-glycoprotein (Pgp, ABCB1) and murine breast cancer resistance protein (Bcrp, ABCG2) transporters. Lapatinib, at concentrations comparable to the human Cmax (up to 2.4 µg/mL [4.1 µM]), inhibited human Pgp, murine Bcrp and human organic anion transporting polypeptide (OATP1B1) in vitro. At a single test concentration of 30 µM, lapatinib inhibited human organic anion transporter (OAT) hOAT3 by 59.8% whereas there was less than 50% inhibition of the uptake via hOAT1, hOAT2, hOAT4, hOCT1, hOCT2, hOCT2-A, hOCT3 and hURAT1. Studies using Wistar Han rats dosed with a Pgp inhibitor (GF120918) or in Pgp-deficient mice indicated that CNS penetration but not gut absorption of lapatinib was attenuated by Pgp.

Tissue distribution was studied using whole body autoradiography in albino and pigmented male rats that had received a single oral dose of ^{14}C-lapatinib at 10 mg/kg. The absorbed radioactivity was well

distributed into the tissues in most instances at concentrations above that in blood, with peak concentrations generally at 4 hours post-dose and largely cleared from most tissues by 24 hours after dosing. In pigment-containing tissues, particularly the uveal tract, radioactivity was retained at 168 hours suggesting that drug-related material was bound to melanin.

- Metabolism

The in vitro metabolism of ^{14}C-lapatinib was compared in mouse, rat, monkey and human hepatocytes. The main biotransformations common to all of the species in 4 hour incubations were: oxidation, N- and O-dealkylation and sulfate conjugation. Mouse, rat, monkey and human hepatocytes gave qualitatively similar metabolite profiles, differing primarily in the extent of metabolism.

Metabolism of lapatinib was assessed both quantitatively and qualitatively in the plasma and excreta of rats (10 mg/kg), dogs (10 mg/kg), mice (30 mg/kg) and humans (250 mg) following a single oral administration of ^{14}C-lapatinib. In general, ^{14}C-lapatinib was primarily metabolized, secreted in the bile and eliminated in the faeces. In the nonclinical and clinical metabolism studies, urine samples were not analyzed due to the low percentage of the dose excreted by this route. In plasma, ^{14}C-lapatinib represented the largest single component in all species. Lapatinib was more extensively metabolised in male rats than in female rats, however the metabolic profiles were similar. In dogs and humans, ^{14}C-lapatinib was the only quantifiable peak present. In humans, lapatinib accounted for only approximately half of the radioactivity in the plasma. The remaining radioactivity was attributed to at least 8 metabolites detected by LC-MS but below the limit of radiochemical quantification (~5% of the total radioactivity in pooled plasma). These metabolites were attributed to the N-oxidation cascade that was also observed in vitro as well as in rats and mice. In both mice and rats, only a few of these metabolites were quantifiable in plasma by radiochemical detection, but all were characterized by mass spectrometry. Thus, no unique circulating metabolites were observed in humans

The oxidation of ^{14}C-lapatinib by the CYP and flavin containing monooxygenase (FMO) enzymes in human liver microsomes, or by individual recombinant CYPs showed that CYP3A4/5 was the primary route of metabolism. To a lesser extent CYP1A2, 2D6, 2C8, 2C9 and 2C19 oxidized lapatinib, while FMO, CYP2A6, CYP2B6 or CYP2E1 did not appear to be involved. CYP3A4 activity was inhibited by lapatinib by competitive as well as non-competitive mechanisms (mixed type inhibition) in human liver microsomes with an apparent Ki of 4 μM (2.3 μg/mL). CYP2C8 activity was also inhibited by lapatinib in human liver microsomes with an apparent Ki of 0.6μM (0.3 μg/mL). Lapatinib inhibited the metabolism of paclitaxel by CYP3A4 (Ki = 1.1 μM). Lapatinib had only a modest effect (<2-fold) on the microsomal half-life of docetaxel and vinorelbine.

The potential of lapatinib to induce CYP enzymes via activation of the human Pregnane X Receptor (PXR) in a reporter gene assay was found to be low. In primary cultures of human hepatocytes, lapatinib did not increase the catalytic activity of CYP1A2, 2C9 or 3A4.

- Excretion

After administration of a single oral dose of ^{14}C-lapatinib, the predominant route of elimination of drug-related material in the mouse, rat and dog was in the faeces, with very little urinary excretion. Most of the dose was eliminated within 48 hours post-dose.

- Pharmacokinetic drug interactions

There are no non-clinical studies on drug interactions. A potential for kinetic interactions is suggested from the facts that lapatinib is metabolized mainly by CYP3A4 and 3A5, is a substrate for the human Pgp and murine Bcrp efflux transporters and that lapatinib at relevant human concentrations inhibits 3A4 and other CYPs and inhibits the transporters human Pgp, murine Bcrp and OATP 1B1.

- Other pharmacokinetic studies

None

Toxicology

- Single dose toxicity

Single dose toxicity studies are summarised in Table 3:

Table 3 - Single dose toxicity studies

Species/ Sex/Number/Group	Dose/Route	Observed max non-lethal dose	Major findings
Mouse 6M/6F	0, 2000 mg/kg oral	2000 mg/kg	Slight body weight reduction, mucosal hyperplasia and/or atrophy in stomach
Mouse 6M/6F	0, 46 mg/kg i.v.	46 mg/kg	None
Rat 6M/6F	0, 2000 mg/kg oral	2000 mg/kg	Slight body weight reductions, mucosal atrophy in glandular stomach
Rat 6M/6F	0, 21.2 mg/kg i.v.	21.2 mg/kg	None

- Repeat dose toxicity (with toxicokinetics)

Repeat-dose toxicity studies with lapatinib are summarised in the Table 4:

Table 4 - Major findings in the repeat-dose toxicity programme for lapatinib

Study	Number/ Sex/Group	Dose (mg/kg)	Major findings
Mouse **14 days** Non-GLP	10	100 300 1000	**1000 mg/kg:** All animals killed on day 8 due to body weight decrease, decreased food consumption and general declining health **≥100 mg/kg**: Dose-dependent effects on erythroid parameters
Mouse **13 weeks** GLP	28	50 100 200	**200 mg/kg:** ↑bilirubin, liver centrilobular hypertrophy (M), mucosal hyperplasia of colon **≥100 mg/kg:** mucosal hyperplasia of caecum (M), increased incidence and severity of chronic inflammation of the preputial gland (M)
Rat **7 days** Non-GLP	3M	60 120 240	**≥60 mg/kg:** prostatic atrophy (1M/dose), increased adrenal weight
Rat **14 days** GLP	10 + 5 recovery in control and high dose (11 days)	60 240 1000	**1000 mg/kg:** Female rats exhibited severe clinical signs and killed on day 10. **≥240 mg/kg:** Alterations in multiple haematologic and clinical chemistry parameters, decreased prostate and increased adrenal weights, thymic weight and size reduction, macroscopic observation of yellow tissues and stomach contents, and target organ morphologic changes in gastrointestinal organs, accessory digestive organs, lymphoreticular organs, skeletal muscle, lung, adrenal gland, prostate and mammary gland. **Recovery:** Rapid resolution of most gastrointestinal effects. Minor effects in the mammary gland, lung and prostate persisted during recovery; while all other treatment-related effects showed a trend toward resolution, total recovery was incomplete.

Rat **13 weeks** GLP	12 + 8 recovery in control and high dose (22 days)	20 60 180	**180 mg/kg:** ↓Body weight, and food consumption (F). Treatment-related clinical signs (distended abdomen, loose feces, bruising of the mouth and lips, hair loss, scabs, a piloerect coat, red staining and yellow skin colour), primarily in F. Leukocytosis, ↑reticulocytes. ↑bile acids. ↑adrenal glands, lungs, spleen and liver weights (F). ↓uterus weight. Skin lesions (M+F), glandular dilation in the stomach, glandular hyperplasia in the caecum, acinar atrophy in the salivary glands, infiltration of pigmented macrophages and lymphoid depletion in the lymphoid tissues, cortical hypertrophy of the adrenal cortex, alveolar histiocytosis in the lung, pigment accumulation and degeneration in the mammary gland, and zymogen granule depletion in the pancreas. Cardiomyopathy. Trabecular atrophy of femur (F) **≥60mg/kg:** ↑prothrombin time, ↑ALT, AST. Lymphoid hyperplasia (F), Skin lesions (F), Hepatocellulary hypertrophy (F) **Recovery:** Persistence of skin lesions **NOAEL:** 60 mg/kg (M), 20 mg/kg (F)
Rat **26 weeks** GLP	12 + 8 recovery in control and high dose	M F 20 10 60 60 180 120	No significant additional toxicological effects as compared to previous studies of shorter duration (14 days and 13 weeks). **NOAEL:** 60 mg/kg (M), 10 mg/kg (F)
Dog **7 days** Non-GLP	3 M	30 60 120	Mild effects, limited to loose faeces were noted throughout the study.
Dog **14 days** GLP	3 + 2 recovery in control and high dose	10 60 360	**360 mg/kg:** Salivation, dehydration, emesis. ↓spleen and thymus weights ↑WBC, ↑alkaline phosphatase, bilirubin and bile acids. Gastric lesions with degeneration and necrosis of mucous glands and villous atrophy in the small intestine. Inflammatory changes in tongue and gingival tissues, atrophic changes involving skeletal muscle, depletion of zymogen in the acinar pancreas and depletion of glycogen in the liver **≥60mg/kg:** Weight loss and decreased food consumption. Looses faeces, decreased activity. ↓Lymphocytes, eosinophils. Gastric lesions (M). Depletion of lymphocytes and accumulation of macrophages in lymphoid tissues. **Recovery:** At the end of the recovery period, there were no treatment-related macroscopic findings. Lymphoid depletion of the thymus and atrophy of skeletal muscle (1M) present at the end of recovery period, other microscopic changes absent.

Dog **13 weeks** GLP	4 + 2 recovery in control and high dose (22 days)	10 40 160	**160 mg/kg:** Body weight loss. Skin and mucous membrane lesions with hair and discoloration. ↑WBC (F), ↑bilrubin, bile acids, alkaline phosphatise, ALT, globulin, cholesterol. ↓Thymus weight. ↑Relative adrenal gland an liver weight (M) **≥40 mg/kg:** Epidermal changes in the paws. ↑Relative lung weight (M). Lymphoid depletion in multiple tissues (GI tract, lymph nodes, spleen and thymus); glycogen depletion and vacuolization in the liver; mucosal atrophy of the GI tract, tongue and oral cavity ulceration/inflammation; skeletal muscle atrophy and pancreas zymogen depletion. Liver (chronic inflammation and bile duct hyperplasia); adrenal gland (cytoplasmic alteration); mammary glands (reduced proliferation); bone marrow (hypocellularity); epididymis (epithelial vacuolization) and skin (dermal chronic inflammation with associated epidermal hyperplasia and erosion). There was also a generalized increase in pigment deposition in multiple tissues (adrenal gland, GI tract, liver, lung, lymph node, spleen, skin, thymus, kidney, lachrymal gland, tongue, mammary gland, ovary and uterus). **Recovery:** Persistence of: increased pigment deposition in many tissues (liver, thymus, paw skin, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, mammary gland, ovaries, uterus, mesenteric lymph nodes and mandibular lymph nodes) and increased severity of thymic lymphoid depletion (M+F). hepatocellular glycogen depletion, increased severity of liver chronic inflammation and dermal chronic active inflammation of the paw skin with associated epidermal hyperplasia, epidermal erosion and/or *Demodex* spp. infestations (F). **NOAEL:** 10 mg/kg
Dog **39 weeks**	4 + 2 recovery in control and high dose	10 40 100	With the exception of hepatocellular degeneration/necrosis and cholestasis in two pre-terminal males and one terminal female dosed at 100 mg/kg, there was no significant toxicity in addition to that observed in previous studies of shorter duration. **NOAEL: 10 mg/kg**

In conclusion, the repeat-dose toxicity studies have not revealed any important safety concerns others than what would be expected from the mode of action (epithelial effects mainly in skin and GI tract), effects which have been well characterised in the clinic.

- Toxicokinetics

Toxicokinetics studies performed with lapatinib are summarised in Table 5:

Table 5 - Summary of toxicokinetics data

Study ID	Period	Dose (mg/kg/day)	Animal AUC (ng.h/ml)		Cmax (ng/ml)		Exposure multiple (AUC)	
			♂	♀	♂	♀	♂	♀
Mouse **14 days**	Day 1	100 300 1000	123343 272380 540545	58752 251379 806704	15220 27077 23788	14057 23224 29924	3.4 7.5 15	1.6 6.9 22
Mouse **13 weeks**	Day 28	50 100 200	20621 57683 116278	15092 38215 85981	5324 7901 10675	4611 7127 8638	0.57 1.6 3.2	0.42 1.1 2.4
Rat **14 days**	Day 1	60 240 1000	39743 178315 297944	219857 2015001 1131015	4753 5604 7507	13996 46238 37015	1.1 4.9 8.2	6.1 56 31
Rat **13 weeks**	Day 22	20 60 180	5796 28417 117966	56682 318476 692018	1026 4234 7983	6646 23355 40306	0.16 0.78 3.3	1.6 8.8 19

Rat **26 weeks**	Day 85	10 20 60 120 180	7621 23765 92604	21124 195282 384908	2327 3401 10607	3320 20976 24949	0.21 0.66 2.6	0.58 5.4 11
Dog **7 days**	Day 7	30 60 120	16436 30876 85961		1470 2092 6225		0.45 0.85 2.4	
Dog **14 days**	Day 1	10 60 360	4206 60253 145880	8685 46256 352644	663 3239 6629	972 3716 9083	0.12 1.7 4.0	0.24 1.3 9.7
Dog **13 weeks**	Day 29	10 40 160	3748 20767 79204	8182 36302 107409	451 1640 4183	1008 2525 5560	0.10 0.57 2.2	0.23 1.0 3.0
Dog **39 weeks**	Week 26	10 40 100	5593 14117 70468	7900 42980 93499	683 1110 4305	1002 2922 5592	0.15 0.39 1.9	0.22 1.2 2.6

- Genotoxicity

Lapatinib showed no genotoxic potential in a standard test battery (gene mutations in bacteria and mammalian cells, chromosomal aberrations *in vitro* in CHO cells and human lymphocytes and *in vivo* in rat bone marrow).

- Carcinogenicity

No carcinogenicity studies have been submitted by the applicant.

- Reproduction Toxicity

Studies on reproductive and developmental toxicity of lapatinib are summarised in Table 6:

Table 6 - Summary of reproductive and developmental toxicity findings for lapatinib

Study type/ Study ID / GLP	Animals Route	Dose (mg/kg)	Dosing period	Major findings
Male fertility Rat GLP	25M Oral gavage	20 60 180	63 to 67 days (4 weeks prior to co-habitation, during co-habitation and to study termination)	No drug-related effects on mating, fertility or gonadal function at any dose
Female fertility Rat GLP	25F Oral gavage	20 60 120	15 days prior to co-habitation, during co-habitation and to Day 6 of gestation	No drug-related effects on gonadal function, mating or fertility. Maternal toxicity at ≥60 mg/kg. Developmental toxicity demonstrated by reduced fetal body weight at ≥60 mg/kg, increased embryo-lethality at 120 mg/kg
Pregnant rat – dose range finding Non-GLP	3F	5 30 60 180	Days 7 to 19 of gestation	180 mg/kg: Significant reductions in body weight and food consumption, increase in embryofetal mortality.
Pregnant rat – dose range finding Non-GLP	3F	90 120	Days 7 to 20 of gestation	120 mg/kg: Slight reductions in body weight gain and food consumption
Embryo-fœtal development Rat GLP	24F	30 60 120	Days 7 to 17 of gestation	Maternal effects: 120 mg/kg: Reduction in body weight gain (31%) and food consumption Embryo-foetal effects: 120 mg/kg: Higher incidence of left-sided umbilical artery and cervical rib,

				≥60 mg/kg: Precocious ossification NOAEL: Maternal: 60 mg/kg Developmental: 120 mg/kg (according to study report, see discussion below)
Non pregnant rabbit dose range finding Non-GLP	3	30 60 120 180	2 weeks	A single rabbit at 180 mg/kg loose faeces, reduced body weight and food consumption.
Non pregnant rabbit dose range finding Non-GLP	3F	400	7 days	Reduced body weight and reduced food consumption
Pregnant rabbit dose range finding Non-GLP	3F	90 120 200 300	Days 8 to 20 of gestation	≥200 mg/kg: significant reduction in food consumption and slight weight loss. No treatment-related effecs on foetal parameters measured (no foetal examinations were performed).
Embryo-fœtal development Rabbit RD2001/00010/00 GLP	20F	30 60 120	Days 7 to 20 of gestation	Maternal effects : 120 mg: One death, four abortions ≥60 mg/kg : Decrease in body weight and food consumption Foetal effects: ≥60 mg/kg : Decreased foetal body weight (5-10%) and increase in the number of foetuses with alterations, primarily minor skeletal variations (irregularities of ossification of the scull, angulated alae of the hyoid NOAEL: Maternal 30 mg/kg Developmental 30 mg/kg
Peri & postnatal Rat GLP	24F	20 60 120	Day 6 of gestation to day 20 of lactation	Maternal effects: 120 mg/&kg: Reduced body weight gain ≥60 mg/kg: Reduced food consumption F1 effects: ≥60 mg/kg: Decreased post-natal survival, decreased body weight and body weight gain No effects on F1 reproductive, F1 parental and F2 developmental endpoints at 20 and 60 mg/kg (no extended evaluation of 120 mg/kg due to the loss of litters
Cross foster study Rat Non-GLP	15F	120	Day 6 of gestation to day 20 of lactation. After parturition, pups from lapatinib-treated rats and control rats were cross-fostered.	A drug-related 79% reduction in postnatal survival was observed in pups exposed in utero only. Postnatal growth retardation was observed in pups exposed only via milk. Mammary gland morphology was normal in rats treated throughout pregnancy.

Toxicokinetics

A summary of the toxicokinetics is shown in Table 7

Table 7: Summary of toxicokinetics studies

Study	Dose (mg/kg/day)	AUC (ng.h/mL)	C_{max} (ng/mL)	Exposure multiple[a] (AUC)
Embryo-fœtal development Rat WD2001/00237/00	30	48941	5540	1.4
	60	149729	17423	4.1
	120	294641	21401	8.1
Embryo-fœtal development Rabbit RD2001/00010/00	30	1032	144	0.03
	60	2943	418	0.08
	120	8453	667	0.2

a : Human AUC = 36200 ng.h/ml; 14 day PK study (EGF10005), 1250 mg/day

Lapitinib showed no effects on mating, fertility or gonadal function in male and female rats. There was reduced fetal body weight and increased embryo-lethality in rats exposed to lapatinib during early embryonic development.

There were no evidence for teratogenicity from studies in rats and rabbits. Lapatinib was associated with growth retardation and developmental variations in rats at 4-fold clinical exposure and in rabbits at 8 to 23% of the clinical exposure.

In a peri & postnatal toxicity study in rats, reduced post-natal survival and body weight was observed in the offspring. A non-GLP cross-fostering study showed that the lethality was due to exposure of the dam, while growth retardation was seen in pups which were exposed via milk.

- Local tolerance

Dermal and ocular irritancy studies were performed in New Zealand white rabbits, and skin sensitization studies were performed in Hartley guinea pigs. All studies were performed using the ditosylate monohydrate salt of lapatinib. Lapatinib did not act as a local irritant, in the skin or in the eye and also did not appear to be a dermal sensitizer.

- Other toxicity studies

Antigenicity
A sensitisation study was performed in guinea pigs. Lapatinib was not a dermal sensitiser.

Immunotoxicity
A study was conducted to determine the effect of lapatinib on the immune function of Wistar Han rats administered oral doses for 4 weeks. The rats were immunised with KLH on day 14 and the antibody response to KLH was determined on day 19 and day 29. No significant effect of lapatinib on the IgM or IgG resonse to KLH was observed.

Other studies
In a whole body autoradiography study in rats, radioactivity was retained in the uveal tract of pigmented rats, suggesting binding to melanin. In the absorption spectrum for lapatinib, there are peaks in the UVA/UVB region with a λmax at approximately 200 nm and smaller peaks at 260, 320 and 360 nm. No studies have been conducted to specifically assess the photoxic potential of lapatinib. No ocular toxicity has occurred in studies up to 9 months duration in dogs and 6 months duration in albino rats.

Ecotoxicity/environmental risk assessment

The ERA is not yet complete. In order to comply with the CHMP guideline on Environmental Risk Assessment, data on the PBT assessment and PEC/PNEC ratios for the aquatic, terrestrial, and if applicable the sediment are needed.

Discussion on the non-clinical aspects

Pharmacology
Lapatinib is an inhibitor of tyrosine kinase on the growth factor receptors ErbB1 (epidermal growth factor receptor, EGFR) and ErbB2 (HER2). I*n vivo* lapatinib showed therapeutic potential in the treatment of tumours where ErbB1 and/or ErbB2 are of importance for tumour growth. Lapatinib showed similar activity on rat, dog and human ErbB1. Based on sequence considerations, it is predicted that lapatinib binds to rat and dog ErbB2 with similar potency as the human receptor. However, to provide further insight on the pharmacology in animal species compared to humans the applicant will perform measurements with recombinant rat and dog ErbB1 and ErbB2 as a follow-up study. Safety pharmacology studies in rats and dogs showed no important safety concerns.

Pharmacokinetics
Absorption and bioavailability of lapatinib were moderate. There were no important differences in pharmacokinetic parameters between the tested animal species and humans. A pronounced gender difference was observed in rats, with higher exposures in females. This is likely to be due to lower levels of CYP3A in female rats.

Binding to plasma proteins was high (>99%) with no observed species differences. Lapatinib was well distributed into tissues. Lapatinib was retained in pigment-containing tissues, particularly the uveal tract. Placental transfer of lapatinib has not been addressed. Although acceptable for the current indication, such data are of importance for the evaluation for developmental toxicity and if lapatinib is developed for more benign indications, such data should be presented.

Lapatinib was metabolised mainly by CYP3A4/5. No important differences in metabolism between the animal species and humans were observed. No unique human metabolite was observed. Lapatinib was a substrate for efflux transporters (Pgp and Brp) and an inhibitor of human Pgp and murine Bcrp in vitro. Lapatinib also inhibited CYP3A and CYP2C8 in vitro at relevant concentrations. Lapatinib showed no potential for CYP induction.

Toxicity
The major findings in repeat dose toxicity studies were attributed to exaggerated pharmacology, most importantly epithelial effects in the skin and the gastrointestinal tract. These toxic events occurred at exposures close to the human exposure at the recommended dose. Repeat-dose toxicity studies have not revealed any important safety concerns others than what would be expected from the mode of action (epithelial effects mainly in skin and GI tract), effects which have been well characterised in the clinic.

Carcinogenicity studies were not considered necessary for the current indication, refractory advanced or metastatic breast cancer, where the life expectancy of the patient is short. However, carcinogenicity studies are currently being conducted to determine the tumorigenic potential of lapatinib when administered by the oral route to CD-1 mice and Wistar Han rats and they will be provided as a follow-up measure.

A cross-fostering study showed that the lethality was due to exposure of the dam, while growth retardation was seen in pups which were exposed via milk. These data suggest that milk from lapatinib-treated mothers may have negative effects on the child. Section 5.3 of the SPC warns regarding use during pregnancy, and a strong recommendation is stated against use during breast feeding.

No studies have been conducted to specifically assess the phototoxic potential of lapatinib. According to the CPMP Note for Guidance on Photosafety Testing (CPMP/SWP/3989/01), photosafety testing is warranted for those chemicals that absorb light in the wavelength of 290-700 nm and are either topically/locally applied or reach skin or eyes following systemic exposure. Since lapatinib absorbs

light 320 and 360 nm and it has been show to be retained in pigment containing tissues, a study program on photosafety according to the mentioned guideline will be provided as a follow-up measure.

A revised ERA presenting the PBT assessment and PEC/PNEC ratios for the aquatic, terrestrial, and if applicable the sediment compartment will be provided as a follow-up measure.

2.4 Clinical aspects

Introduction

Lapatinib, in combination with capecitabine, is indicated for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress ErbB2 (HER2) and who have received prior therapy including trastuzumab. The recommended doses of the combination are: lapatinib, 1250 mg once daily continuously plus capecitabine, 2000 mg/m^2/day taken in 2 doses 12 hours apart on days 1-14 in a 21 day cycle. The proposed commercial formulation of lapatinib ditosylate monohydrate is the same as the 250 mg tablet used in the pivotal clinical study.

The clinical development of lapatinib includes a Phase I clinical trial in cancer patients in which the 'optimally tolerated regimen' (OTR) of lapatinib plus capecitabine was identified, two phase II monotherapy studies in breast cancer, and one pivotal Phase III study in patients with ErbB2 receptor over-expressing advanced or metastatic breast cancer, using the OTR of the drug combination. In addition, the safety profile of lapatinib as monotherapy or in combination with other treatments has been evaluated in several completed or ongoing Phase I and II studies in patients with various types of cancer and in healthy volunteers.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

Clinical Pharmacology

Pharmacokinetics

The clinical pharmacology studies with lapatinib include eight studies in healthy volunteers, five studies in subjects with solid tumours and one study in subjects with hepatic impairment. The highest doses administered to healthy volunteers are single doses of 250 mg or repeated doses of 175 mg for 8 days. Patients have received multiple doses of up to 1800 mg daily. There are no apparent differences in pharmacokinetics between healthy subjects and patients with cancer.

Four different HPLC-MS/MS assays were developed and validated for the determination of lapatinib in plasma. Pharmacokinetic parameters were calculated using non-compartmental methods.

- Absorption

Absorption has been evaluated in 3 bioavailability studies in healthy volunteers and two studies in patients, including food effect. Lapatinib absorption is characterized by low solubility, low permeability and affinity for intestinal efflux transporters. Oral absorption of lapatinib is incomplete and variable likely due to poor aqueous solubility with peak concentrations occurring on average 4 hours after dosing. After dosing, a lag time in absorption is observed averaging 15 minutes.

Lapatinib absorption is affected if administered with food. A study performed in cancer patients (highest dose tested at 1500 mg) evaluated the effect of a low-fat as well as a high-fat meal. In this study, the AUC_∞ was 2.67-fold higher when lapatinib was dosed with a low-fat meal, and 4.25-fold higher with a high-fat meal. C_{max} was 2.42-fold and 3.03-fold higher, respectively. T_{max} was 1.09 hours later and 2.53 hours later, respectively. Lapatinib bioavailability also reflects extensive metabolism in the gut and liver by CYP3A5 and 3A4.

The absolute bioavailability of lapatinib has not been determined because of difficulty in formulating the product for IV administration. The results of food effect studies suggest that mean absolute bioavailability in the fasting state must be lower than 25%. However, the variability was large. In the dose ranging studies, when lapatinib was administered in the fasted state, coefficient of variation (CV) ranged between 45% and 99% for AUC (inter-individual variability). The estimated *intra*-individual variability was 30-36% for AUC based on e.g. a bioequivalence study where repeated administration was performed.

The solubility of lapatinib *in vitro* declines dramatically at pH values above 4. The possibility of interaction with proton-pump inhibitors (PPI) or histamine-2- receptor antagonists (H2RA) was explored by reviewing concomitant medications reported in 8 patients undergoing pharmacokinetic assessment. Results were not sufficient to exclude the possibility of an interaction.

In a mass-balance study, single 250mg doses of 14C-labelled lapatinib administered to 6 healthy volunteers produced serum concentrations of radio-labelled material representing parent drug and metabolites that peaked 4 hr after the dose and declined with a median half-life of 6 hr. Plasma concentrations of lapatinib declined with a half-life of 14 hours. In plasma, lapatinib accounted for approximately 50% of radio-labelled material, the remainder being comprised of metabolites, none of which achieved a plasma concentration of more than 10% of parent drug.

The ditosylate monohydrate salt has better solubility than the free lapatinib base. In an early study in healthy volunteers, the free base was shown to have 33% lower bioavailability than the ditosylate salt in the fasted state. In the fed state, however, there was no significant difference in bioavailability between the salt and the free base. Apart from this early study, the lapatinib ditosylate salt was administered in all clinical studies. The commercial tablet is the same formulation as that used in pivotal clinical trials and therefore does not require bioequivalence studies.

- Distribution

The distribution of lapatinib is influenced by interactions with several proteins. It is highly bound (>99%) to human serum proteins *in vitro* (albumin and α_1-acid glycoprotein). Lapatinib is also a substrate and inhibitor of the efflux transporters P-glycoprotein (Pgp, ABCB1) and breast cancer resistance protein (BCRP, ABCG2).

- Elimination

Plasma concentrations of lapatinib decline with measured half-lives of up to 14 hours. However, accumulation with daily dosing achieves steady-state in 6-7 days, suggesting an effective half-life of 24 hours. In the mass-balance study, plasma and faeces samples were collected prior to dosing and for 168 hours following dosing. Overall recovery of total radioactivity accounted for 61.6% to 99.7% of the dose in this study. Recovery of total radioactivity in urine accounted for less than 2% of the dose for all subjects. Unchanged lapatinib was not quantified in urine. Recovery in faeces accounted for a median of 92% (60-98%). Unchanged lapatinib in faeces accounted for a median of 27% (3-67%) of the dose.

Lapatinib undergoes extensive metabolism in humans to numerous oxidated and N- and O-dealkylated products. *In vitro* studies using human hepatocytes and microsomes indicated that lapatinib is primarily metabolised by CYP3A4 and CYP3A5, with smaller contributions from CYP2C8. Additional studies indicated that CYP1A2, 2D6, 2C9 and 2C19 may also be involved, but to a lesser extent. The most prominent metabolites are the carboxylic acid GW42393 and the O-dealkylated phenol GW690006. N-oxidation of the secondary aliphatic amine produced a cascade of about 8 minor metabolites. Relative to parent drug, GW690006 produced approximately equipotent inhibition of ErbB1-dependent tumour cell growth *in vitro*, but was approximately 100-fold less potent in ErbB2-dependent tumour cells. GW342393 was found to be approximately 40-fold less potent than parent drug in both ErbB1- and ErbB2-dependent tumour cells. They are unlikely to contribute to the biological activity of lapatinib.

- Dose proportionality and time dependencies

Dose-escalation was studied in healthy volunteers administered with single doses of lapatinib up to 250 mg. The half-life appeared to increase with dose from 6 hours at 10 mg to 9 hours at 250 mg. The C_{max} and AUC increased in a slightly more than dose-proportional manner, with the dose-normalised AUC of the 250 mg dose being 1.6 times that of the 10 mg dose. In a study in patients with higher, multiple Day 14 steady-state AUCτ and C_{max} increased in a less than proportional manner at once daily as well as bid dosing.

In a multiple-dose study in healthy volunteers, doses of up to 175 mg were administered once daily for 8 days. Steady state was reached in 6-7 days. The increase in AUC was suggested to exceed the degree of accumulation expected from the observed half-life. Higher doses were administered in a dose-escalating study in patients with solid tumours. They received either 175-1800 mg once daily or 500-900 mg twice daily. After once daily dosing, lapatinib appeared in plasma after lag times of up to 1.1 hours and thereafter increased to achieve peak concentrations at medians of 3-8 hours (range 0.8-16 hours). Accumulation was observed at each dose with geometric mean accumulation ratios ranging from 1.32- to 2.42-fold. BID dosing led to approximately 4-fold accumulation and a systemic exposure that was approximately 2-fold higher than that observed at an equivalent total daily dose when given once daily

Also, in a PK/PD study where cancer patients received multiple daily doses of 500 to 1600 mg, AUCτ increased with increasing dose in a less than proportional manner. Accumulation based on AUCτ was observed at all doses, with geometric mean accumulation ratios ranging from 1.13- to 3.13-fold, indicating an alteration in pharmacokinetics (increased bioavailability or decreased clearance) over time at all doses.

In healthy subjects, overall variability from bioequivalence studies ranged from 39 to 79%, for Cmax, from 31 to 90% for AUC and from 15 to 96% for T_{half}.

- Special populations

A specific study was performed to evaluate the effect of moderate and severe hepatic impairment on lapatinib pharmacokinetics after a single dose of 100 mg. The study included eight subjects with moderate impairment (Child-Pugh 7-9), 4 subjects with severe impairment (Child-Pugh >9) and 8 healthy subjects. Based on comparison of log-transformed data, the exposure (AUC) increased by 56% and 85% in the moderate and severe impairment groups, respectively. C_{max} increased in the moderate impairment group, but there was no effect on $t_{1/2}$. In the severe impairment group there was no effect on C_{max}, but $t_{1/2}$ was prolonged. Variability was high in the severe hepatic impairment group.

No specific studies have been performed for gender, weight, race, or elderly. Overall analysis across clinical pharmacology studies did not indicate an effect of any of them on lapatinib pharmacokinetics. Due to the minor importance or renal excretion for the elimination of lapatinib, a relevant effect of renal impairment on lapatinib pharmacokinetics is not expected. There is no pharmacokinetic data in children.

- Pharmacokinetic interaction studies

Effects of other substances on lapatinib:
In vitro, the major enzyme catalysing lapatinib metabolism is CYP3A4/5 with smaller contribution of CYP2C8 and potentially CYP1A2, 2D6, 2C9 and 2C19. Therefore, mainly CYP3A4/5 inhibitors and inducers would be expected to affect lapatinib elimination. Lapatinib is also a substrate for the Pgp/ABCB1 and Bcrp/ABCG2 transporters. Inhibitors of these transporters may affect lapatinib distribution. In addition, the metabolism of lapatinib was inhibited by docetaxel at clinically relevant concentrations (IC_{50} = 1.3 µM = 1.05 µg/mL).

The dependence of lapatinib metabolism on CYP3A4 was assessed *in vivo* in two drug-drug interaction studies in healthy volunteers. The effect of potent inhibition was examined after administration of ketoconazole 200mg twice daily for 7 days, which resulted in a 3.6-fold increase in AUC and a 1.7-fold increase in t½ of lapatinib. Administration of carbamazepine, a CYP3A4 inducer, was also examined when administered at 100mg twice daily for 3 days and 200mg twice daily for 17 days. In this case lapatinib concentrations (AUC∞) were reduced 72% after CYP3A4 induction by carbamazepine. No *in vivo* drug-drug interactions have been detected with concomitant therapy with capecitabine and trastuzumab.

Effects of lapatinib on other substances:
Clinically relevant concentrations of lapatinib inhibit *in vitro* CYP3A4 (K_i values of 1.1 to 4 µM=0.6 to 2.3 µg/mL) and CYP2C8 (K_i = 0.6 µM=0.3 µg/mL) but not CYP1A2, CYP2C9, CYP2C19, CYP2D6 or UGT activity. Lapatinib modestly inhibits its own metabolism by CYP3A4. Lapatinib does not induce CYP enzymes. Lapatinib also inhibited the efflux transporters Pgp/ABCB1 (IC_{50} = 3.91 µM= 2.3 µg/mL) and Bcrp/ABCG2, and the hepatic uptake transporter OATP 1B1 (IC_{50} = 4.02 µM= 2.3 µg/mL). At a single test concentration of 30 µM, lapatinib inhibited human organic anion transporter (OAT) hOAT3 by 59.8%.

Pharmacodynamics

- Mechanism of action

No clinical studies investigating the mechanism of action have been conducted.

- Primary and Secondary pharmacology

Biological activity in terms of inhibition of ErbB1/2 activation and down stream signalling has been demonstrated in tumour biopsies from heavily pre-treated patients. No obvious relationship between dose/concentration and biological activity was identified, but the sample size was small and the population heterogeneous. Despite signs of biological activity, the response rate was low.

A relatively extensive biomarker programme is underway, but until now no markers predictive of anti-tumour activity or resistance to lapatinib have been identified.

From a repeat-dose dose finding study combining capecitabine and lapatinib including 45 patients, the recommended phase III dose was lapatinib 1250 mg/d OD and capecitabine 1000 mg/m2/day BID 14/21 days. The dose-limiting toxicity was determined to be diarrhoea and rash. An additional study including patients with breast cancer and other solid tumours was also pertinent for the analysis of dose-response. A total of 81 subjects were randomized in this study and received at least one dose of lapatinib. In this study once daily administration of lapatinib at doses ranging from 175 to 1800 mg resulted in approximately a 2-fold accumulation, while twice daily administration of lapatinib at doses ranging from 500 to 900 mg resulted in approximately 4-fold accumulation. Systemic exposure was approximately 2-fold higher after twice daily dosing compared to once daily dosing at the same total daily dose.

The skin and the intestinal mucosa were the main non-tumoral targets for lapatinib action, with diarrhoea being prominent as dose-limiting in dose-finding studies.

Discussion on Clinical Pharmacology

Discussion on clinical PK

Lapatinib displays high pharmacokinetic variability, which is not unexpected considered the physicochemical properties and the different mechanisms involved in its absorption and elimination.

Administration of lapatinib with food results in an average 3- to 4-fold increase in systemic exposure at clinically relevant doses. This increase appears to be positively related to the fat and/or caloric content of the meal. A further pharmacokinetic study will be provided as a follow-up measure to characterise the pharmacokinetics of lapatinib administration according to the currently proposed recommendations with different types of meals. Until results are available, it is agreed to maintain the recommendation that lapatinib should be taken 1 hour before or 1 hour after food and it has been properly stated in section 4.2 of the SPC. A warning of possible interactions with food and drink has also been included in section 4.5 of the SPC.

The solubility of lapatinib is pH-dependent, but no clinical study has been performed to evaluate whether changes in gastric pH due to anti-acidic treatment may alter lapatinib bioavailability. The Applicant has committed to perform a study as a follow-up measure; until results are available a warning has been included in sections 4.4 and 4.5 of the SPC.

From the mass balance study it is apparent that biliary excretion plays an undetermined role. The recovery of unchanged lapatinib in faeces may be due mainly to biliary excretion of unchanged parent compound rather than to incomplete absorption, which seems plausible. Biliary excretion may therefore be a relatively important route of elimination for lapatinib.

It has not been considered possible to give clear dose adjustment recommendations based on the results of the study in hepatic impairment. That study was performed at a much lower dose than the proposed dose for Tyverb and, due to non-linear pharmacokinetics, the results of the study (i.e. the observed increase in exposure) cannot readily be extrapolated to the clinical dose. There was also a large variability in the study, as will be expected also in clinical practice due to different types of heptatic disease. The impact of the type of hepatic impairment (e.g. metabolic impairment, cholestasis etc.) and whether the included subjects had hepatic disease that would be expected to have a marked effect on lapatinib pharmacokinetics have not been addressed.

Lapatinib pharmacokinetics have not been specifically studied in patients with renal impairment or in patients undergoing haemodialysis. Available data suggest that no dose adjustment is necessary in patients with mild to moderate renal impairment however caution is advised if lapatinib is prescribed to patients with severe renal impairment as stated in section 4.2, 4.4 and 5.2 of the SPC.

Lapatinib is a substrate for the transport proteins Pgp and BCRP and has been shown to inhibit both of them in vitro as well as the hepatic uptake transporter OATP1B1. Inhibitors (ketoconazole, itraconazole, quinidine, verapamil, cyclosporine, erythromycin) and inducers (rifampin, St John's Wort) of these proteins may alter the exposure and/or distribution of lapatinib. A warning has been included in section 4.5 and 5.2 of the SPC.

Due to lapatinib inhibitory effect on CYP3A4, coadministration of lapatinib with strong CYP3A4 inhibitors (e.g. ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, nefazodone) or inducers (e.g. rifampicin, rifabutin, carbamazepine, phenytoin or Hypericum perforatum [St John's wort]) should be avoided. Coadministration of lapatinib with moderate inhibitors of CYP3A4 should proceed with caution and clinical adverse reactions should be carefully monitored. A warning has been included in sections 4.4 and 4.5 of the SPC.

The Applicant has suggested making a dose recommendation if concomitant use of a CYP3A4 inhibitor cannot be avoided, and that the dose should be monitored based on tolerability. The latter is,

however, not considered possible for the currently indicated patient population, since lapatinib should be co-administered with capecitabine, which has overlapping toxicity. It might therefore be difficult to identify potential under- or over-exposure of lapatinib at a decreased dose. Moreover, the ketoconazole interaction study was performed with a dose of lapatinib within the low dose range (100 mg) where non-linearity was in the opposite direction compared with at higher doses, and the magnitude of the effect might possibly be different at the clinical dose. The effect of different inhibitors might be highly variable. The proposed recommendation has not been tested, and the variability in the resulting exposure is unknown. Thus, combination with potent CYP3A4 inhibitors should be avoided.

The effect of 1500 mg OD lapatinib on the pharmacokinetics of midazolam administered orally and intravenously will be provided. The final clinical study report for this study is planned for completion in June 2008. Preliminary results indicate that lapatinib decreased midazolam clearance 18% and increased midazolam bioavailability 19%, resulting in AUC_{IV} increasing 22% after IV and 45% after PO administration. Based on these findings, co-administration of lapatinib with drugs that are substrates of CYP3A4 and have narrow therapeutic windows should be undertaken with caution. This is addressed in Section 4.5 of the SPC.

Clinical efficacy

The main clinical efficacy trial was a phase III trial comparing lapatinib in combination with capecitabine with capecitabine alone in the treatment of women with ErbB2 overexpressing advanced or metastatic breast cancer who had received prior anthracyclines, taxanes and trastuzumab.

- Main study

Study EGF100151

This was a phase III, randomized, open-label, multicentre study comparing lapatinib plus capecitabine versus capecitabine alone in women with ErbB2 overexpressing advanced or metastatic breast cancer who had received prior treatment with anthracyclines, taxanes and trastuzumab.

METHODS

Study Participants
The key inclusion criteria were:

1. Histologically confirmed invasive breast cancer with stage IIIb or stage IIIc with T4 lesion, or stage IV disease. Subjects were required to have measurable disease as defined by RECIST, an Eastern cooperative oncology group (ECOG) Performance Status of 0 or 1 and a life expectancy of ≥12 weeks.
2. ErbB2 overexpression (immunohistochemistry IHC 3+ or IHC2+ with fluorescence in situ hybridization FISH confirmation).
3. Documented progressive advanced or metastatic breast cancer, defined as appearance of any new lesion or increase of 25% or more in existent lesions.
4. Refractory breast cancer defined as progression or relapse within 6 months of completing adjuvant therapy. Prior therapies must have included, but were not limited to anthracyclines, taxanes and trastuzumab. Prior treatment with capecitabine was not permitted.

The study was conducted by 246 investigators at 128 centres in the following countries: Argentina, Australia, Brazil, Canada, Finland, France, Germany, Greece, Hong Kong, Ireland, Israel, Italy, Poland, Portugal, Russia, Republic of South Africa, Spain, Switzerland, United Kingdom, and the United States.

Treatments
Subjects were randomized to one of two treatment groups, to receive either lapatinib 1250mg/day daily continuously and capecitabine 2000mg/m^2/day on Days 1-14 of a 21-day treatment cycle or single-agent capecitabine 2500mg/m^2/day on Days 1-14 of a 21-day cycle.

Treatment was administered until disease progression or withdrawal from study due to unacceptable toxicity or other reasons. Treatment could have been delayed up to 2 weeks or a single reduction in the lapatinib dose was allowed to 1000 mg/day to allow for resolution of toxicity. A delay for up to 2 weeks and dose reductions to 50% of the starting dose were also permitted for capecitabine.

Objectives
The primary objective was to evaluate and compare time to progression (TTP) in subjects with refractory advanced or metastatic breast cancer treated with lapatinib and capecitabine versus capecitabine alone.

Secondary objectives were to evaluate and compare the two treatment arms with respect to: Overall survival (OS), progression-free survival (PFS), overall response rate (complete and partial responses), clinical benefit response rate (complete response, partial response or stable disease for at least 6 months) and change in quality of life (QOL) status. They also included comparison of the qualitative and quantitative toxicity, comparison of the tumour response rates and on-treatment serum concentrations of ErbB1 and ErbB2, to further characterize the patient population by determination of intra-tumoral expression of ErbB1, ErbB2 and downstream biomarkers and to determine the intra-tumoral genetic changes (i.e., mutations, copy number variability, expression levels) that may correlate with response to lapatinib.

Outcomes/endpoints
Time to progression (TTP, disease progression or death due to breast cancer prior to progression), was established by an independent review committee (IRC), who were blinded to study treatment, after radiological assessment including a chest CT (or MRI) scan including liver or alternatively, separate chest and abdominal CT (or MRI) scan and a bone scan. As secondary assessment, physicians involved in the trial also evaluated the subject's tumour response/disease status. Pelvic scan and MRI (CT) of the head were performed when clinically indicated.

Radiographic disease assessments were obtained every 6 weeks for the first 24 weeks, followed by every 12 weeks (within 7 days +/- window) or sooner if clinically indicated. The same physician evaluated the subject's tumour response/disease status when possible. If the lesion(s) noted at screening were not evaluated at the end of the efficacy evaluation interval, this will be noted as 'not done' (ND) in the CRF.

The response confirmation requirements were a confirmatory disease assessment no less than 4 weeks after the criteria for response are first met, a disease evaluation (e.g. radiologic, medical photography) on all sites with lesions present at the baseline assessment, and a bone scan to rule out the presence of new bone lesions or progression of existing bone lesions.

The clinical benefit response rate was defined as the percentage of subjects with evidence of complete or partial tumour response or stable disease for at least 6 months (24 weeks).

For subjects who had CR or PR, the duration of response was defined as the time from first documented evidence of PR or CR until the first documented sign of disease progression or death due to breast cancer.

Sample size
The study was originally designed with 90% power and Type I error of 0.05 to detect a 50% increase in median TTP in subjects who received lapatinib+capecitabine assuming a median time to progression of 3 and 4.5 months in the capecitabine and lapatinib plus capecitabine arms, respectively. The study was subsequently amended so it was also powered to detect a difference in overall survival (a secondary study endpoint). A maximum of 457 deaths were required for the analysis of overall

survival to have an 80% chance of successfully detecting a 30% increase in median survival time in subjects who received lapatinib plus capecitabine, based on median survival times of 8 and 10.4 months in the capecitabine and lapatinib plus capecitabine arms, respectively, i.e. a hazard ratio of 0.769. To achieve the 80% power an estimated total of 528 subjects would have been required.

Randomisation
Subjects were randomized to receive lapatinib plus capecitabine or capecitabine alone and were assigned to study treatment in accordance with a 1:1 randomization schedule.
Randomization was stratified according to three categories based on stage and site of disease:

- Disease Stage IIIb or IIIc with T4 lesions;
- Disease Stage IV / Visceral site (any visceral); and
- Disease Stage IV / Non-visceral site.

Blinding (masking)
No blinding performed (open-label study).

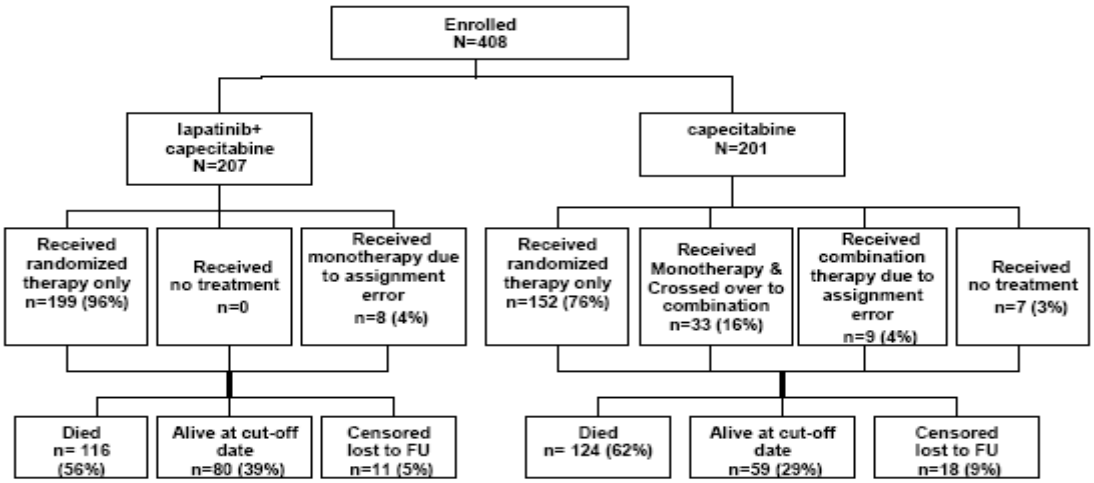
Statistical methods
The primary population for the analysis of the efficacy results was the Intent to Treat (ITT) population, which included all randomized subjects whether they received study medication or not. The Per-Protocol (PP) population was composed of all randomized and treated subjects who had no major protocol deviations. The PP population was used to provide a supplementary analysis of time to progression only.

The Safety population was composed of all randomized subjects who received at least one dose of randomized therapy and was based on the actual treatment received, if this differed from that to which the subject was randomized.

For TTP, there were a maximum of two interim analyses planned, to occur at approximately equally spaced numbers of events: 133 and 266 investigator-determined events. O'Brien-Fleming stopping boundaries with one-sided 2.5% significance level were used. All p-values presented are two-sided unless otherwise stated.

RESULTS

Participant flow



* At 03 April 2006 when enrolment to EGF100151 was halted, nine patients were in screening; these patients were allowed to continue on-study and received treatment with lapatinib plus capecitabine

Recruitment

Patients were enrolled between the 29th March 2004 and the 3rd April 2006. The interim analysis was performed after 146 investigator-identified events (321 subjects) (disease progression or death due to breast cancer prior to progression) were observed with a clinical cut-off date of 15 November 2005. The independent review committee (IRC) who were blinded to study treatment identified 114 events. As the primary analysis of TTP was based on events determined by the IRC, the power of the interim analyses was decreased. As a result of the lower number of events, new O'Brien-Fleming stopping boundaries were calculated based on 114 events and one-sided p-values - the futility boundary for 114 events was crossed if the log-rank test resulted in $p \geq 0.4516$, (for 133 events, the futility boundary was crossed if $p \geq 0.3308$) and the superiority boundary for 114 events was crossed if the log-rank test resulted in $p \leq 0.0014$, (based on 133 events, the boundary for superiority was crossed if the log-rank test resulted in $p \leq 0.0028$).

After review by the Independent Data Monitoring Committee (IDMC) the applicant was recommended to halt further enrolment into the study. GlaxoSmithKline decided to terminate study enrolment and subjects in the control arm were given the opportunity to cross-over and receive the combination of lapatinib and capecitabine.

After the interim analysis there have been three further database freezes as summarized in Table 8:

Table 8 - Database freezes for Study EGF100151

Data Analyses for EGF100151	Date
First Database Freeze: Interim Analysis (All efficacy endpoints including TTP & OS)	15 November 2005
Second Database Freeze: Updated Analyses for the CHMP / FDA (All efficacy endpoints including TTP & OS)	03 April 2006
Third Database Freeze: Updated Analyses for the CHMP - OS only	15 March 2007
Fourth Database Freeze: Updated Analyses for the CHMP - OS only	28 September 2007

OS = overall survival; TTP = time-to-progression.

Conduct of the study
There were in all 7 amendments to the protocol. None of them constitutes a concern as regards study integrity.

Major protocol deviations occurred in 17 (10%) patients in the experimental arm and in 31 (19%) patients in the control arm. No major imbalances were detected between arms on this regard. Due to a technical problem with the randomization system, seven subjects were randomized to the lapatinib+capecitabine group but received capecitabine monotherapy and nine subjects were randomized to the capecitabine group but received lapatinib+capecitabine (see Table 12).

Baseline data
The main baseline characteristics are provided in Tables 9-11.

Table 9 - Baseline Demographic Characteristics (ITT Population, 3 April 2006 cut-off)

Demographic Characteristic	**Lapatinib+Capecitabine N=198**	**Capecitabine N=201**	**All Subjects N=399**
Age, years			
n	198	201	399
Mean (SD)	53.6 (10.54)	51.5 (10.34)	52.5 (10.48)
Median (range)	54 (26 – 80)	51 (28 – 83)	53 (26 – 83)
Age Group, n (%)			
n	198	201	399
<65 years	165 (83)	177 (88)	342 (86)
≥65 years	33 (17)	24 (12)	57 (14)
Race, n (%)			
n	198	201	399
White	181 (91)	181 (90)	362 (91)
Asian	6 (3)	8 (4)	14 (4)
American Hispanic	4 (2)	6 (3)	10 (3)
Black	5 (3)	3 (1)	8 (2)
Other	2 (1)	3 (1)	5 (1)
ECOG Performance Status[1], n (%)			
n	177	173	350
0	103 (58)	104 (60)	207 (59)
1	71 (40)	66 (38)	137 (39)
Unknown	3 (2)	3 (2)	6 (2)

1. ECOG PS as determined pre-dose on Day 1.

Table 10 - Baseline Disease Characteristics and Medical History (ITT Population, 3 April 2006 cut-off)

	Lapatinib+ Capecitabine N=198 n (%)	Capecitabine N=201 n (%)	All Subjects N=399 n (%)
ErbB2 Overexpression Status[1]			
Overexpressed	197 (>99)	201 (100)	398 (>99)
Not overexpressed	1 (<1)	0	1 (<1)
Histology at First Diagnosis			
Infiltrating duct NOS	163 (82)	177 (88)	340 (85)
Other	23 (12)	13 (6)	36 (9)
Lobular invasive	8 (4)	8 (4)	16 (4)
Tubular	2 (1)	1 (<1)	3 (<1)
Mucinous	1 (<1)	1 (<1)	2 (<1)
Adenocystic	0	1 (<1)	1 (<1)
Papillary	1 (<1)	0	1 (<1)
Disease Stage at First Diagnosis			
I	15 (8)	22 (11)	37 (9)
II	85 (43)	91 (45)	176 (44)
III	74 (37)	65 (32)	139 (35)
IV	23 (12)	23 (11)	46 (12)
Unknown	1 (<1)	0	1 (<1)
Baseline Disease Stage			
Stage IV – visceral	148 (75)	158 (79)	306 (77)
Stage IV – non-visceral	43 (22)	35 (17)	78 (20)
Stage IIIb or IIIc with T4 lesion	7 (4)	8 (4)	15 (4)
Local Recurrence after Surgery			
n	181	188	369
Yes	51 (28)	59 (31)	110 (30)
No	129 (71)	129 (69)	258 (70)
Unknown	1 (<1)	0	1 (<1)
Receptor Status[1]			
ER- / PR-	95 (48)	101 (50)	196 (49)
ER+ / PR+	49 (25)	48 (24)	97 (24)
ER+ / PR-	18 (9)	25 (12)	43 (11)
ER+ / PR unknown	16 (8)	10 (5)	26 (7)
ER- / PR+	13 (7)	10 (5)	23 (6)
ER- / PR unknown	4 (2)	6 (3)	10 (3)
ER unknown / PR unknown	3 (2)	1 (<1)	4 (1)
Number of Metastatic Sites			
≥3	98 (49)	96 (48)	194 (49)
2	61 (31)	61 (30)	122 (31)
1	39 (20)	44 (22)	83 (21)

1. Done by local laboratory testing.

ER=estrogen receptor; PR=progesterone receptor; NOS=not otherwise specified

Table 11 - Summary of Prior Anti-Cancer Therapies of Interest (ITT Population, 3 April 2006 cut-off)

ATC Category	Lapatinib+Capecitabine N=198 n (%)	Capecitabine N=201 n (%)
Any medication	**198 (100)**	**201 (100)**
All medications (taxane+anthracycline+trastuzumab)	**191 (96)**	**188 (94)**
Taxanes	**198 (100)**	**199 (>99)**
Docetaxel	143 (72)	154 (77)
Paclitaxel	93 (47)	83 (41)
Anthracyclines	**194 (98)**	**199 (>99)**
Doxorubicin hydrochloride	98 (49)	97 (48)
Epirubicin	61 (31)	63 (31)
Doxorubicin	35 (18)	41 (20)
Mitoxantrone	11 (6)	4 (2)
Epirubicin hydrochloride	5 (3)	8 (4)
Anthracyclines (not specified)	1 (<1)	1 (<1)
Trastuzumab	**196 (99)**	**197 (98)**
Hormonals	**99 (50)**	**93 (46)**
Navelbine	**93 (47)**	**92 (46)**
Gemcitabine	**32 (16)**	**22 (11)**

Numbers analysed
All patients were included in the ITT efficacy analyses and description of baseline characteristics. The numbers are summarized in Table 12.

Table 12 - Summary of Analysis Populations (3 April 2006 cut-off)

	Lapatinib+Capecitabine N=198	Capecitabine N=201	Total N=399
All subjects	198	201	399
ITT population	198	201	399
Safety population	198	191	389
Per-protocol population	180	168	348

Outcomes and estimation

- Primary endpoint:

Results of TTP and Kaplan Meier estimates as evaluated by investigator assessment and independent review at the end of enrolment (3 April 2006) are shown in Tables 13-15:

Table 13 - TPP Evaluated by Investigator Assessment and Independent Review (ITT Population)

	Investigator assessment		Independent assessment	
	Lapatinib + capecitabine	**Capecitabine alone**	**Lapatinib + capecitabine**	**Capecitabine alone**
	(N = 198)	**(N = 201)**	**(N = 198)**	**(N = 201)**
Number of TTP events	121	126	82	102
Median TTP, weeks	23.9	18.3	27.1	18.6
Hazard Ratio	0.72		0.57	
(95% CI)	(0.56, 0.92)		(0.43, 0.77)	
P value	0.00762		0.00013	
Response rate (%)	31.8	17.4	23.7	13.9
(95% CI)	(25.4, 38.8)	(12.4, 23.4)	(18.0, 30.3)	(9.5, 19.5)

Figure 1 - Kaplan Meier Estimates of Investigator-Evaluated Time to Progression (ITT Population)

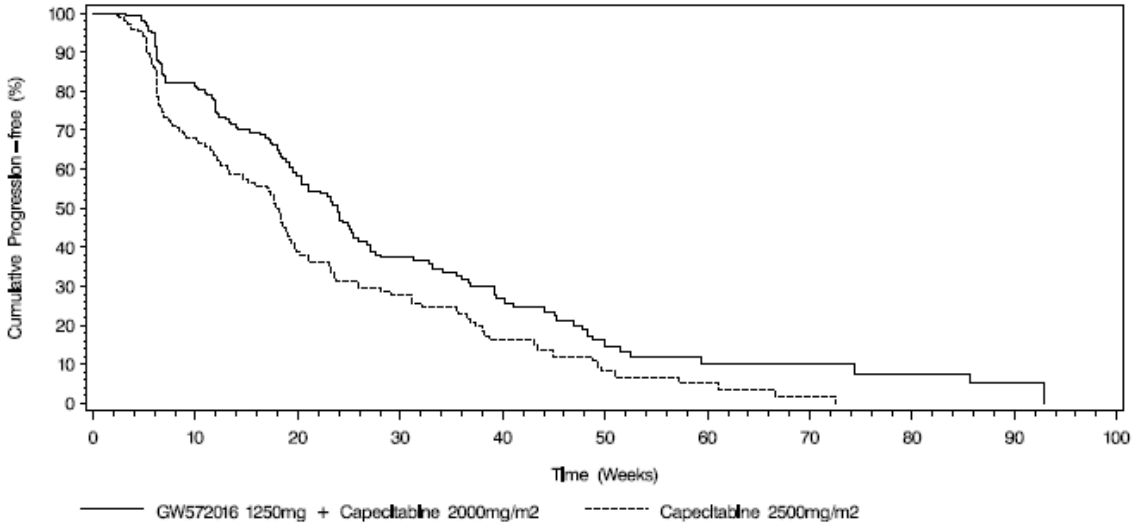
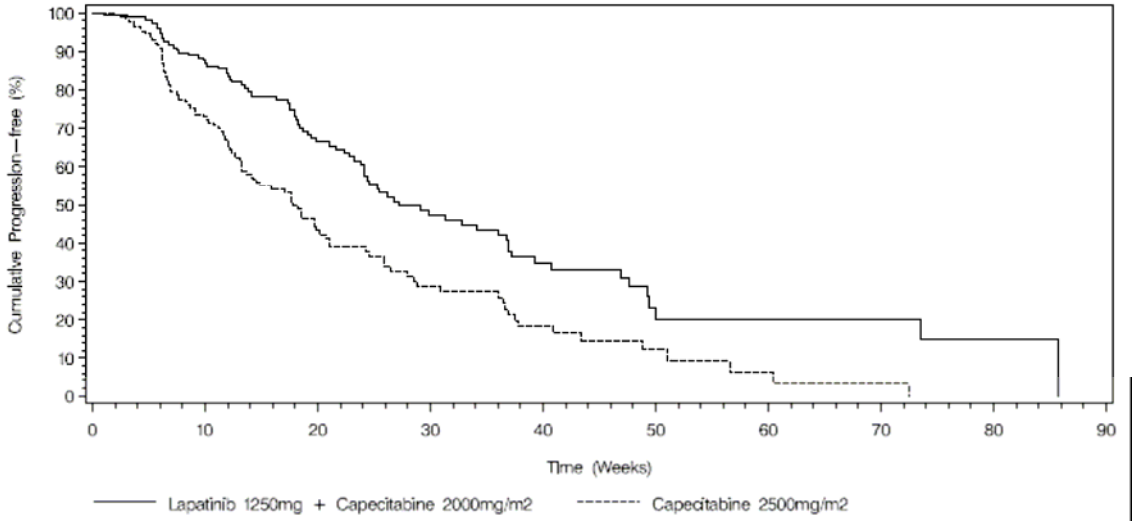


Figure 2 - Kaplan Meier Estimates of Independent Review Panel-Evaluated Time to Progression (ITT)



- Secondary endpoints:

Progression Free Survival (PFS)

At the cut-off point for interim analysis (15 November 2005), the independently assessed median time for progression-free survival (PFS) was 36.7 weeks in the lapatinib+capecitabine group and 17.9 weeks in the capecitabine group; hazard ratio of 0.47 (95% CI: 0.33, 0.67, p-value: 0.000023)

Up to 3 April 2006 the independently assessed median progression-free survival (PFS) was 27.1 weeks in the lapatinib+capecitabine group and 17.6 weeks in the capecitabine group with a hazard ratio of 0.55 (95% CI: 0.41, 0.74, two-sided p=0.000033).

Sensitivity analyses fell in between the results reported by IRC and investigators. Results from the "Earliest Date" analysis are shown in Table 14. The median difference is 5.8 weeks, which is a likely underestimate since the median difference is about 6 weeks in the investigator analysis.

Table 14 - Progression-free Survival, Independent review (ITT Population, 3 April 2006)

	Lapatinib+ Capecitabine N=198	Capecitabine N=201
Censoring Status, n (%)		
Progressed or died	135 (68)	144 (72)
Censored, follow-up ended	6 (3)	13 (6)
Censored, follow-up ongoing	57 (29)	44 (22)
Kaplan Meier estimate of PFS, weeks		
1st Quartile	10.3	6.3
Median	19.1	13.3
3rd Quartile	35.1	23.6
Hazard ratio		
Estimate, [95% CI][1]	0.67 [0.53, 0.85]	
Log-rank p-value[2]	0.000786	

Response Rate (RR)

At the cut-off point for interim analysis (15 November 2005), independently reviewed response rate (complete or partial response) was 22% in the lapatinib+capecitabine group versus 14% in the

capecitabine group. The odds ratio was 1.7 (95% CI: 0.9, 3.2, p-value: 0.091). This compares to the investigator assessment of response rate for the lapatinib+capecitabine group (29%) and the capecitabine group (17%). This odds ratio was 2.1 (95% CI: 1.2, 3.7; p-value: 0.011)

Up to 03 April 2006, independently reviewed response rate (complete or partial response) was 24% in the lapatinib+capecitabine group versus 14% in the capecitabine group. The odds ratio was 1.9 (95% CI: 1.1, 3.4, p=0.017).

Overall Survival

The results of overall survival analysis at 4 different cut-off time points are shown in Table 15. At the time of the latest analysis (28 Sept 2007), 148 subjects (71%) in the lapatinib+capecitabine group and 154 subjects (77%) in the capecitabine group had died. At this time point 25% of subjects in the lapatinib+capecitabine group and 20% of subjects in the capecitabine group were still being followed for survival and were censored for these analyses. In addition, 3% of subjects in the both the lapatinib+capecitabine group and the capecitabine group were no longer being followed for survival but were alive when their follow-up ended.

Table 15 - Summary of Overall Survival (ITT Population)

Dataset/Subjects/Events	Median OS (weeks)		HR (95% CI) (p value)
	C	L+C	
15 November 2005 / 324 / 71	NR	58.9	0.92 (058, 1.46) 0.717
03 April 2006 / 399 / 119	66.6	67.7	0.78 (0.55, 1.12) 0.177
15 March 2007 / 408 /240	65.9	76.3	0.86 (0.67, 1.11) 0.242
28 September 2007/408/302	**65.9**	**74.0**	**0.9 (0.71, 1.12) 0.336**

Clinical Benefit Rate

Using the independent assessment a greater proportion of subjects in the lapatinib+capecitabine group (29%) than in the capecitabine group (17%) achieved clinical benefit (odds ratio: 2.0, 95% CI: 1.2, 3.3, two-sided p-value: 0.008; cut-off date 3 April 2006). Using the investigator assessment of the clinical benefit response rate a greater proportion of subjects in the lapatinib+capecitabine group (37%) than in the capecitabine group (21%) achieved clinical benefit (two-sided p-value: 0.001).

Duration of Response

For subjects who responded to treatment, the median duration of response was 32.1 weeks in the lapatinib+capecitabine group and 30.6 weeks in the capecitabine group (cut-off date 3 April 2006)

Ancillary analyses

1. Cox regression analyses on overall survival

A stepwise model-building approach using Cox Regression was employed to evaluate the effects of baseline disease history and prognostic factors on the overall survival (see Table 16). Treatment was retained in the model, while the prognostic factors (number of sites of disease, ECOG performance status and liver metastases) were evaluated using stringent criteria for inclusion using entry/exit criteria of $\alpha \leq 0.05$.

Table 16 - Summary of Cox Regression Model for Overall Survival Considering Main Effect Terms Including Liver Metastases ITT Population (15 March 2007)

Covariate	Effect Tested	HR [95% CI][1]	P-value
Treatment Group	Lapatinib+Capecitabine/ Capecitabine	0.81 [0.62, 1.04]	0.100
Number of Metastatic sites	< 3 sites / ≥ 3 sites	0.72 [0.56, 0.94]	0.014
ECOG Performance Status	0/ ≥1	0.51 [0.39, 0.66]	<0.001
Liver Metastases	No/ Yes	0.51 [0.39, 0.66]	<0.001

HR <1 indicates a lower risk.

The same prognostic covariates identified were included in Cox regression analyses using the three cut-off datasets (see Table 17).

Table 17 - Comparison of Cox Regression Survival Analyses Over Time

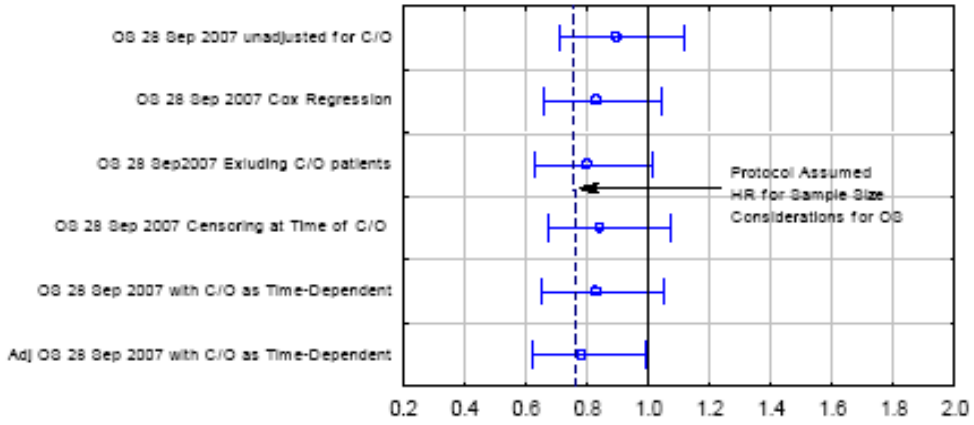
Dataset/Subjects/Events	Adjusted		
	Median OS (weeks)		HR (95% CI) (p value)
	C	L+C	
15 November 2005 / 324 / 71	58.9	NR	0.91 (0.57, 1.14) 0.705
03 April 2006 / 399 / 119	60	71	0.74 (0.51, 1.07) 0.113
15 March 2007 / 408 /240	67.7	76.3	0.81 (0.562, 1.04) 0.100

C = capecitabine; L = lapatinib; NR = not reached.

2. Analyses addressing the effect of cross-over

Out of 39 patients "at risk" for cross over, a total of 36 patients did cross over from monotherapy to combination therapy after April 2006. Of these 36 patients, (at least) 29 crossed over prior to progression on monotherapy. Median time to cross-over was 17.8 weeks to be compared with time to progression being 18.6 weeks in the capecitabine arm (IRC).
In order to address the possible confounding effect of cross-over different approaches were undertaken by the sponsor (censoring of cross-over patients at baseline, at time of cross-over, or as time-dependent covariate) (See Figure 3):

Figure 3 - Hazard Ratio and 95% CIs for Overall Survival (OS) Analyses Adjusting for Cross-Over (ITT Population, 28th September 2007)



3. Effect of next-line therapies

Other subsequent, 'next-line' anticancer therapy was received by 277 subjects (141 subjects treated with lapatinib + capecitabine and 136 subjects treated with capecitabine). Administration of these subsequent therapies was balanced between the two treatment groups. Trastuzumab-containing regimens (monotherapy or in combination with vinorelbine, taxanes, gemcitabine, bevacizumab, capecitabine, or cisplatin) were the most common next-line regimens in follow-up treatment (26% of patients randomised to lapatinib + capecitabine, and 21% patients randomised to capecitabine). The next most common regimens for first follow-up treatment were vinorelbine, gemcitabine, capecitabine, hormonal agents, anthracycline, and taxanes. Other treatments included radiotherapy, surgery, experimental agents, CMF, liposomal doxorubicin, carboplatin, and cisplatin, either as monotherapy, or in combinations other than with trastuzumab.

4. Q-TWiST analysis

There was no significant difference between groups in mean duration of grade 3/4 AEs prior to progression (lapatinib + capecitabine 1.7 weeks, capecitabine 1.5 weeks). A threshold utility analysis (using utility weights of 0.5 for both TOX and REL, i.e. counting 2 days of TOX or REL as equivalent to 1 day of TWiST) resulted in a clinically meaningful difference in quality-adjusted survival favouring lapatinib + capecitabine (p=0.0013) of approximately 7 weeks. The Q-TWiST difference was significant across a broad range of possible utility weights and results were robust in sensitivity analyses including all AEs or only treatment-related AEs.

- Studies in special populations

No specific studies have been made available.

- Supportive studies

EGF30001: Lapatinib plus Paclitaxel in First-Line Metastatic Breast Cancer

A multicentre, multinational, double-blind Phase III study of lapatinib plus paclitaxel versus paclitaxel alone in the first-line treatment of subjects with metastatic breast cancer (MBC) whose ErbB2 receptor status at entry was either unknown or negative. Subjects were randomised to paclitaxel 175 mg/m2 q3w and oral lapatinib 1500 mg OD or paclitaxel 175 mg/m2 q3w and placebo OD. Preliminary data are shown in Table 18:

Table 18 - Efficacy Data in ErbB2+ Population

	Paclitaxel + Lapatinib (n=52)	Paclitaxel + Placebo (n=39)	Hazard Ratio (CI) P-value
Median TTP, months (1Q, 3Q)	8.1 (4.6, 12.9)	5.8 (4.6, 8.3)	HR 0.57 (0.34, 0.93) p=0.011
Median PFS, months (1Q, 3Q)	7.9 (4.3, 12.8)	5.2 (3.0, 7.9)	HR 0.56 (0.34, 0.90) p=0.007
RR, % (95% CI)	59.6 (45.1, 73.0)	35.9 (21.2, 52.8)	OR 2.9 (1.1, 7.9) p=0.027
CBR, % (95% CI)	65.4 (50.9, 78.0)	38.5 (23.4, 55.4)	OR 3.2 (1.2, 8.7) p=0.0135
Median OS, months (95% CI)	24.0 (17.7, -)	19.0 (9.8, -)	HR 0.64 (0.3, 1.2) p=0.160

EGF105084: Lapatinib Therapy in Patients with Brain Metastases

This study was a phase II single-arm, open-label, multicentre trial of lapatinib monotherapy (750 mg BD) in patients with recurrent brain metastases from ErbB2-positive breast cancer. Eligible patients had radiographic evidence of progressive brain metastases at study entry, and had received prior trastuzumab and cranial radiotherapy. All subjects had undergone prior cranial radiotherapy, received extensive prior systemic therapy, and must have had radiographic evidence of CNS disease progression upon study entry. A total of 242 patients were enrolled. High resolution brain MRI scanning was performed every 8 weeks to precisely measure the volume of the tumours in the brain.

At disease progression with lapatinib monotherapy, patients could continue into an extension treatment arm and receive lapatinib + capecitabine (the same regimen as used in study EGF100151). Altogether 16/242 (monotherapy) and 10/49 (combination) experienced ≥ 50% volumetric reduction. PFS data is shown in Table 19:

Table 19 - Median Progression-Free Survival (PFS) (Study EGF105084)

Lapatinib monotherapy	
Median PFS (95% CIs)	9.3 weeks (8.14, 12.14)
Lapatinib + Capecitabine extension arm	
Median PFS (95% CIs)	15.8 weeks (10.57, 19.00)

Study EGF103659 and the **ATU (Authorisation Temporaire d'Utilisation) in France**

These studies were started after enrolment to EGF100151 was stopped. Both used the same lapatinib + capecitabine regimen as in EGF100151, and patient eligibility criteria were similar. Globally, EGF103659 has enrolled 2570 patients at 198 sites and in Europe, the study is being conducted in 27 countries and has enrolled 1137 patients (September 2007). The French ATU has enrolled 760 patients in 250 sites (to the same cut-off date).

Of 1189 patients enrolled at these sites, 137 (12%) entered EGF103659/ATU with brain metastases at baseline. Data regarding progressive CNS metastases upon entry, method of CNS evaluation, dates and response of CNS evaluations, dates and response of any non-CNS disease, presence of tumour related neurological symptoms at entry, and change in symptomatology were collected. The results are shown in Table 20:

Table 20 - Best Response for EGF103659 / ATU Subjects with Progressive CNS Metastases at Baseline

	N=137 n
Complete Response	3 (2%)
Partial Response	21 (15%)
Stable Disease	56 (41%)
Progressive Disease	14 (10%)
Unknown	43 (31%)

There were 92 subjects with available treatment start date and date of response assessments, for whom the median time on treatment was 13 weeks (range: 1 week to 107 weeks). Of these 92 subjects, treatment is ongoing for 54 (59%) subjects. For reference, the median duration of therapy with lapatinib + capecitabine therapy in EGF100151 was 19 weeks with 23% of subjects on therapy at the time of the analysis (03rd April 2006 data set). In addition, improvement in neurological signs and symptoms (NSS) was observed in at least one quarter of subjects, with few subjects requiring an increase in steroids.

Discussion on clinical efficacy

This submission relies on a single pivotal Phase III randomised, open label, active controlled trial conducted in breast cancer patients with good performance status, essentially normal cardiac, renal and hepatic function. Patients eligible for enrolment were ErbB2 over-expressing, locally advanced or metastatic breast cancer, progressing after prior treatment that included taxanes, anthracyclines and trastuzumab.

The primary endpoint was time to progression (TTP) as assessed by an independent review panel. The study was halted based on the results of a pre-specified interim analysis that showed an improvement in TTP (51 % reduction in the hazard of disease progression) for patients receiving lapatinib plus capecitabine. Various estimates of treatment effect are available, according to different adjudications (investigator, IRC) and analysis updates. Estimates based on IRC assessment are likely to overestimate the difference between study arms in terms of TTP due to the consequences of non-confirmation of investigator assessed events of progression and absence of follow-up imaging. A reasonable estimate in terms of HR and based on several sensitivity analyses is most likely slightly below 0.7 and about 6 to 8 weeks difference in median time to progression.

Generally, when survival is expected to be short and if there are no evidence-based next-line therapies available, confirmatory studies should be designed to show a survival benefit. The pivotal study was designed to demonstrate a survival benefit but as a secondary endpoint. Due to premature termination of enrolment based on the first interim analysis of PFS, it is difficult to assess whether the combination of lapatinib plus capecitabine is significantly different from capecitabine in terms of overall survival. An updated analysis of the overall survival data to 28 September 2007 (proportion of events observed >70%) indicated that there was a trend to improved survival in the combination arm. The median overall survival was 74.0 weeks in the lapatinib + capecitabine group and 65.9 weeks in the capecitabine alone group (Hazard Ratio: 0.9 [95 % CI: 0.71, 1.12]). No bias related to next line therapies was identified and cross-over to lapatinib appeared unlikely to constitute a major confounding factor. In this patient population however, the expected median survival in the reference arm (8 months according to the protocol), turned out to be about 20 weeks longer and time to death after progression about 40 weeks longer. Longer survival after progression might reflect a longer effect of previous trastuzumab therapies.

In addition, a reduced incidence of CNS metastases has been observed in secondary analyses in the pivotal study which was just statistically significant although no clear effect was seen in other

analyses. On the combination arm, there were 9/207 (1.5 %) progressions in the central nervous system as first site of progression as compared with 18/201 (9.0%) progressions on the capecitabine alone arm (investigator assessment, cut-off date of March 2007). There is a need to prospective confirmation of the effect on reducing the incidence of CNS metastases.

Clinical safety

The Safety population was composed of all randomized subjects who received at least one dose of randomized therapy and was based on the actual treatment received, if this differed from that to which the subject was randomized.

- Patient exposure

The number of subjects treated with Lapatinib is summarized in Table 21:

Table 21 - Subjects Treated in Completed GSK-Sponsored Studies with Lapatinib

	Lapatinib/ capecitabine combination	**Lapatinib monotherapy**	**Capecitabine monotherapy**	**Lapatinib in combination with other treatment**
Completed key studies (final CSR included in submission)				
Refractory Metastatic Breast Cancer	164[1]	307	152[2]	
Other Solid Tumours	45[3]			
Subtotal key studies	**209[4]**	**307**	**152[2]**	
Other completed studies (final CSR included in submission)				
Metastatic breast cancer				54[5]
Other cancer/ Solid tumours		320		
Healthy subjects		235		24
Subtotal other studies		**555**		**78**
Total	**209[4]**	**862**	**152[2]**	**78**

1. Received study drug; 163 were enrolled and randomized as of 15 November 2005 (up to 3 April 2006, 198 subjects were randomized and received study drug).
2. 161 were enrolled and randomized as of 15 November 2005 (up to 3 April 2006, 201 subjects were randomized and 191 subjects received study drug).
3. Includes 7 subjects with breast cancer in the Phase 1 Study EGF10005.
4. Received study drug; 208 enrolled and randomized as of 15 November 2005 (up to 3 April 2006 N=243).
5. Study EGF10023.

For Study EGF100151 the duration of exposure is shown in Table 22:

Table 22 - Duration of Exposure in Study EGF10151 (Safety Population, 3 April 2006 Cut-off)

	Lapatinib+Capecitabine N=198		Capecitabine N=191
Medication	**Lapatinib**	**Capecitabine**	**Capecitabine**
Duration of Treatment, weeks			
n	198	196	191
Mean (StdD)	21.6 (18.14)	20.7 (17.35)	15.1 (13.80)
Median	19.0	17.5	9.7
Min – Max	0 – 100	0 – 90	0 – 67
Daily Dose, mg or mg/m^2			
n	198	196	191
Mean (StdD)	1252.0 (164.77)	1864.0 (292.25)	2273.6 (302.24)
Median	1250.0	2000.0	2413.8
Min – Max	777 – 3036	813 – 2947	1192 – 2549

- Adverse events

Tables 23 and 24 summarize the most common adverse events by body system and by toxicity grade:

Table 23 - Summary of Adverse Events (≥5% Total Incidence) by Body System – Study EGF100151 (Safety Population, 3 April 2006 Cut-off)

Preferred Term	**Lapatinib+Capecitabine N=198 n (%)**	**Capecitabine N=191 n (%)**
Any AE	192 (97)	177 (93)
Diarrhea[1]	128 (65)	76 (40)
PPE syndrome	105 (53)	97 (51)
Nausea	87 (44)	83 (43)
Fatigue	46 (23)	47 (25)
Vomiting	52 (26)	41 (21)
Rash[2]	55 (28)	26 (14)
Anorexia	27 (14)	37 (19)
Abdominal pain	25 (13)	31 (16)
Mucosal inflammation	29 (15)	23 (12)
Stomatitis	27 (14)	21 (11)
Headache	20 (10)	26 (14)
Asthenia	20 (10)	25 (13)
Constipation	20 (10)	22 (12)
Dyspnea	23 (12)	16 (8)
Pain in extremity	24 (12)	14 (7)
Back pain	22 (11)	11 (6)
Dry skin	20 (10)	11 (6)
Insomnia	20 (10)	11 (6)
Dyspepsia	22 (11)	6 (3)

1. Diarrhea includes incidences of diarrhea, loose stools and frequent bowel movements.
2. Rash includes incidences of acne, dermatitis, eczema, erythema, folliculitis, rash, papular rash, and pustular rash.

Table 24 - Incidence of the Six Most Common AEs by Maximum Toxicity Grade Regardless of Relationship – Study EGF100151 (Safety Population, 3 April 2006 Cut-off).

Adverse Event	Number (%) of Subjects[1]					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Lapatinib+ Capecitabine N=198						
Any event	21 (11)	73 (37)	85 (43)	12 (6)	1 (<1)	192
Diarrhea[2]	61 (31)	40 (20)	25 (13)	2 (1)	0	128
PPE syndrome	25 (13)	57 (29)	23 (12)	0	0	105
Nausea	58 (29)	26 (13)	3 (2)	0	0	87
Fatigue	23 (12)	18 (9)	5 (3)	0	0	46
Vomiting	36 (18)	12 (6)	4 (2)	0	0	52
Rash[3]	39 (20)	13 (7)	3 (2)	0	0	55
Capecitabine N=191						
Any event	18 (9)	71 (37)	74 (39)	12 (6)	2 (1)	177
Diarrhea[2]	30 (16)	27 (14)	19 (10)	0	0	76
PPE syndrome	22 (12)	48 (25)	27 (14)	0	0	97
Nausea	52 (27)	28 (15)	3 (2)	0	0	83
Fatigue	21 (11)	19 (10)	6 (3)	1 (<1)	0	47
Vomiting	24 (13)	14 (7)	3 (2)	0	0	41
Rash[3]	17 (9)	7 (4)	2 (1)	0	0	26

1. Subjects who experienced the same event multiple times, but with different toxicities, were only counted once, at the maximum toxicity.
2. Diarrhea includes incidences of diarrhea, loose stools and frequent bowel movements.
3. Rash includes incidences of acne, dermatitis, eczema, erythema, folliculitis, rash, papular rash, and pustular rash.

- Serious adverse event/deaths/other significant events

The SAEs related to study medication are summarized for Study EGF100151 in Table 25 (for a cut-off 3 April 2006). Preliminary SAE data are available from the lapatinib clinical programme (all phases) up to a cut-off date of 30 April 2007. No significant changes were found at this later cut-off, where a total of 7859 subjects were enrolled in phase I, II and III studies (approximately 5975 subjects receiving lapatinib). This figure is approximate since some studies are ongoing and remain blinded. A total of 2986 SAEs were reported from 1595 individual subjects (see ten most frequently reported drug-related SAE in Table 26).

Table 25 - SAEs Related to Study Medication – Study EGF100151 (Safety Population, 3 April 2006 Cut-off)

Preferred Term	Lapatinib+Capecitabine N=198 n (%)	Capecitabine N=191 n (%)
Any related SAE	**23 (12)**	**18 (9)**
Diarrhea1	10 (5)	10 (5)
Dehydration	5 (3)	2 (1)
Ejection fraction decreased	5 (3)	0
Anemia	2 (1)	1 (<1)
Hypokalemia	2 (1)	1 (<1)
Mucosal inflammation	1 (<1)	2 (1)
Neutropenia	1 (<1)	2 (1)
Pulmonary embolism	1 (<1)	2 (1)
Vomiting	1 (<1)	2 (1)
Thrombocytopenia	0	2 (1)
Pyrexia	1 (<1)	1 (<1)
Rash2	1 (<1)	1 (<1)
Acute myeloid leukemia	1 (<1)	0
Deep vein thrombosis	0	1 (<1)
Dry mouth	0	1 (<1)
Escherichia sepsis	1 (<1)	0
Gastric ulcer	0	1 (<1)
Hypercalcemia	0	1 (<1)
Hyponatremia	1 (<1)	0
Hypovolemia	0	1 (<1)
Infectious diarrhea	0	1 (<1)
Pain of skin	1 (<1)	0
Prinzmetal angina	1 (<1)	0
Nausea	0	1 (<1)
Peripheral neuropathy	1 (<1)	0
Small intestinal obstruction	0	1 (<1)
Vasovagal syncope	1 (<1)	0
Ventricular dysfunction	0	1 (<1)

1. Diarrhea includes incidences of diarrhea, loose stools and frequent bowel movements.
2. Rash includes incidences of acne, dermatitis, eczema, erythema, folliculitis, rash, papular rash, and pustular rash.

Table 26 - Ten Most Frequently Reported Drug-Related SAE from the lapatinib clinical program (cut-off date of 30 April 2007)

MedDRA PT	Drug Related	Total (All Causalities)
Diarrhoea*	169	209
Vomiting*	66	134
Neutropenia	72	87
Ejection Fraction Decreased*	70	85
Dehydration*	59	113
Nausea*	44	77
Febrile Neutropenia	23	33
Left ventricular dysfunction*	22	26
Mucosal inflammation	18	21
Pyrexia	16	82

*Included in the proposed lapatinib SPC.

Deaths
Deaths within 30 days of the last dose were reported for 11 (6%) subjects in the lapatinib plus capecitabine group and 12 (6%) subjects in the capecitabine group (up to the 3 April 2006 cut-off date).

Hepatic safety
From a combined dataset of clinical trials and post-marketing data, there were 216 reports of hepatic events retrieved from the GlaxoSmithKline safety database as of 31 December 2007. A total of 11551 subjects were enrolled in the lapatinib clinical trials programme, of which it is estimated that 8702 subjects had received lapatinib and exposure to marketed products was estimated as 1318 patient-years as of September 2007, based on a 1250 mg daily dose. From the resulting subset of assessable reports, 39 'key' cases were identified (see Table 27 for a summary of reasons for exclusion). This yields an approximate incidence of 0.4% (32/8702) of hepatobiliary events in the lapatinib clinical programme and 0.5% (7/1318 patient-years) from the post-marketing surveillance data. Of these 39 key cases: 22 recovered upon discontinuation of treatment, 5 improved conditions, 9 unresolved and 3 were fatal. The median time to event was 49 days, being transaminase elevations the most frequently reported hepatic event. The data is suggestive of a drug-related effect.

Table 27 - Reasons for Excluding Assessable Reports from the Set of Key cases

Reason*	Number of Reports
Description of event is inconsistent with diagnostic criteria/definition	5
Time to onset is inconsistent with a possible drug effect	0
Alternative diagnosis or concurrent disease is very much more likely to have caused the event	130
Concurrent drug is very much more likely to have caused the event	22
Total number of assessable reports excluded from set of Key cases	177

*Only one reason for exclusion was allocated to each case and this is the first appropriate reason as listed above.

A summary of patients with liver-related AEs according to treatment arm, including a summary of AEs which occurred after the cross-over is included in Table 28 for study EGF100151 and in Table 29 for study EGF30001:

Table 28 - Summary of Patients with Hepatic Laboratory Abnormalities EGF100151

Hepatic Lab Abnormality, n (%)	Lapatinib+ Capecitabine (N=207)	Capecitabine	
		Monotherapy (N=201)	Cross-Over [a] (N=36)
>3 X ULN AST and/or ALT & >1.5 X ULN TBL [b]	3 (1.45)	7 (3.48)	1 (2.78)
>3 X ULN AST and/or ALT & >2 X ULN TBL [b]	3 (1.45)	5 (2.49)	1 (2.78)
ALT & AST elevations			
≥3 X ULN	7 (3.38)	7 (3.48)	1 (2.78)
≥5 X ULN	0	1 (0.5)	0
≥10 X ULN	0	0	0
≥20 X ULN	0	0	0
ALT elevations			
≥3 X ULN	8 (3.86)	12 (5.97)	1 (2.78)
≥5 X ULN	3 (1.45)	3 (1.49)	0
≥10 X ULN	0	1 (0.5)	0
≥20 X ULN	0	0	0
AST elevations			
≥3 X ULN	18 (8.7)	13 (6.47)	4 (11.11)
≥5 X ULN	5 (2.42)	6 (2.99)	1 (2.78)
≥10 X ULN	2 (0.97)	2 (1.0)	0
≥20 X ULN	1 (0.48)	0	0
TBL elevations			
>1.5 X ULN	42 (20.29)	27 (13.43)	5 (13.89)
>2 X ULN	20 (9.66)	17 (8.46)	3 (8.33)
ALP			
>1.5 X ULN	41 (19.81)	45 (22.39)	5 (13.89)

a. represents patients on capecitabine monotherapy who crossed-over to lapatinib plus capecitabine at the time of disease progression

b. Does not take into consideration an ALP of <2xULN as seen with Hy's Law criteria

c. Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase; ALP=alkaline phosphatase; TBL=total bilirubin; ULN upper limit normal

Table 29 - Summary of Patients with Hepatic Laboratory Abnormalities EGF30001

Hepatic Lab Abnormality, n (%)	Lapatinib + Paclitaxel (N=293)	Paclitaxel (N=286)
>3 X ULN AST and/or ALT & >1.5 X ULN TBL [d]	8 (2.73)	6 (2.1)
>3 X ULN AST and/or ALT & >2 X ULN TBL [d]	6 (2.05)	5 (1.75)
ALT & AST elevations		
≥3 X ULN	22 (7.51)	18 (6.29)
≥5 X ULN	8 (2.73)	5 (1.75)
≥10 X ULN	1 (0.34)	2 (0.7)
≥20 X ULN	0	1 (0.35)
ALT elevations		
≥3 X ULN	30 (10.24)	26 (9.09)
≥5 X ULN	12 (4.1)	10 (3.5)
≥10 X ULN	3 (1.02)	3 (1.05)
≥20 X ULN	1 (0.34)	1 (0.35)
AST elevations		
≥3 X ULN	34 (11.6)	34 (11.89)
≥5 X ULN	15 (5.12)	16 (5.59)
≥10 X ULN	4 (1.37)	5 (1.75)
≥20 X ULN	0	2 (0.7)
TBL elevations		
>1.5 X ULN	18 (6.14)	12 (4.2)
>2 X ULN	9 (3.07)	7 (2.45)
ALP		
>1.5 X ULN	81 (27.65)	68 (23.78)

d. patients received lapatinib plus paclitaxel 175 mg/m^2 every 3 weeks for 6 cycles followed by lapatinib monotherapy at the investigator's discretion

e. Does not take into consideration an ALP of <2 × ULN as seen with Hy's Law criteria

Due to the confounding effect of liver metastasis, data from adjuvant trials were analysed. As of December 2007, approximately 2593 subjects have been enrolled in two adjuvant studies (EGF106708 ALTTO and EGF105485 TEACH). Overall it is estimated that approximately 1354 of these 2593 adjuvant subjects will have received lapatinib. There were no hepatic events reported from study EGF106708 as of 31 December 2007. A sub-set of 9 adjuvant hepatic cases were identified from study EGF105485 (see laboratory abnormalities in Table 30). Of these 9 cases, 6 were identified as 'key' cases. Lapatinib was discontinued at the time of the hepatic event in all 6 subjects. Five subjects recovered (positive de-challenge), the sixth subject improved. A total of 4 (in the fifth case according to the table above, there was underlying progressive disease) subjects were identified as potential Hy's Law cases. All four subjects had received prior chemotherapy which included drugs such as anthracyclines (e.g. epirubicin), cyclophosphamide and tamoxifen which have been associated with hepatotoxicity. The crude incidence of hepatobiliary events in the adjuvant programme was estimated as 0.4% (6/1354).

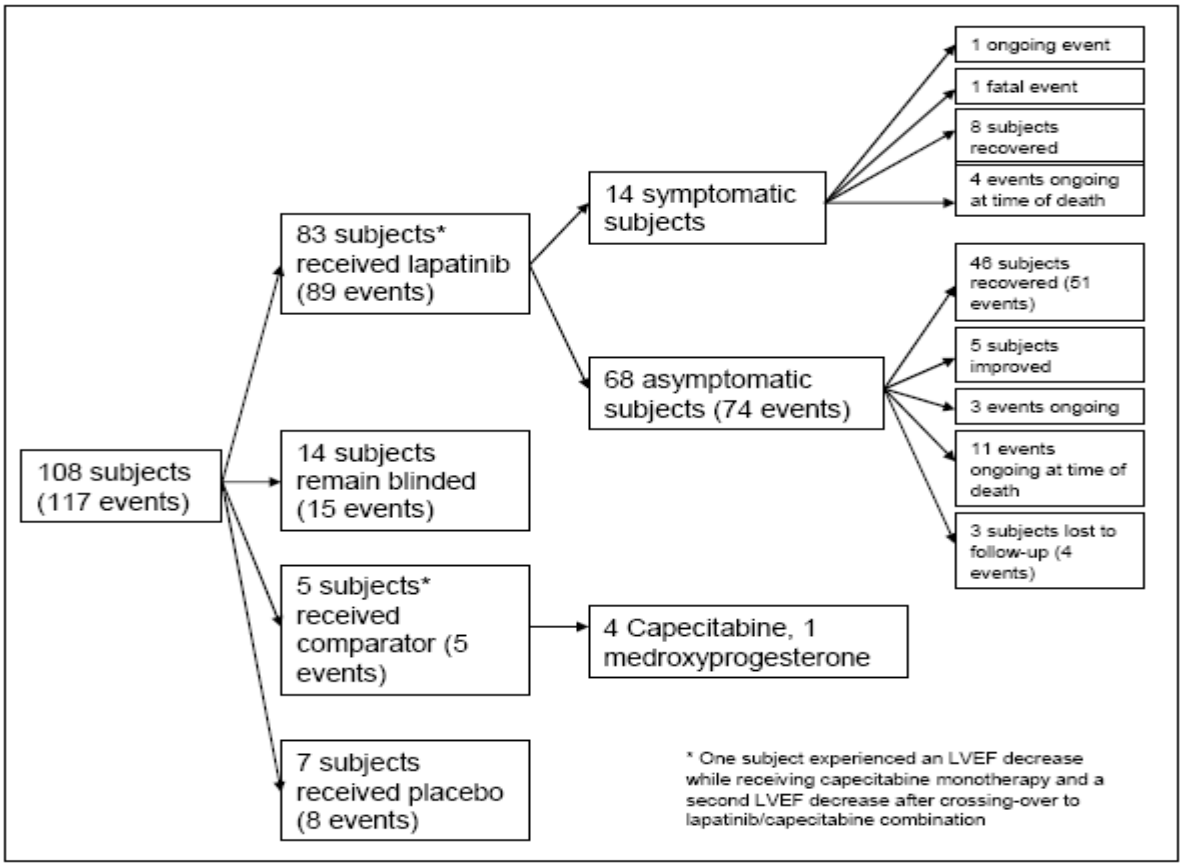
Table 30 - Summary of Patients with Hepatic Laboratory Abnormalities from Study EGF105485 ("TEACH")

Hepatic Lab Abnormality	Safety Population (N=2095) N (%)
>3 X ULN AST and/or ALT & >1.5 X ULN total bilirubin	5 (0.24)
>3 X ULN AST and/or ALT & >2 X ULN total bilirubin	3 (0.14)
ALT & AST elevations	
≥3 X ULN	17 (0.81)
≥5 X ULN	11 (0.53)
≥10 X ULN	4 (0.19)
≥20 X ULN	1 (0.05)
ALT elevations	
≥3 X ULN	29 (1.38)
≥5 X ULN	12 (0.57)
≥10 X ULN	5 (0.24)
≥20 X ULN	1 (0.05)
AST elevations	
≥3 X ULN	20 (0.95)
≥5 X ULN	14 (0.67)
≥10 X ULN	5 (0.24)
≥20 X ULN	2 (0.1)
Total bilirubin elevations	
>1.5 X ULN	20 (0.95)
>2 X ULN	7 (0.33)
Alkaline phosphatase	
>1.5 X ULN	24 (1.15)

Cardiac Safety

A summary of the decreased LVEF reports from the lapatinib clinical program (all phases) up to a cut-off date of 30 April 2007 is shown in Figure 4. The mean time to onset of decreased LVEF in the 83 lapatinib-treated subjects was 17 weeks (range: 2 weeks to 1 year). The mean LVEF decrease relative to baseline value was 28.3% (range: 20% to 66.7%). This corresponded to a mean absolute LVEF decrease of 18.4% from baseline (range: 11% to 46%). None of the cases was fatal.

Figure 4 - Summary of Reports of Decreased LVEF which met the Protocol Specific Definition (as of 30 April 2007) in 5975 lapatinib Subjects.



From the data collected from Study EGF100151 up to the 15 March 2007 cut-off, 2.1%s subjects both in the lapatinib plus capecitabine group and capecitabine group experienced decreased LVEF during the study. A total of 241 subjects received lapatinib + capecitabine (including patients who crossed over) and 191 subjects received capecitabine monotherapy.

Diarrhoea
From the 3 April 2006 dataset, diarrhoea was reported as an AE among 65% of subjects in the lapatinib plus capecitabine group and 40% of subjects in the capecitabine group. The severity of diarrhea was grade 1 or 2 in most subjects; however, grade 3 diarrhea was reported for approximately 12% of the subjects in the lapatinib plus capecitabine group and 11% of the subjects in the capecitabine group.

Rash
Rash was reported as an AE among 28% of subjects in the lapatinib plus capecitabine group and 14% of subjects in the capecitabine group (3 April 2006 cut-off, Study EGF100151). Most cases of rash were considered drug related and not serious (grades 1 or 2). Approximately two-thirds of subjects had one occurrence. Rash resolved in most cases in either group and did not lead to discontinuation from the study; no action was taken with respect to study medication in the majority of cases.

Palmarplantar erythrodysaethesia (PPE)
Approximately half the subjects in the study (3 April 2006 cut-off, Study EGF100151) had PPE (53% for lapatinib+capecitabine, 51% for capecitabine); most events were considered by the investigator to be drug related. The majority of these events were grade 1 or 2 and resolved without treatment or with dose adjustment.
The median time of onset was longer in the lapatinib plus capecitabine group than in the capecitabine group (median, 40 days versus 21 days) and the median duration was greater in the lapatinib plus capecitabine group than in the capecitabine group (median, 25.5 days vs. 17 days).

Few subjects in either treatment group withdrew from treatment because of PPE events (lapatinib plus capecitabine: 3%, capecitabine: 3%). Similar results were observed regardless of age group.

- Laboratory findings

A summary of the clinical chemistry parameters is shown in Table 31:

Table 31 - Summary of Maximum Toxicity Grade for Selected Clinical Chemistry Parameters at Any Post-Screening Visit – Study EGF100151 (Safety Population, 3 April 2006 cut-off)

Parameter	Visit	n	Number (%) of Subjects				
			Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Lapatinib + Capecitabine, N=198							
Haemoglobin	Screen	196	134 (68)	53 (27)	9 (5)	0	0
	Any Post	195	86 (44)	84 (43)	24 (12)	1 (<1)	0
Platelets	Screen	196	183 (93)	12 (6)	1 (<1)	0	0
	Any Post	195	160 (82)	33 (17)	1 (<1)	1 (<1)	0
Total WBC	Screen	196	174 (89)	20 (10)	2 (1)	0	0
	Any Post	195	122 (63)	53 (27)	19 (10)	0	1 (<1)
Neutrophils	Screen	186	176 (95)	6 (3)	2 (1)	2 (1)	0
	Any Post	189	147 (78)	23 (12)	13 (7)	5 (3)	1 (<1)
Granulocytes	Screen	9	9 (100)	0	0	0	0
	Any Post	24	20 (83)	2 (8)	1 (4)	0	1 (4)
Lymphocytes	Screen	195	141 (72)	28 (14)	22 (11)	4 (2)	0
	Any Post	195	108 (55)	40 (21)	31 (16)	15 (8)	1 (<1)
Capecitabine, N=191							
Hemoglobin	Screen	188	134 (71)	45 (24)	5 (3)	3 (2)	1 (<1)
	Any Post	187	88 (47)	83 (44)	14 (7)	2 (1)	0
Platelets	Screen	188	185 (98)	3 (2)	0	0	0
	Any Post	187	156 (83)	28 (15)	1 (<1)	1 (<1)	1 (<1)
Total WBC	Screen	188	161 (86)	21 (11)	5 (3)	1 (<1)	0
	Any Post	187	104 (56)	53 (28)	28 (15)	1 (<1)	1 (<1)
Neutrophils	Screen	175	163 (93)	9 (5)	2 (1)	0	1 (<1)
	Any Post	177	122 (69)	24 (14)	25 (14)	4 (2)	2 (1)
Granulocytes	Screen	13	10 (77)	1 (8)	1 (8)	1 (8)	0
	Any Post	17	12 (71)	2 (12)	2 (12)	0	1 (6)
Lymphocytes	Screen	188	127 (68)	34 (18)	22 (12)	5 (3)	0
	Any Post	187	93 (50)	41 (22)	36 (19)	15 (8)	2 (1)

There were no apparent differences in haematologic abnormalities at baseline or during therapy between treatment groups. Only neutropenia was slightly more commonly reported for the capecitabine monotherapy arm (grade 2 14 vs. 7%).

Hepatic Laboratory Abnormalities:

See hepatic safety section.

- Safety in special populations

Age: About 85% of the patients in the pivotal study were below 65 years of age and 1% above 75.

Hepatic impairment: About 50% of the patients in the pivotal study had liver metastases, but data from patients with more than mild impairment are sparse. Lapatinib is metabolised by the liver and moderate impairment increased systemic exposure about 50%.

Ethnicity: No specific analysis was presented. About 90% of the patients in the pivotal study were Caucasians. Ethnicity might be of importance with respect to pulmonary safety.

Renal impairment: No specific analysis was presented. Estimated creatinine clearance >50 was required for inclusion in the pivotal study.

- Safety related to drug-drug interactions and other interactions

No studies have been submitted.

- Discontinuation due to adverse events

Adverse events that led to discontinuation from the study were reported for 24% of subjects in the lapatinib plus capecitabine group and 23% of subjects in the capecitabine group from the 3 April 2006 dataset. The most common reason for discontinuation from the study medication was diarrhoea (7% in the lapatinib plus capecitabine group and 6% in the capecitabine group) as shown in Table 32:

Table 32 - Summary of AEs Leading to Discontinuation of Study Medication Reported by More than One Subject Regardless of Relationship – Study EGF100151 (Safety Population, 3 April 2006 cut-off)

Preferred Term	Lapatinib+Capecitabine N=198 n (%)	Capecitabine N=191 n (%)
Any SAE	**48 (24)**	**44 (23)**
Diarrhoea[1]	13 (7)	11 (6)
Dehydration	6 (3)	4 (2)
Dyspnea	3 (2)	3 (2)
Ejection fraction decreased	5 (3)	2 (1)
Vomiting	4 (2)	4 (2)
Hypokalemia	3 (2)	1 (<1)
Nausea	1 (<1)	3 (2)
Pulmonary embolism	2 (1)	2 (1)
Pyrexia	2 (1)	2 (1)
Anemia	2 (1)	1 (<1)
Mucosal inflammation	1 (<1)	2 (1)
Neutropenia	1 (<1)	2 (1)
CNS metastases	2 (1)	0
Erysipelas	2 (1)	0
Thrombocytopenia	0	2 (1)
Ventricular dysfunction	0	2 (1)
Convulsion	1 (<1)	1 (<1)
Disease progression	1 (<1)	1 (<1)
Peripheral edema	1 (<1)	1 (<1)
Pleural effusion	1 (<1)	1 (<1)
Rash2	1 (<1)	1 (<1)

Data Source: Table 8.9

1. Diarrhea includes incidences of diarrhea, loose stools and frequent bowel movements.
2. Rash includes incidences of acne, dermatitis, eczema, erythema, folliculitis, rash, papular rash, and pustular rash.

- Post marketing experience

As of 31st May 2007, 105 adverse events have been received from 33 subjects in the French nominative ATU ("temporary authorisation for use") programme for lapatinib and capecitabine in the treatment of metastatic breast cancer. Overall enrolment for the ATU programme was 403 patients as of 31 May 2007. Diarrhoea, nausea, vomiting, erythema and fatigue were the most frequently reported events.

There were ten (10) deaths reported from the ATU programme. All were indicated to be associated with the advance clinical condition and cancer progression in these subjects. There have been no reports of decreased left ventricular ejection fraction or interstitial pneumonitis from the ATU as of 31 May 2007.

Discussion on clinical safety

The most common adverse reactions (>25%) during therapy with lapatinib plus capecitabine were gastrointestinal (diarrhoea, nausea, and vomiting) or dermatologic (palmar-plantar erythrodysesthesia [PPE] and rash). Diarrhoea was the most common adverse reaction resulting in discontinuation of treatment (lapatinib plus capecitabine: 5%, capecitabine: 3%). The incidence of PPE was similar in both lapatinib plus capecitabine and capecitabine alone treatment arms.

Left ventricular ejection fraction (LVEF) decreases have been reported in approximately 2.1 % of patients receiving lapatinib and were asymptomatic in more than 90% of cases. LVEF decreases resolved or improved in more than 60% of cases on discontinuation of treatment with lapatinib. Symptomatic LVEF decreases were observed in approximately 0.1% of patients who received lapatinib monotherapy. Observed symptoms included dyspnoea, cardiac failure and palpitations. All events resolved promptly on discontinuation of lapatinib. LVEF decreases were reported at the same frequency in patients who received lapatinib in combination with capecitabine, as compared to patients receiving capecitabine alone. Warnings addressing this risk have been included in sections 4.2, 4.4 and 4.8 of the SPC.

Hyperbilirubinemia is a common event for this patient population (EGF100151, EGF30001). In addition, available results from the adjuvant setting (TEACH study), e.g. with respect to symptomatic events (4 per 1000+), are clearly compatible with an overall hepatic event rate higher than 1%. As add-on to paclitaxel, ALT and ALP events also increased with more than 1%. Hepatotoxicity has been included as a "common" adverse event in section 4.8 of the SPC. In addition a warning addressing this risk has been included in the SPC in section 4.4.

Diarrhoea occurred in approximately 58% of patients who received lapatinib monotherapy. Most cases of diarrhoea were grade 1 or 2 and did not result in discontinuation of treatment with lapatinib, however, warnings have been included in section 4.4 and 4.8 of the SPC.

Rash occurred in approximately 37% of patients who received lapatinib monotherapy. Rash was generally low grade and did not result in discontinuation of treatment with lapatinib (risk stated in section 4.8 of the SPC.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan

Table Summary of the risk management plan

Safety concern	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
Hepatic events	Routine pharmacovigilance Pharmacogenetics study of subjects who experienced hepatic events (subject to representative availability of DNA samples and clinical phenotype from ongoing and future lapatinib clinical studies).	Proposed Warning in Section 4.4 of the SPC (Proposed wording: "*Hepatotoxicity has occurred with lapatinib use and may in rare cases be fatal. Liver function (transaminases, bilirubin and alkaline phosphatase) should be monitored before initiation of treatment and monthly thereafter, or as clinically indicated. Lapatinib dosing should be discontinued if changes in liver function are severe and patients should not be retreated.*"). Proposed addition to Adverse Reactions in Section 4.8 of the SPC "***Hepatobiliary disorders**: Common - hyperbilirubinaemia, hepatotoxicity*"
Decreased LVEF	Routine pharmacovigilance Pharmacogenetics study of subjects who experienced decreased LVEF	Warning in section 4.4 of the SPC (*LVEF should be evaluated in 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. LVEF should continue to be evaluated during treatment with lapatinib to ensure that LVEF does not decline to an unacceptable level*) and information in dose/administration section Adverse Reactions in section 4.8 of the SPC
Pneumonitis	Routine pharmacovigilance Study of lapatinib/capecitabine combination safety in Japanese patients (EGF1009749 - to start June 2007)	Warning in section 4.4 of the SPC (*Patients should be monitored for symptoms of pulmonary toxicity*) Adverse Reactions in section 4.8 of the SPC
Diarrhoea	Routine pharmacovigilance Pharmacogenetics study of subjects who experienced diarrhoea	Warning in section 4.4 of the SPC (*Proactive management of diarrhoea with anti-diarrhoeal agents is important. Severe cases of diarrhoea may require administration of oral or intravenous electrolytes and fluids, and interruption or discontinuation of lapatinib*) Adverse Reactions in section 4.8 of the SPC
Rash	Routine pharmacovigilance Pharmacogenetics study of	Adverse reaction in section 4.8 of the SmPC

	patients who experienced rash.	
No thorough QT/QTc study can be conducted due to unfavourable risk in healthy volunteers	QT/QTc sub-study to be included in Phase III study in women with early-stage breast cancer (EGF105485).	Activity to be determined if safety signal is identified
Children and the Elderly	Routine pharmacovigilance	Comment in section 4.2 of the SPC
Pregnant or lactating females	Routine pharmacovigilance	Warning in section 4.6 of the SPC (*Lapatinib should not be used during pregnancy unless clearly necessary. Women of childbearing potential should use contraception and avoid becoming pregnant while receiving treatment with lapatinib*)
Patients with hepatic disease	Routine pharmacovigilance	Warning in section 4.2 of the SPC (*Administration of lapatinib to patients with moderate to severe hepatic impairment should be undertaken with caution due to increased exposure to the medicinal product. Insufficient data are available in patients with hepatic impairment to provide a dose adjustment recommendation*)
Patients with renal disease	Routine pharmacovigilance	Warning in section 4.2 of the SPC (*No dose adjustment is necessary in patients with mild to moderate renal impairment. Caution is advised in patients with severe renal impairment as there is no experience of lapatinib in this population*)
Patients with low cardiac ejection fraction	Routine pharmacovigilance	Warning in sections 4.2 and 4.4 of the SPC (*Caution should be taken if lapatinib is to be administered to patients with conditions that could impair left ventricular function*) Adverse Reactions in section 4.8 of the SPC
Patients of different racial and / or ethnic origins	Routine pharmacovigilance Study report (EGF20009) in preparation	Activity to be determined if safety signal is identified
Potential for medication errors	Routine pharmacovigilance	Section 4.1 and 4.2 of the SPC

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this medicinal product is considered satisfactory when used with the conditions defined in the SPC. The documentation provided for the active substance lapatinib is comprehensive and adequately detailed. The pharmaceutical development is adequate for this oral formulation and took into consideration properties such as particle size and the stability of the active substance. The excipients are those typically used for tablets. Similarly, the packaging material is well documented and no incompatibility has been noticed. The validation of the manufacturing process ensures consistency and reproducibility of the finished product. The finished product has been satisfactorily controlled and stability studies conducted under ICH conditions showed that the product is stable throughout the proposed shelf life.

Non-clinical pharmacology and toxicology

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 umbilical artery, cervical rib and precocious ossification) occurred in rats at ≥60 mg/kg/day (4 times the expected human clinical exposure). In rabbits, lapatinib was associated with maternal toxicity at 60 and 120 mg/kg/day (8% and 23% of the expected human clinical exposure, respectively) and abortions at 120 mg/kg/day. At ≥60 mg/kg/day there were decreased foetal body weights, and minor skeletal variations. In the rat pre- and postnatal development study, a decrease in pup survival occurred between birth and postnatal day 21 at doses of 60 mg/kg/day or higher (5 times the expected human clinical exposure). The highest no-effect dose for this study was 20 mg/kg/day.

There were no effects on male or female rat gonadal function, mating, or fertility at doses up to 120 mg/kg/day (females) and up to 180 mg/kg/day (males) (8 and 3 times the expected human clinical exposure, respectively). The effect on human fertility is unknown.

Lapatinib was not clastogenic or mutagenic in a battery of assays including the Chinese hamster chromosome aberration assay, the Ames assay, human lymphocyte chromosome aberration assay and an *in vivo* rat bone marrow chromosome aberration assay.

Efficacy

This submission relies on a pivotal Phase III randomised, open label, active controlled trial conducted in ErbB2 over-expressing, locally advanced or metastatic breast cancer patients, who were progressing after prior treatment that included anthracyclines, taxanes and trastuzumab. Patients were randomized to receive either lapatinib 1250 mg once daily (continuously) plus capecitabine (2000 mg/m^2/day on days 1-14 every 21 days), or to receive capecitabine alone (2500 mg/m^2/day on days 1-14 every 21 days). The primary endpoint was time to progression (TTP) as assessed by an independent review panel. A delay of the median time to progression in the order of 6 to 8 weeks was observed for the combination of lapatinib plus capecitabine compared to capecitabine alone.
No statistically significant effect has been observed on overall survival for the combination of lapatinib plus capecitabine compared to capecitabine alone.

A reduced incidence of CNS metastases has been observed in secondary analyses. On the combination arm, there were 9 (1.5 %) progressions in the central nervous system as compared with the 18 (9%) progressions on the capecitabine alone arm.

Safety

Overall, the tolerability of the combination regimen proposed for licensing appears rather similar to capecitabine monotherapy at the licensed, slightly higher dose intensity (2500 versus 2000 mg/m2/day in combination with lapatinib). An increased incidence of diarrhoea is observed (58% of patients), while fatigue is less frequently reported. Rash occurred in approximately 37% of patients who received lapatinib monotherapy. Rash was generally low grade and did not result in discontinuation of treatment with lapatinib

With respect to severe and serious adverse reactions there is no overall difference, but similar to what is reported for trastuzumab, there were cardiac events, the cumulative incidence of decreased LVEF in the lapatinib clinical programme being about 2%, with few patients experiencing symptomatic decreases. The majority of the LVEF decreases were reversible. The incidence of hepatotoxicity is estimated to be about 1% or higher. Other events with putative casual relationship to lapatinib include interstitial pneumonitis.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The user testing report submitted is adequate and in accordance with current recommendations.

Risk-benefit assessment

Lapatinib treatment was associated with an increased time to progression. Although reduced incidence of CNS metastases has been suggested it needs to be confirmed prospectively and no survival benefit has been demonstrated for this patient population. On the other hand, treatment with lapatinib was associated with mild toxicity including frequent low grade diarrhoea, skin toxicity, hepatotoxicity and infrequent cardiac and possibly pulmonary toxicity. These concerns do not constitute blocking issues for an anti-cancer compound and therefore, the benefit-risk is concluded to be favourable. However, there is a need to gain more understanding about the benefit-risk profile of the lapatinib plus capecitabine combination and it is important to further confirm the effect on reducing the incidence of CNS metastases and the effect on overall survival.

As per CHMP request, an oncology Scientific Advisory Group (SAG) meeting was convened on 5 September 2006 to provide advice on the following questions raised by the Committee

The first question related to the discrepancy between TTP/PFS data and survival, especially in relation to the most mature data set, i.e. the first 2x100 patients enrolled in the pivotal study. The experts were asked if based on their experience and the data presented, is it likely that imbalances as regards prognostic factors can explain this imbalance or if it is more likely that differential activity of administered next-line therapies is an explanation; alternatively it was asked if a difference in TTP in this study population a poor predictor of a difference in survival, taking into account also that TTP and survival in the capecitabine alone arm were better than expected based on historical data. The SAG agreed unanimously that the data presented by the applicant, both TTP/PFS and OS have been properly analysed and that possible imbalances arising from cross-over, baseline characteristics or next line therapies are unlikely to affect the overall conclusions. The sensitivity analyses provided by the applicant proved consistency in the results and possible sources of bias have been taken into account. The SAG expressed its concerns about the lack of a statistically significant overall survival data for the patients following the treatment with Tyverb. The SAG acknowledged that the prolonged time to death after tumour progression seen in this particular trial might have diluted the apparent treatment effect, however, due to the short survival expectancy in this group of patients, OS would have been a more adequate primary endpoint.

The SAG was also asked if the estimated benefit in terms of TTP for lapatinib as add-on to capecitabine of about 6 weeks was considered clinically meaningful. By majority, the SAG was of the opinion that 6 weeks improvement in median TTP is not clinically meaningful in the context of treatment of advanced breast cancer in late lines of treatment. The SAG considered that additional evidence of efficacy should be presented by the applicant in order to justify a positive benefit for the treatment, especially considering that overall survival could not be demonstrated in the pivotal trial.

Following the SAG advice the CHMP considered that further data was needed in order to further clarify the clinical meaningfulness of the efficacy seen in terms of TTP and that additional evidence should be provided confirming the effect on reducing the incidence of CNS metastases and overall survival. The applicant presented an updated overall survival analysis showing a trend to improved survival in the combination arm. In addition a reduced incidence of CNS metastases was observed in secondary analyses (see clinical efficacy). The applicant presented a number of arguments at an oral explanation with the CHMP. In summary, the applicant argued that there are no approved ErbB2-directed therapy after trastuzumab, that treatment with lapatinib plus capecitabine was associated with a number of important clinical benefits in terms of TTP, response rate, overall survival, incidence of brain metastasis as 1st site of recurrence, time without symptoms as measured by QTWiST, and that it has a number of favourable characteristics in that it is an oral treatment, that does not prolong hospitalizations or impair health-related quality of life. Furthermore, treatment with lapatinib plus capecitabine was associated with minimal severe or life-threatening toxicity, low cardiotoxicity, and minimal lung toxicity. The applicant concluded that the observed benefits of the combination largely exceeded the risk for the patients in the target indication, and that unmet needs will be met.

The CHMP considered all the new evidence submitted by the applicant and the argumentation put forward by the applicant and the SAG experts. The CHMP considered that the benefit-risk balance for the combination of lapatinib plus capecitabine was positive. There is a need however to obtain further data on the incidence of CNS metastases and the effect on overall survival. Thus, the CHMP proposed a conditional marketing authorisation, after having consulted the applicant. The CHMP considered that lapatinib is a medicinal product which aims at the treatment of a life-threatening disease, and therefore falls within the scope of Regulation (EC) No 507/2006, and that fulfils the requirements of Article 4 of Regulation (EC) No 507/2006 based on the following grounds:

a. Efficacy in terms of TTP prolongation has been demonstrated in a pivotal Phase III randomised, open label, active controlled trial conducted in ErbB2-overexpressing, locally advanced or metastatic breast cancer patients, who were progressing after prior treatment that included taxanes, anthracyclines and trastuzumab. Overall, a delay of the median time to progression in the order of 6 to 8 weeks was observed. A favourable effect of lapatinib plus capecitabine combination compared to capecitabine alone was also observed in terms of secondary endpoints including progression-free survival, response rate and duration of response. In addition a reduced incidence of CNS metastases has been observed in secondary analyses. Treatment with lapatinib was associated with mild toxicity including frequent low grade diarrhoea and skin toxicity and infrequent cardiac and possibly pulmonary toxicity. These concerns do not constitute blocking issues for an anti-cancer compound in this indication. Therefore, the risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive.

b. There is a need to gain more understanding about the benefit-risk profile of the lapatinib plus capecitabine combination. To this end, it is important to further confirm the effect on reducing the incidence of CNS metastases and the effect on overall survival. The applicant will provide comprehensive clinical data in a new Phase III randomised, controlled clinical study to evaluate a decreased incidence of brain metastases as a site of relapse with a lapatinib-containing therapy compared with an appropriate, trastuzumab-containing control arm. The applicant has provided a detailed proposal about this study and estimated timelines for completing the trial. In addition the applicant will perform and submit an updated analysis of survival data for study EGF100151. Thus, it is likely that the applicant will be in a position to provide the comprehensive clinical data.

c. Currently there are only few treatment options approved for the treatment of advanced or metastatic breast cancer patients, who were progressing after prior treatment that included taxanes,

anthracyclines and trastuzumab. Lapatinib in combination with capecitabine has shown to prolong time to progression and this effect was clinically significant in this patient population. Lapatinib may in addition have a positive effect on the incidence of brain recurrence, although this effect will need to be confirmed. In accordance to the definition of Article 4, paragraph 2, of Regulation (EC) No 507/2006, the medicinal product concerned will be of major therapeutic advantage to those affected. Therefore, unmet medical needs will be fulfilled.

d. In view of the favourable benefit-risk profile, the immediate availability on the market outweighs the risk inherent in the fact that additional data are still required.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the risk-benefit balance of Tyverb in combination with capecitabine in the treatment of:

Patients with advanced or metastatic breast cancer whose tumours overexpress ErbB2 (HER2). Patients should have progressive disease following prior therapy which must include anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting

was favourable, and therefore recommended the granting of a conditional marketing authorisation.

Divergent opinions were based on the following considerations:

- No clear effect has been shown in terms of overall survival and other clinical benefit endpoints. The activity observed in terms of TTP or PFS is low and it is highly questionable whether this constitutes a meaningful clinical benefit for ErbB2 over-expressing, locally advanced or metastatic breast cancer patients, who were progressing after prior treatment that included taxanes, anthracyclines and trastuzumab.

- Treatment with lapatinib was associated with frequent, low grade diarrhoea and skin toxicity and infrequent but significant cardiac and possibly pulmonary toxicity.

- The activity observed for lapatinib was too low to outweigh the risks associated with treatment with lapatinib.

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