



Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report
for
Lapatinib

Proprietary Product Name: Tykerb
Submission No: PM-2009-01276-3-4
Sponsor: GlaxoSmithKline Australia Pty Ltd



June 2010

Contents

I.	Introduction to Product Submission	3
	Submission Details.....	3
	Product Background.....	3
	Regulatory Status	4
	Product Information	4
II.	Quality Findings	4
	Quality Summary and Conclusions.....	4
III.	Nonclinical Findings	5
	Introduction.....	5
	Pharmacology.....	5
	Pharmacokinetics	5
	Toxicology	6
	Nonclinical Summary and Conclusions	9
IV.	Clinical Findings	10
	Introduction.....	10
	Pharmacokinetics	10
	Pharmacodynamics	12
	Efficacy	12
	Safety	19
	Clinical Summary and Conclusions	29
V.	Pharmacovigilance Findings	31
	Risk Management Plan	31
VI.	Overall Conclusion and Risk/Benefit Assessment	32
	Quality.....	32
	Nonclinical	32
	Clinical.....	32
	Risk Management Plan (RMP)	34
	Risk-Benefit Analysis	34
	Outcome	36
	Attachment 1. Product Information	36

I. Introduction to Product Submission

Submission Details

<i>Type of Submission</i>	Extension of Indications
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	26 May 2010
<i>Active ingredient(s):</i>	Lapatinib
<i>Product Name(s):</i>	Tykerb
<i>Sponsor's Name and Address:</i>	GlaxoSmithKline Australia Pty Ltd 1061 Mountain Highway Boronia Vic 3155
<i>Dose form(s):</i>	Tablets
<i>Strength(s):</i>	250 mg
<i>Container(s):</i>	Foil blister pack
<i>Pack size(s):</i>	Packs of 70, 84 and 168
<i>Approved Therapeutic use:</i>	<p>Tykerb in combination with an aromatase inhibitor is indicated for the treatment of post-menopausal women with hormone receptor-positive metastatic breast cancer whose tumours overexpress HER2 (ErbB2) and for whom hormonal therapy is indicated.</p> <p>Tykerb, in combination with capecitabine, is indicated for the treatment of patients with advanced/metastatic breast cancer whose tumours overexpress HER2 (ErbB2) and whose tumours have progressed after treatment with an anthracycline, a taxane and trastuzumab.</p>
<i>Route(s) of administration:</i>	Oral
<i>Dosage:</i>	1500 mg once daily until disease progression or unacceptable toxicity (the currently approved dose in combination with capecitabine is 1250 mg daily).
<i>ARTG Number:</i>	132305

Product Background

Lapatinib is a tyrosine kinase inhibitor that inhibits the epidermal growth factor receptor proteins EGFR (ErbB1) and HER2 (ErbB2). HER2 is overexpressed in HER2-positive breast cancer. Lapatinib arrests the growth of EGFR- and HER2-dependent tumours. It is currently registered for the treatment, in combination with capecitabine, of advanced HER2-positive breast cancer after an anthracycline, a taxane and trastuzumab. Aromatase inhibitors (for example, letrozole, exemestane, anastrozole) inhibit oestrogen synthesis and are registered for the treatment of post-menopausal women with hormone receptor-positive breast cancer.

Lapatinib absorption is slow and variable with a mean time to maximal concentration (t_{max}) of 4 hours. The drug is extensively metabolized and has an effective elimination half-life of 24 hours. Interactions with other drugs are likely. Common adverse reactions are decreased left ventricular

ejection fraction, hyperbilirubinaemia, gastrointestinal effects, fatigue and rash. Serious effects in addition to decreased ejection fraction are hepatotoxicity and interstitial lung disease.

The registered aromatase inhibitors letrozole, exemestane and anastrozole are rapidly absorbed, extensively metabolized and have terminal half-lives of 1-2 days. The recommended dose is one tablet daily (2.5 mg letrozole, 25 mg exemestane or 1 mg anastrozole). Adverse effects are due to oestrogen deprivation and include hot flushes, arthralgia, nausea, fatigue and osteoporosis. Cytochrome P450 isozyme 3A4 is common to the metabolism of two of the aromatase inhibitors (letrozole, exemestane) and lapatinib.

Trastuzumab (Herceptin), marketed by Roche, is a drug with a similar but more selective action than lapatinib. It is a monoclonal antibody directed against the HER2 receptor. In advanced HER2-positive breast cancer, trastuzumab is registered for the following indication: “in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone receptor positive metastatic breast cancer”. It is also registered for first line treatment of metastatic breast cancer in combination with a taxane.

Lapatinib is presently approved to be utilised in combination with capecitabine as indicated for the treatment of patients with advanced/metastatic breast cancer whose tumours overexpress HER2 and whose tumours have progressed after treatment with an anthracycline, a taxane and trastuzumab. The proposed new indication is for patients with metastatic breast cancer as follows:

Lapatinib in combination with an aromatase inhibitor is indicated for the treatment of patients with hormone sensitive metastatic breast cancer whose tumours overexpress HER2.

Regulatory Status

A similar application to the current Australian submission was approved in the USA on 29 January 2010 with the following indication:

In combination with letrozole for the treatment of postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated.

A similar application to the current Australian submission was granted a Positive Opinion by the European Union (EU) Committee for Medicinal Products for Human Use (CHMP) on 18 February 2010 and the date of the European Commission’s adopted decision was 5 May 2010. The indication in the EU is:

For the treatment of patients with breast cancer, whose tumours overexpress HER2 (ErbB2); in combination with an aromatase inhibitor for postmenopausal women with hormone receptor positive metastatic disease, not currently intended for chemotherapy. The patients in the registration study were not previously treated with trastuzumab or an aromatase inhibitor.

Similar applications are presently under review in Canada, New Zealand and Switzerland and further applications are planned.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Quality Summary and Conclusions

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical Findings

Introduction

Tykerb (lapatinib) is currently approved, in combination with capecitabine, for the treatment of patients with advanced/metastatic breast cancer whose tumours overexpress HER2 (ErbB2) and whose tumours have progressed after treatment with an anthracycline, a taxane and trastuzumab. GlaxoSmithKline Australia Pty Ltd has applied to extend the indications for lapatinib to include, in combination with an aromatase inhibitor, the treatment of patients with hormone sensitive metastatic breast cancer whose tumours overexpress HER2 (ErbB2).

In support of the current application, the sponsor submitted two *in vitro* studies (one primary pharmacology study and one haemolysis study). The haemolysis study is not directly relevant to the current application but is included here for completeness. Two carcinogenicity studies were submitted previously for changes to the PI accompanying a Safety Notification. These studies have been included in this evaluation.

The proposed indication involves a change in dose for lapatinib, from 1250 mg/day to 1500 mg/day. Therefore a comparison of exposures from each dose along with a re-evaluation of impurity levels is included in this report.

Pharmacology

Primary pharmacology

Lapatinib inhibits autophosphorylation and substrate phosphorylation activity of the epidermal growth factor receptor (EGFR) and the ErbB2 receptor, and has been shown to inhibit the proliferation of cell lines that overexpress these receptors. In the newly submitted *in vitro* pharmacology study, gene expression profiling indicated the addition of lapatinib increased the level of oestrogen and progesterone receptors in ErbB2 overexpressing cell lines, suggesting a possible interaction of the ErbB receptors and the steroid hormone pathway. However, the efficacy of a lapatinib/aromatase inhibitor combination has not been assessed in nonclinical models.

Pharmacokinetics

Pharmacokinetic Drug Interactions

No pharmacokinetic drug interaction studies with the proposed combinations were submitted in the nonclinical package. The sponsor provided a discussion of potential pharmacokinetics drug interactions with the 3 currently-registered aromatase inhibitors, letrozole, anastrozole and exemestane, based on information contained in the relevant PI documents (Femara, Armidex and Aromasin), respectively. It was noted that information about the pharmacokinetics of lapatinib and letrozole following co-administration was contained in the clinical data submitted and therefore was not evaluated by the nonclinical evaluator. Relevant details of possible interactions between lapatinib and the other aromatase inhibitors are outlined below.

The metabolism of lapatinib involves oxidation, as well as N- and O-dealkylation, reactions involving primarily cytochrome P450 (CYP) 3A4/5 with some involvement from CYP2C8 and CYP2C19. While anastrozole inhibited CYP3A4 *in vitro*, it is unlikely to result in clinically-significant inhibition. Exemestane does not inhibit CYPs. Therefore, neither anastrozole nor exemestane is likely to affect the rate of lapatinib metabolism. Lapatinib is an inhibitor of CYP3A4, CYP2C8, CYP1A2, CYP2C9, CYP2C19 and CYP2D6. Though exemestane is metabolised by CYP3A4, based on clinical data in the Aromasin PI, there is unlikely to be an effect on its exposure due to CYP3A4 inhibition. As the enzymes involved in anastrozole metabolism, which involves N-dealkylation, hydroxylation and glucuronidation, have not been identified, possible CYP-mediated interactions between lapatinib and this compound cannot be predicted.

The distribution of lapatinib is modulated by P-glycoprotein and the breast cancer resistance protein (BCRP). The interaction of anastrozole and exemestane with transporters is not known. The sponsor states that exemestane is highly lipophilic and unlikely to interact with transporters. However, the potential for interactions between anastrozole and lapatinib via transporters remains largely unknown.

Taken together, there is unlikely to be clinically significant CYP-mediated pharmacokinetic interactions between lapatinib and exemestane. Based on clinical data in the submission, there do not appear to be noticeable interactions with the lapatinib-letrozole combination. However, there is insufficient information available to determine if there are potential interactions between lapatinib and anastrozole. This would need to rely solely on clinical data.

Relative exposure

The application for the extension of indications for lapatinib includes an increase in the dose of lapatinib from 1250 mg/day to 1500 mg/day. Animal to human exposure ratios used to determine safety margins in the original application for lapatinib were calculated using a clinical area under the plasma concentration time curve from zero to 24 hours (AUC_{0-24h}) of ~ 45.5 $\mu\text{g}\cdot\text{h}/\text{mL}$ and a maximal plasma concentration (C_{max}) of 3.2 $\mu\text{g}/\text{mL}$ obtained from Study EGF10005 in which patients received 1250 mg/day lapatinib with capecitabine. Though it is unclear if the AUC_{0-24h} and C_{max} data reported in Clinical Study Report EGF10030 refer to a 1250 mg or a 1500 mg dose, the values are within ranges previously reported for a 1600 mg dose of lapatinib (that is, AUC_{0-24h} 26-29 $\mu\text{g}\cdot\text{h}/\text{mL}$ and C_{max} 1.9-2.1 $\mu\text{g}/\text{mL}$) and are considered acceptable for toxicological exposure margin determinations for the higher dose, 1500 mg. As the AUC and C_{max} for lapatinib when co-administered with the aromatase inhibitor, letrozole, appear to be lower (27 $\mu\text{g}\cdot\text{h}/\text{mL}$ and 1.9 $\mu\text{g}/\text{mL}$), there are no additional toxicological concerns with the proposed higher dose.

Toxicology

Nonclinical studies with the proposed combinations have not been conducted. Previous toxicological studies with lapatinib suggested the target organs as the skin (lesions, ulcerations, erosions), gastrointestinal tract (mucosal/mucosal gland atrophy/degeneration/necrosis, erosions/ulcerations), liver (hepatocyte hypertrophy, centrilobular degeneration), lungs (macrophage infiltrates), and lymphoid organs (lymphoid hyperplasia, macrophage infiltration and haematopoiesis of the spleen and/or thymus). Leukocytosis and mild anaemia with bone marrow hypercellularity were also observed. The majority of these toxic effects occurred at clinically relevant exposures.

Shared target organs of toxicity for lapatinib and the aromatase inhibitors include the skin (dermal lesions, epidermal ulceration, hyperkeratosis; letrozole), the liver (hepatocellular hypertrophy, vacuolation; anastrozole, letrozole and exemestane), lymphoid tissue (depletion/atrophy and haematopoiesis in the spleen and/or thymus; anastrozole and letrozole), and bone marrow (hypercellularity; anastrozole and letrozole). Gastrointestinal (GI) tract toxicity with mucosal gland necrosis occurred with exemestane. Leukocytosis and anaemia have been observed with anastrozole and letrozole. Therefore, effects on the skin, liver, GI tract and lymphoid tissue maybe expected to be greater with the proposed combinations compared with the individual components.

Carcinogenicity

The carcinogenic potential of lapatinib by the oral route was investigated in 2-year studies in mice and rats (GLP compliant). Group sizes were appropriate and dual vehicle control groups were used, as recommended in the EU guideline on carcinogenic potential (3BS7a).¹ Relative exposures in the

¹ The Note for Guidance 3BS7a has been updated to CPMP/SWP/2877/00 Note for Guidance on Carcinogenic Potential to include International Conference on Harmonization (ICH) guidelines on carcinogenic testing and other relevant ICH guidelines.

carcinogenicity studies were calculated using a clinical AUC of 45.5 µg.h/mL to remain consistent with existing exposure margin determinations (Table 1).

Table 1: Relative exposure in submitted carcinogenicity studies

Species (Strain)	Study	Treatment duration	Sex	Dose (mg/kg/day)	Exposure		Exposure ratio ^a	
					AUC _{0-24h} (µg·h/mL)	C _{max} (µg/mL)	AUC	C _{max}
Mouse (CD-1)	RD2003/00251/00	104 weeks	♂/♀	75	25	5.0	0.5	1.6
				150	51	7.2	1.1	2
				300	86	7.7	1.9	2
Rat (Wistar Han)	RD2003/00250/00	104 weeks	♂	60	24	4.3	0.5	1.3
				120	38	6.1	0.8	12
				240	58	6.6	1.3	2
				500	86	9.8	1.9	3
			♀	20	44	8.3	1.0	3
				60	226	27	5	8
				180	363	30	8	9
				300	534	32	12	10
Human	EGF10005	7 days	♂/♀	[1250 mg] ^b	45.5	3.2	–	–

^acalculated as animal:human AUC_{0-24h} or C_{max}; ^bco-administration with 1000 mg/m² bid capecitabine (from Study EGF10005); data are for the sexes combined (except in rats), and averages across sampling days

Exposures achieved in the studies were generally at or up to 2 times the clinical exposure (except in female rats where higher exposures were achieved), but the Maximum Tolerated Dose (MTD) was clearly attained. The highest dose levels used in each of the studies (300 mg/kg/day in mice, and 500 and 300 mg/kg/day in male and female rats, respectively) produced excessive mortality, necessitating early termination of dosing in the high-dose groups (in week 44 and 93 for male and female mice, respectively; and week 104 and 19 for male and female rats, respectively). Given the late stage of termination of female mice and male rats, this is not considered to have adversely affected the adequacy of these groups to reveal potential carcinogenic effects as there were sufficient numbers of surviving animals for post-mortem histological examination. However, for male mice and female rats, the second highest dose is considered to be the highest one adequately tested for carcinogenic potential.

No treatment-related increases in tumour incidence were observed in the mice study; exposure ratios (based on AUC) at the highest adequate doses were 1-2. However, in the rat carcinogenicity study an increased incidence of benign haemangiomas of the mesenteric lymph node was observed at doses >60 mg/kg/day. Though the incidence level was within those reported for historical controls, the higher level of tumour incidence in treated animals compared with concurrent controls, as well as a dose-related increase in incidence in both males and females, suggest a relationship of tumour formation with lapatinib treatment cannot be dismissed. The AUC at the No Observable Effect Level (NOEL) was 0.5 and 5 times the anticipated clinical AUC in males and females, respectively.

In the rat carcinogenicity study, a decrease in the incidence of spontaneous mammary tumours was observed in treated females. This is consistent with the previous finding where reduced cellular proliferation of mammary glands at metestrus was seen in lapatinib-treated female rats.

Pregnancy Category

Consistent with the individual components, the proposed free combinations should not be used in pregnancy. Though letrozole has a Category D pregnancy designation, the other 2 aromatase inhibitors have a Category C designation. The existing Category C pregnancy designation for lapatinib is considered adequate for all possible combinations.

Haemolysis

An *in vitro* haemolysis study was submitted in anticipation of future intravenous studies and not directly relevant to this submission. Nonetheless, concentrations of lapatinib up to 0.5 mg/mL (final concentration) had limited haemolytic activity on human blood.

Impurities

The impurity specifications for the drug product and drug substance remain unchanged but the proposed indication includes a higher dose of lapatinib ditosylate (1500 mg/day). The specifications of a number of impurities in the drug substance were above 0.15% or 1 mg/day and required qualification according to ICH Guidelines (ICHQ3A(R)). Previously, batch data from repeat-dose studies and a rat micronucleus study were used to qualify the proposed specifications. Based on repeat-dose toxicity studies with dose ratios based on body surface area (BSA) greater than 1, and a negative result in the micronucleus assay at sufficiently high levels, the impurities GW684529, GW560231, GW574783 and GW562778 have been adequately qualified (Table 2). The proposed specifications for the impurities GW680835, GW680445 and GW684528 can be considered qualified based on the micronucleus assay data only.

The synthetic impurity, GW397339, was shown to be genotoxic *in vitro* and *in vivo*. In the micronucleus assay, the NOEL was considered to be 20 mg/kg/day. The specification for this impurity is 0.0004% or 5 µg/day at the currently-approved dose, and 6 µg/day at the proposed dose of 1500 mg Tykerb per day. These levels exceed the threshold of toxicological concern (1.5 µg/day). However, the NOEL for genotoxicity is about 30,000 times the anticipated dose, based on body surface area (BSA), for a daily dose of 1500 mg to a 50 kg individual. Given the life-threatening condition of the proposed patient population and the significant safety margin, a daily dose of 6 µg for this impurity can be considered acceptable.

Table 2: Dose Comparison for Specified Impurities^a

Impurity	Study (Batch)	Lapatinib dose (mg/kg/day)	Impurity level (%)	Impurity dose		Specification (NMT %)	Maximum human dose (mg/m ² /day) ^b		Animal/human dose ratio by BSA	
				mg/kg/day	mg/m ² /day		current indication	new indication	current indication	new indication
<u>Non-genotoxic impurities</u>										
GW680835	RD1999/02634/00 (U14572/31/5)	360	0.08	0.288	5.76	0.9	7.43	8.91	0.8	0.6
	RD2000/01601/00 (U14572/39/3) ^c	2000	0.07	1.4	8.4				1.1	0.9
GW684529	RD1999/02634/00 (U14572/31/5)	360	0.10	0.36	7.2	0.5	4.13	4.95	1.7	1.5
GW560231	RD1999/02634/00 (U14572/31/5)	360	0.11	0.396	7.92	0.3	2.48	2.97	3.2	2.7
GW574783	RD1999/02634/00 (U14572/31/5)	360	0.47	1.69	33.8	0.6	4.95	5.94	6.8	5.7
GW562778	RD1999/02634/00 (U14572/31/5)	360	0.22	0.79	15.8	0.5	4.13	4.95	3.8	3.2
GW680445	RD1999/02391/00 (U14572/39/3)	240	0.03	0.072	0.43	0.1	0.83	0.99	0.5	0.4
	RD2000/01601/00 (U14572/39/3) ^c	2000	0.03	0.6	3.6				4.4	3.6
GW684528	RD1999/02634/00 (U14572/31/5)	360	0.00035	0.126	2.5	0.5	4.13	4.95	0.6	0.5
	RD2000/01601/00 (U14572/39/3) ^c	2000	0.0006	1.2	7.2				1.7	1.5
<u>Genotoxic impurity</u>										
GW397339	WD2005/00458/00 (0203021)	–	–	20	120	0.0004	3.3×10 ⁻³	4.0×10 ⁻³	36000	30000

^aAll studies performed in rats or dogs with mg/kg to mg/m² conversion factors of 6 for rats, 20 for dogs and 33 for humans; ^bBased on a 1250 mg or 1500 mg dose to a 50 kg individual for the current and new indications, respectively;

^cRat micronucleus study

Nonclinical Summary and Conclusions

Lapatinib appeared to induce the expression of oestrogen and progesterone receptors in ErbB2 overexpressing cell lines, suggesting possible interactions of the ErbB receptors and the steroid hormone pathway.

There are unlikely to be significant CYP-mediated pharmacokinetic interactions with the combination of lapatinib and the aromatase inhibitor, exemestane or letrozole. Pharmacokinetic interactions with other aromatase inhibitors would need to rely on clinical data.

As the systemic exposure to lapatinib is not apparently higher at the dose of 1500 mg/day compared with 1250 mg/day, there are unlikely to be additional toxicological concerns with the higher proposed dose.

Repeat-dose studies with the proposed combinations have not been conducted. Based on shared target organs, greater toxicity to the skin, liver, GI tract and lymphoid tissue may be expected with the proposed combinations compared with the individual components.

No treatment-related increase in tumour-incidence was observed in mice in a 2-year oral carcinogenicity study with lapatinib. Exposure ratios (based on AUC) at the highest adequate doses were 1-2. However, in a rat 2-year carcinogenicity study, an increased incidence of benign haemangiomas of the mesenteric lymph node was observed at doses >60 mg/kg/day. Though the incidence level was within historical control data, a relationship of tumour formation with lapatinib treatment cannot be dismissed. The AUC at the NOEL was 0.5 and 5 times the anticipated clinical AUC in males and females, respectively.

The specification of a genotoxic impurity, GW397339, in the drug substance would result in a daily dose of 6 µg/day, which is greater than the threshold of toxicological concern. Given the life-threatening condition of the targeted patient population the proposed specification for this impurity might be considered acceptable.

There are no toxicological concerns with the higher proposed dose but the absence of toxicity studies with the proposed combinations is considered a major deficiency of the application. Based on nonclinical data for the individual components, the skin, liver, gastrointestinal tract and lymphoid organs would be expected to be the target organs for toxicity. It is of note that these organs are also the target organs for toxicity of many oncology drugs, including capecitabine.

In the absence of nonclinical data with the proposed combinations, potential safety issues will need to be addressed by the clinical data.

IV. Clinical Findings

Introduction

Two studies were provided in this submission. The first is a pivotal Phase III trial EGF30008, which was a randomised double-blind placebo-controlled multi-centre study comparing lapatinib and letrozole versus letrozole alone in patients with oestrogen/progesterone receptor positive advanced or metastatic breast cancer. The other study provided is a Phase I trial EGF10030, which was an open label study of the safety, tolerability and pharmacokinetics of lapatinib in combination with letrozole in cancer patients. Full data for both of these trials were provided in the submission and included summaries, final reports and appropriate tables.

Pharmacokinetics

Lapatinib is a potent small molecule reversible inhibitor of both epidermal growth factor receptor (EGFR) and HER2 tyrosine kinases. Both EGFR and HER2 are the members of the type I receptor tyrosine kinase family overexpressed in several cancers including breast cancer. Lapatinib induces growth arrest and apoptosis in EGFR and HER2 dependent tumour cell lines or xenografts.

Full data on pharmacology was provided in an earlier submission and the only extra pharmacological data provided in this submission relates to pharmacokinetics undertaken in the Phase I trial EGF10030.

This trial is an open-label repeat dose escalation study of oral lapatinib and letrozole given to subjects with advanced breast cancer and other solid tumours. Oral doses of both lapatinib and letrozole were administered in combination once daily on a continuous schedule. Eligible patients were 18 years of age or older with ER+ or PR+ advanced breast cancer not likely to benefit from standard therapy or another cancer that is likely to respond to this combination, for example ovarian or endometrial cancers.

Patients were enrolled into one of three cohorts:

- (i) A dose escalation cohort with a dose of lapatinib escalated from a starting dose of 1250 mg per day to a maximum dose of 1500 mg per day with letrozole fixed at 2.5 mg per day using a standard 3+3 design.
- (ii) An extension cohort to further evaluate safety and tolerability at the optimally tolerated regimen (OTR) dose level of the lapatinib plus letrozole combination.
- (iii) A pharmacokinetic (PK) cohort to assess the potential for a drug interaction affecting either lapatinib or letrozole at steady state. Subjects in this cohort were randomly assigned to two treatment groups and each group were randomised to one of two sequences. In group I the effect of letrozole on the pharmacokinetics of lapatinib was determined and in group II the effect of lapatinib on the pharmacokinetics of letrozole was determined.

The dose of letrozole administered to all patients in this study was 2.5mg per day.

RECIST guidelines were used to assess clinical activity and disease status.² Safety assessments included vital signs, clinical laboratory tests, 12 lead electrocardiograms (ECGs), monitoring for adverse effects, Karnosky performance status and multi-gated angiogram or echocardiogram. For pharmacokinetic analyses regular blood samples were obtained from the two patient cohorts at generally 24 hour intervals over a number of days.

A total of 39 female patients were enrolled in this study including 12 in the dose escalation cohort, seven in the OTR safety and tolerability cohort and 20 in the pharmacokinetic cohort. The majority of patients had breast cancer (N=18) or ovarian cancer (N=16).

PK data were obtained from 18 evaluable patients. Geometric mean square treatment ratios and associated 90% confidence intervals (CIs) for the area under the plasma concentration-time curve for a dosing interval (AUC_{τ}), C_{max} and the concentration over a dosing interval (C_{τ}) for both drugs indicated a tendency for lower systemic exposure that was neither statistically or clinically relevant.

Although there was tendency towards lower concentrations of lapatinib in the presence of letrozole and lower concentrations of letrozole in the presence of lapatinib, no clinically meaningful difference emerged from the inherent variability in the lapatinib exposure. A summary of the pharmacokinetic parameters is given in Table 3.

It is appropriate to indicate at this time that the combination of letrozole plus lapatinib was generally well tolerated in study EGF10030 and data suggested the adverse event profile of letrozole and lapatinib in combination was similar to that seen with each drug individually. The optimally tolerated regimen (OTR) was defined as 1500mg of lapatinib with 2.5mg letrozole.

Evaluator Comment

The OTR has been defined as 1500mg lapatinib with 2.5mg letrozole which is appropriate for further study in the Phase III trial EGF30008. Despite a tendency for lower exposure to both drugs no statistically or clinically significant difference in the pharmacokinetics of lapatinib and letrozole were observed when these two agents were co-administered.

² RECIST: The Response Evaluation Criteria in Solid Tumors (RECIST) is a voluntary, international standard using unified, easily applicable criteria for measuring tumor response using X-ray, CT and MRI.

Table 3: Pharmacokinetic Parameters for Lapatinib and Letrozole, Alone and in Combination

Table 1 Summary of Pharmacokinetic Parameters for Lapatinib Administered Alone and in Combination with Letrozole

Parameter (units)	Lapatinib alone* (n=9)	Lapatinib + Letrozole* (n=10)	Comparison** (n=9)
AUCtau (h*µg/L)	31.9 (17.2-59.2)	27.0 (13.3-54.8)	0.84 (0.62-1.13)
Cmax (µg/L)	2.47 (1.47-4.13)	1.94 (1.13-3.34)	0.78 (0.57-1.06)
Ctau (µg/L)	0.78 (0.37-1.66)	0.72 (0.30-1.73)	0.90 (0.63-1.28)

* Geometric mean (95% confidence interval)

** Geometric LS mean ratio (90% confidence interval)

Table 2 Summary of Pharmacokinetic Parameters for Letrozole Administered Alone and in Combination with Lapatinib

Parameter (units)	Letrozole alone* (n=8)	Letrozole + Lapatinib* (n=8)	Comparison** (n=8)
AUCtau (h*ng/mL)	2228 (1339-3708)	2085 (1302-3339)	0.94 (0.79-1.11)
Cmax (ng/mL)	136 (82-225)	122 (78-190)	0.90 (0.79-1.02)
Ctau (ng/mL)	91 (48-172)	78 (47-130)	0.86 (0.71-1.05)

* Geometric mean (95% confidence interval)

** Geometric LS mean ratio (90% confidence interval)

Pharmacodynamics

There were no pharmacodynamics data presented in the submission.

Efficacy

Pivotal Study EGF30008

The pivotal trial in this submission was Phase III study EGF30008. This was a randomised double-blind placebo-controlled parallel group multi-centre Phase III trial. The study was designed to evaluate the efficacy and tolerability of letrozole and lapatinib compared with letrozole and placebo. The study population was comprised of women who were post-menopausal with hormone receptor positive (ER+ and/or PgR+) advanced metastatic breast cancer who had not received prior therapy for advanced metastatic disease.

Eligible patients were post-menopausal females with histologically confirmed stage IIIB or IV ER+ and/or PgR+ regardless of HER2 status invasive breast cancer. Subjects had an ECOG performance status of 0-1 and measurable or non-measurable disease according to standard RECIST criteria.³

³ ECOG Performance Status. The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:

0 - Fully active, able to carry on all pre-disease performance without restriction

1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work

2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours

3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours

4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

5 - Dead

Patients who had received prior chemotherapy, endocrine therapy, immunotherapy, biological therapy or anti-HER2 therapy for advanced and metastatic disease were not eligible.

Patients were randomly assigned (randomisation was stratified by site of disease and time since prior adjuvant endocrine therapy, for example tamoxifen) on a one-to-one basis to receive either letrozole 2.5 mg once daily with oral lapatinib 1500 mg once daily or letrozole 2.5 mg once daily with placebo (visually matching lapatinib tablets). The therapy with lapatinib or placebo was administered daily until disease progression or withdrawal from therapy (for example, due to unacceptable toxicity, withdrawal of consent). Letrozole dosing could be withheld for three days if this was thought necessary by the investigator.

Safety assessments were performed every 4 weeks until Week 108 of treatment, and thereafter at 12-week intervals. Efficacy assessments were performed on all patients at 12-week intervals and more frequently if clinically indicated. Patients withdrawn from treatment without progressive disease had a radiological assessment performed every 12 weeks until disease progression or until the patient began a new anti-cancer therapy or death. All patients would be followed for survival information until death.

The primary endpoint was to evaluate the investigator-evaluated progression free survival (PFS) in patients with ER+ or PgR+ HER2+ advanced or metastatic breast cancer treated with letrozole and lapatinib compared with letrozole and placebo. In a closed hierarchical testing procedure, the secondary endpoint was to evaluate investigator-evaluated progression free survival in the intention to treat (ITT) population. Other secondary endpoints of the study were to evaluate and compare the two treatment groups with respect to overall survival (OS), overall response rate (ORR), continuous best response, time to response, duration of response, incidence of brain metastases and time to tumour progression.

A cut-off date for closure of data was 3 June 2008. At the time of data cut-off enrolment was complete with the last patient being randomised on 29 December 2006 with 198 patients remaining on study treatment with 495 patients in follow up for survival.

Disease progression and response evaluations were determined according to the definitions established in RECIST. Any patient who was randomised to therapy was considered eligible for response to treatment.

Investigator assessment of primary and secondary endpoints was the principal evaluation process in this trial. Nevertheless an independent board of review of radiological scans as a supportive analysis was performed by an independent review committee and the results used as a confirmatory analysis of the primary efficacy measure of investigator-evaluated PFS. The committee reviewed all scans and, for patients with skin lesions, photographs also.

There were three key efficacy populations evaluated in study EGF30008 as shown in Table 4.

A further population of patients – “the HER2 missing population” - was defined as an exploratory population where HER2 status was either missing or unevaluable. At the time of data cut-off a total of 1286 patients had been randomised into the trial with the study having been conducted in 29 countries at 212 centres. The majority (57%) of patients who enrolled were in Europe. A breakdown of the key efficacy populations is given in Figure 1. There were equivalent numbers of patients with HER2+ tumours in both treatment groups (108 patients in the letrozole + placebo and 111 patients in the letrozole + lapatinib groups). All other populations also had a similar number of patients in each treatment group including the HER2 missing population.

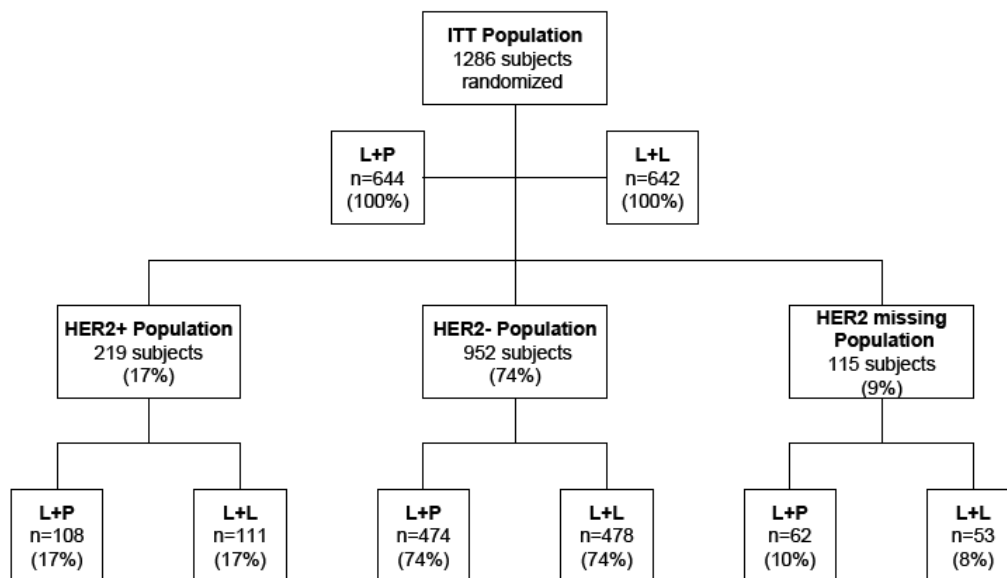
Table 4 Key Efficacy Populations Analyzed in Study EGF30008

Key Populations analyzed	Definition
ErbB2-positive	All randomised subjects who had retrospectively documented amplification of baseline ErbB2 by FISH (≥ 2.0) or 3+ IHC (or 2+ IHC and FISH +) in archived, tumor tissue regardless of whether or not study treatment had been received. The ErbB2-positive population was used for all efficacy analyses.
ITT	All randomised subjects regardless of whether or not study medication had been received. Used for the analysis of all efficacy data
ErbB2-negative	All randomised subjects regardless of whether or not study treatment had been received and who at baseline were evaluated by the central laboratory to have: retrospectively documented non-amplification of ErbB2 by FISH (< 2.0) and documented 0, 1+ or 2+ IHC in tumor tissue; missing FISH amplification and documented 0, 1+ or 2+ IHC in tumor tissue; documented non-amplification of ErbB2 by FISH and missing IHC in tumor tissue. The ErbB2-negative population was used for all displays of efficacy.

FISH: Fluorescence in situ hybridization; IHC: immunohistochemistry.

Figure 1: Key Efficacy Populations

Figure 2 Key Efficacy Populations



L+P = Letrozole plus placebo; L+L = Letrozole plus lapatinib.

In the HER2+ population a total of 18 patients (8%) were still receiving study treatment at the clinical cut-off date. In this patient population the primary reason for discontinuation of study treatment was progression of cancer in both treatment groups. The percentage of patients discontinuing from study treatment was similar between the two treatment groups.

Death due to disease progression was the primary reason for discontinuation from study in each of the two treatment groups.

Demographic characteristics were similar between the two treatment groups for the HER2+ population. The median age for this population was approximately 60 years. Similar demographic characteristics were seen for the HER2+, HER2-negative and ITT patient population.

Baseline disease characteristics for the HER2+ population were again similar between the two treatment groups. The majority of patients had infiltrating ductal histology at diagnosis, 74% of patients overall, and 96% of patients with stage IV disease at screening. A total of 44% of patients overall had three or more metastatic sites, the majority of which were visceral or soft tissue.

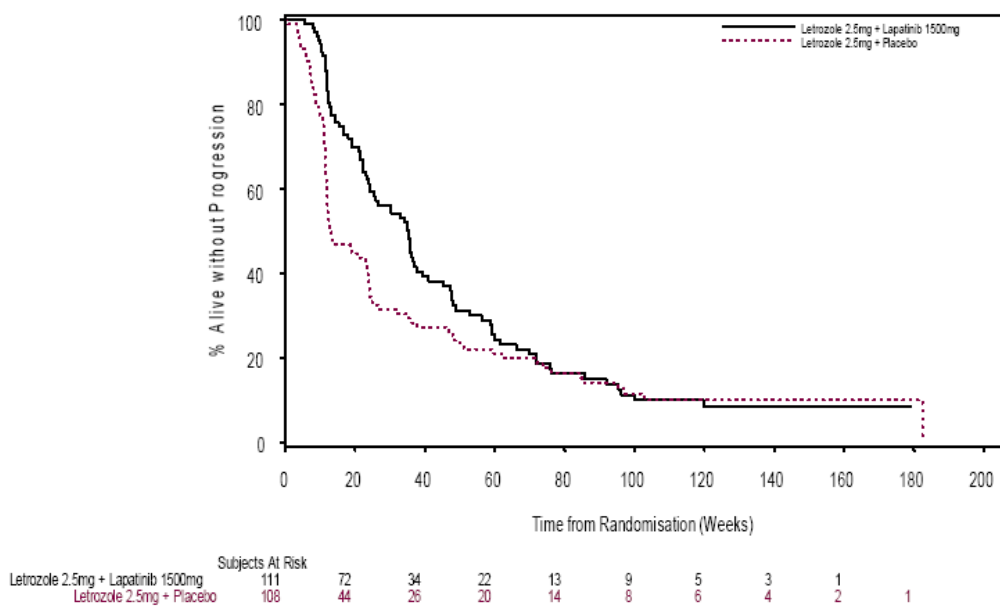
The HER2+ patient population in the two treatment groups were well balanced in relation to hormone receptor status. In the HER2+ population 56% of patients had received prior chemotherapy or endocrine therapy in the adjuvant setting.

Results

Investigator-evaluated progression free survival (PFS) in the HER2+ population was statistically significantly longer in the letrozole plus lapatinib group compared with the letrozole plus placebo group (Figure 2, Table 5). Approximately 81% of patients overall had either died or progressed at the time of analysis and only 7% are still being followed for PFS indicating that the data were mature.

Figure 2: Kaplan-Meier Estimates for Investigator-Evaluated PFS (HER2-Positive Population)

Figure 5 Kaplan-Meier Estimates for Investigator-Evaluated PFS (ErbB2-Positive Population)



A pre-planned supportive Cox analysis of PFS treatment as well as 12 other prognostic factors were examined for their impact on PFS. All main effects were selected using step-wise selection. The treatment covariate demonstrated a significant improvement in PFS in the letrozole plus lapatinib group with a hazard ratio (HR) of 0.65 and p-value 0.008. For the other 12 covariates that were tested in the Cox model, patients who were younger, had a ECOG performance status of <1 or baseline serum extracellular domain (ECD) levels <15 ng/mL had considerably longer progression free survival.

Table 5: Investigator-Evaluated PFS (HER2-Positive Population)

Table 16 Investigator-Evaluated PFS (ErbB2-Positive Population)

	Letrozole 2.5 mg + Placebo (N=108)	Letrozole 2.5 mg + Lapatinib 1500 mg (N=111)
Number (%) of subjects		
Progressed or died due to any cause (event)	89 (82)	88 (79)
Censored, follow up ended	10 (9)	16 (14)
Censored, follow up ongoing	9 (8)	7 (6)
Kaplan-Meier estimate of PFS (weeks)		
1 st Quartile (95% CI)	11.0 (8.7, 11.6)	15.4 (12.3, 22.3)
Median (95% CI)	13.0 (12.0, 23.7)	35.4 (24.1, 39.4)
3 rd Quartile (95% CI)	48.1 (24.9, 76.1)	60.0 (47.9, 76.4)
Hazard ratio		
Estimate ^a (95% CI)	0.71 (0.53, 0.96)	
Log-Rank p-value ^b	0.019	

Source data: Study EGF30008 CSR, [Table 7.2](#)

- Estimate of the treatment HR based on the log-rank test, <1 indicates a lower risk with letrozole 2.5 mg + lapatinib 1500 mg compared with letrozole 2.5 mg + placebo.
- p-value from stratified log-rank test, stratifying for site of disease and time since prior adjuvant endocrine therapy at screening.

Evaluation of overall survival (OS) data for the HER2+ population revealed that this had not matured at the time of data cut-off as only 104 (47%) of patients had died and 41% were still being followed for survival. OS was analysed by both Cox regression modelling and Kaplan-Meier methodology. There was no statistically significant differences in OS between the two treatment groups with the Cox regression model with an HR of 0.77 and P = 0.185. OS as examined by the Kaplan-Meier analysis showed that median overall survival of patients in the HER2+ population was higher in letrozole plus lapatinib group being 144.7 weeks compared with the letrozole plus placebo group being 140.3 weeks. This is not statistically different.

Investigator-evaluated overall response rate (ORR) in the HER2+ population was statistically significantly higher in the letrozole plus lapatinib group compared with letrozole plus placebo group (Table 6).

Review of overall response rate plus stratification factors revealed that in patients with measurable disease, the ORR was higher in patients with soft tissue or visceral disease at screening and patients who discontinued prior adjuvant endocrine therapy at least six months prior to initiation of study therapy or who had never received endocrine therapy.

Review of continuing best response for the two treatment groups in the HER2+ population revealed a statistically significant result favouring the letrozole plus lapatinib group.

Table 6: Investigator-Evaluated ORR (RECIST Criteria)

Table 21 Investigator-Evaluated ORR (RECIST Criteria) for Subjects with Measurable and Non-measurable Disease including Bone Scans (ErbB2-Positive Population)

	Letrozole 2.5 mg + Placebo (N=108)	Letrozole 2.5 mg + Lapatinib 1500 mg (N=111)
Best response, n (%)		
CR	4 (4)	5 (5)
PR	12 (11)	26 (23)
SD	35 (32)	44 (40)
PD	49 (45)	30 (27)
Unknown	8 (7)	6 (5)
ORR (CR or PR)^a		
Percent response rate (95% CI)	14.8 (8.7, 22.9)	27.9 (19.8, 37.2)
Percent difference in response rate (95% CI)	-13.1 (-25.8, -0.3)	
Estimate of common odds ratio for tumor response		
Estimate (95% CI)	0.4 (0.2, 0.9)	
p-value ^b	0.021	

Source data: Study EGF30008 CSR, [Table 7.1070](#).

a. Subjects with unknown or missing response were treated as non-responders.

b. p-value from exact test that common odds ratio equals 1.

Note: 'Including bone scans' indicates that the assessment of CR or PR required confirmation using bone scans, regardless of the presence of bone disease at baseline.

CR: complete response, PR: partial response, SD: stable disease, PD: disease progression

Review of the ITT population again revealed that the investigator-evaluated PFS was statistically significantly longer for the letrozole plus lapatinib group compared with letrozole plus placebo group (Table 7, Figure 3). The median PFS was 47 weeks for the letrozole plus placebo group compared with 51.7 weeks in the letrozole plus lapatinib group.

Table 7: Investigator-Evaluated PFS (ITT Population)

Table 23 Investigator-Evaluated PFS (ITT Population)

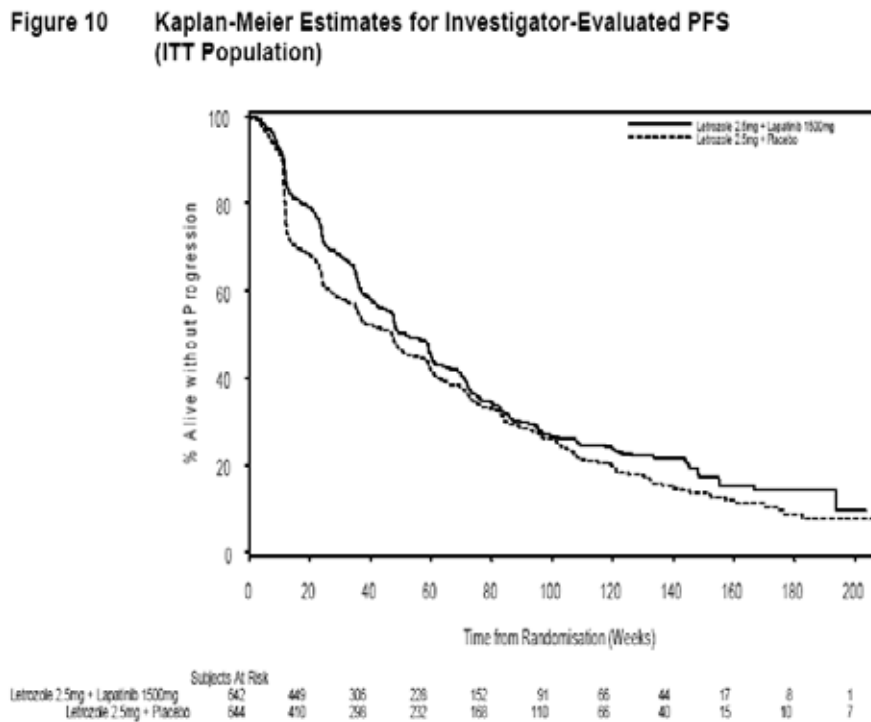
	Letrozole 2.5 mg + Placebo (N=644)	Letrozole 2.5 mg + Lapatinib 1500 mg (N=642)
Number (%) of subjects		
Progressed or died due to any cause (event)	476 (74)	413 (64)
Censored, follow up ended	76 (12)	129 (20)
Censored, follow up ongoing	92 (14)	100 (16)
Kaplan-Meier estimate of PFS (weeks)		
1 st Quartile (95% CI)	12.3 (12.0, 13.6)	23.4 (21.1, 24.3)
Median (95% CI)	47.0 (36.9, 50.9)	51.7 (47.6, 59.6)
3 rd Quartile (95% CI)	101.7 (89.4, 108.7)	108.4 (94.3, 144.1)
Hazard ratio		
Estimate ^a (95% CI)	0.86 (0.76, 0.98)	
Log-Rank p-value ^b	0.026	

Source data: Study EGF30008 CSR, [Table 7.7](#).

a. Estimate of the treatment HR based on the log-rank test, <1 indicates a lower risk with letrozole 2.5 mg + lapatinib 1500 mg compared with letrozole 2.5 mg + placebo.

b. p-value from stratified log-rank test, stratifying for site of disease and time since prior adjuvant endocrine therapy at screening.

Figure 3: Kaplan-Meier Estimates for Investigator-Evaluated PFS (ITT Population)



Review of the PFS data in the HER2-negative patient population revealed there were no statistically significant differences between the two treatment groups.

Review of OS data for the HER2-negative patients revealed that again these had not matured at the time of data cut-off with only 327 patients (34%) having died and 57% still being followed for survival. Neither the Cox regression analysis nor Kaplan-Meier analyses were significantly different for the two treatment groups.

With regards to the ORR in the HER2-negative patient population there is no statistically significant difference between the two groups, with ORRs being 31.6% and 32.6% in letrozole plus placebo and letrozole plus lapatinib groups respectively for HR 0.9, P = 0.726.

Among the HER2 missing population there were 115 patients in this group and review of progression free survival data revealed that there was no statistically significant differences between the two treatment groups as indicated by Kaplan-Meier analysis.

Review of the data by the independent review committee revealed the results of PFS as assessed by this committee were comparable with those seen on the investigator assessment with a statistically significant improvement in PFS in subjects receiving letrozole plus lapatinib compared with patients receiving letrozole plus placebo (60 weeks versus 35.4 weeks, HR 0.64, P = 0.022).

Review of the potential effect of age on results in the HER2+ population in study EGF30008 revealed that for patients <65 years of age the median progression free survival is 34.1 weeks and 12.7 weeks on letrozole plus lapatinib and letrozole plus placebo groups respectively, while in the >65 year old category the median progression free survival was 35.4 weeks and 13.3 weeks respectively confirming the data for the overall patient population.

In both treatment groups in the HER2+ population patients from the >65 year old age group had a higher level of response rate compared with the <65 year old group. In the HER2+ population in the <65 year group the overall response rate was 22.9% and 14.1% in the letrozole plus lapatinib

and letrozole plus placebo groups respectively while in the >65 year old group the overall response rate was 16.2% and 36.6% in the letrozole plus placebo and letrozole plus lapatinib groups.

Evaluator's Comments

The data from this quite large trial have clearly shown that in relation to progression free survival the addition of lapatinib to an aromatase inhibitor results in a significant improvement. The patients who receive letrozole plus lapatinib show a 29% reduction in the risk of disease progression, the data however is still somewhat immature in reference to overall survival. At the present time there is no evidence of a significant benefit in relation to this parameter for the addition of lapatinib to an aromatase inhibitor.

Sub-group analyses and sensitivity analyses have confirmed the robustness of the data from this trial. It is therefore considered that the evidence is solid that the addition of lapatinib to letrozole results in a significant clinical benefit in relation to PFS and response rates. Further follow up is required to ultimately determine benefits in terms of overall survival.

Supportive Study EGF10030

In relation to the supportive study Phase I trial EGF10030 a total of 39 patients were enrolled. The median age of the patient population was approximately 56 years (range 31-73 years). All patients were female and the majority (87%) of patients were white. Eighteen patients had breast cancer and 16 had ovarian cancer. The remaining patients had bladder cancer (1), cervical cancer (1), endometrial cancer (2) and right fallopian tube cancer (1).

The HER2 was reported as being positive in two patients. The majority of patients did not have this tested. Fifteen patients (39%) had both ER and PgR positive and eight patients ER+ only.

The efficacy population consists of 34 patients, four of whom receive letrozole 2.5 mg plus lapatinib 1250 mg and 30 patients who received letrozole 2.5 mg plus lapatinib 1500 mg. Patients who had least one available assessment after their baseline assessment (N=34) were analysed for clinical activity.

Four patients in the letrozole 2.5 plus lapatinib 1250 mg group and 30 patients in the letrozole 2.5 plus lapatinib 1500 mg group were analysed for best response. No patients had a complete response (CR), while two patients had a partial response (PR) and twenty patients had stable disease (SD) and 12 patients progressive disease (PD) as best response.

A summary of best response for patients with breast cancer revealed that of two breast cancer patients who had a lapatinib study dose of 1250 mg per day, one patient had a PR and one patient PD. Out of the 16 breast cancer patients on the lapatinib study dose of 1500 mg per day, four patients had PD, 11 had SD and one patient was not evaluable.

These data provide little worthwhile in terms of supportive evidence of efficacy as the patient population was heavily treated previously and full information regarding HER2 status was not available except for two patients. The results therefore must essentially be considered meaningless.

Safety

The pivotal safety data from this evaluation is in relation to study EGF30008. A total of 1278 patients were considered the study population as eight of the originally randomised patients did not receive any treatment. The safety population in study EGF30008 comprised all patients who received at least one dose of study treatment and was based on the actual treatment received rather than the assigned treatment. 624 patients received letrozole plus placebo and 654 patients received letrozole plus lapatinib.

The supportive study EGF10030 involved 39 patients of whom 38 patients received letrozole plus lapatinib and one letrozole alone.

Safety assessments for study EGF30008 involved reporting of all adverse events regardless of relationship to study treatment from the first dose of study treatment to 28 days after last dose of study treatment. The investigators assessed the intensity of each adverse event reporting it according to National Cancer Institute (NCI) common criteria. Adverse events of special interest included hepatobiliary events, cardiac events including decreased left ventricular ejection fraction (LVEF), diarrhoea, rash and nail disorders and pulmonary events.

Serious adverse events were those resulting in death or life threatening or required hospitalisation or prolongation of existing hospitalisation, resulted in a disability or incapacity or considered a congenital and/or birth defect.

Clinical laboratory evaluations, vital signs, ECG evaluations and echocardiogram scans were undertaken.

In study EGF10030 essentially all the above were also undertaken including description of adverse events. Serious adverse events (SAEs), gradings of the toxicities and laboratory assessments were also undertaken as per study EGF30008. Safety assessments were performed on all patients at four weekly intervals in both studies except for echo scans which were performed every eight weeks and at the end of treatment. In those patients who received study treatment for more than 108 weeks, safety assessments were performed at 12 weekly intervals.

Pivotal Study EGF30008

In study EGF30008 the mean duration of treatment with letrozole in the letrozole plus placebo group was 54.53 weeks (median 37.57 weeks) while for patients receiving letrozole plus lapatinib the mean duration of exposure to letrozole was 55.22 weeks (median 40.29 weeks) and the mean duration of exposure to lapatinib was 55.1 weeks (median 40.14 weeks). Treatment compliance was >80% for the majority of patients in both treatment groups. Only six patients had more than one lapatinib dose reduction. No dose reductions were allowed for letrozole.

A third of patients had their lapatinib dose delayed. The main reason for this was non-haematological toxicity.

At the time of data cut-off 198 patients were continuing treatment. The percentage of patients who discontinued treatment due to adverse events was lower in the letrozole plus placebo group (5%) compared with the letrozole plus lapatinib group (14%). The most common reason for this was diarrhoea in patients on lapatinib. A total of 24 patients (4%) of patients receiving lapatinib ceased therapy because of diarrhoea.

An overview of adverse events for study EGF30008 is given in Table 8. As is expected for combination treatment a higher percentage of patients had adverse events in the letrozole plus lapatinib group. The treatment related adverse events, serious adverse events and adverse events leading to discontinuation of study treatment and adverse events of special interest were all reported more frequently in the letrozole plus lapatinib group.

Adverse events which were reported in at least 10% of patients are shown in Table 9. Overall the most frequently reported adverse events were related to gastrointestinal disorders (diarrhoea and nausea) and skin and subcutaneous disorders (rash).

Table 8: Number (%) of Subjects with Adverse Events (Safety Population)

Table 10 Number (%) of Subjects with Adverse Events (Safety Population): Study EGF30008

Category of adverse event	Number (%) of subjects	
	Letrozole 2.5 mg Placebo (N=624)	Letrozole 2.5 mg + Lapatinib 1500 mg (N=654)
All AEs	536 (86)	628 (96)
Fatal AEs	8 (1)	8 (1)
Fatal AEs related to study treatment ^a	2 (<1)	1 (<1)
SAEs	94 (15)	144 (22)
SAEs related to study treatment ^a	27 (4)	54 (8)
AEs leading to permanent discontinuation of study treatment ^a	35 (6)	95 (15)
AEs related to study treatment ^b	343 (55)	548 (84)
AEs of special interest ^c	228 (37)	533 (81)

Source data: Study EGF30008, Table 8.11.

- Please note the numbers of subjects with AEs leading to permanent discontinuation of study treatment presented in this table are different from those presented in Table 5. This is because the primary reason for discontinuation from treatment was not listed as AE on the case report form for some subjects.
- Assessed by the investigator.
- Included rash, diarrhoea, nail changes, hepatobiliary events, cardiac events, and pulmonary events (see Section 2.1.5).

Table 9: Adverse Events Occurring in 10% or More of Subjects in Study EGF30008

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Module 2.7.4 Summary of Clinical Safety

Table 11 Adverse Events Occurring in 10% or More of Subjects, and at a Higher Incidence in the Letrozole plus Lapatinib Group, by Maximum Toxicity CTCAE Grade (Safety Population): Study EGF30008

System organ class MedDRA preferred term	Number (%) of subjects					
	Letrozole 2.5 mg + Placebo (N=624)			Letrozole 2.5 mg + Lapatinib 1500 mg (N=654)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Metabolism and nutrition disorders						
Anorexia	54 (9)	2 (<1)	0	72 (11)	5 (<1)	0
Nervous system disorders						
Headache	83 (13)	3 (<1)	0	91 (14)	2 (<1)	0
Gastrointestinal disorders						
Diarrhoea	124 (20)	6 (<1)	0	419 (64)	58 (9)	2 (<1)
Nausea	129 (21)	4 (<1)	0	200 (31)	6 (<1)	0
Vomiting	68 (11)	4 (<1)	1 (<1)	109 (17)	7 (1)	1 (<1)
Skin and subcutaneous tissue disorders						
Rash ^a	83 (13)	0	0	290 (44)	7 (1)	0
Pruritus	55 (9)	1 (<1)	0	80 (12)	2 (<1)	0
Alopecia	45 (7)	0	0	85 (13)	1 (<1)	0
Dry skin	27 (4)	0	0	87 (13)	1 (<1)	0
Nail disorder	6 (<1)	0	0	73 (11)	1 (<1)	0
General disorders and administrative site conditions						
Fatigue	108 (17)	3 (<1)	0	134 (20)	10 (2)	0
Asthenia	69 (11)	5 (<1)	0	80 (12)	5 (<1)	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	11 (2)	1 (<1)	0	70 (11)	1 (<1)	0

Source data: Study EGF30008, Table 8.12, Table 8.13, and Table 8.15.

- In addition to the rash reported under "Skin and subcutaneous tissue disorders", 3 additional subjects in each treatment group had a rash reported under "Infections and infestations"; none were Grade 3 or 4. Grade 3=severe AE; Grade 4=life threatening or disabling AE.

As expected diarrhoea and rash were less prevalent in the letrozole plus placebo group (20% and 13%, respectively) compared with the letrozole plus lapatinib group (64% and 44%). In general both diarrhoea and rash were predictable in the majority of patients; >85% of events of both diarrhoea and rash in both treatment groups resulted without action being taken regarding study treatment. The majority of patients who had diarrhoea in the letrozole plus lapatinib group also had at least one event of vomiting (95 of 109 subjects; 87%). Most of the events in both treatment groups were grade I or II in toxicity but the incidence of grade III diarrhoea was 9% of the patients on letrozole plus lapatinib and grade IV in two patients.

The percentage of patients with adverse events considered by the investigator to be related to treatment was lower on the letrozole plus placebo group as might be expected (Table 10). Diarrhoea, nausea and rash were the most frequently reported treatment-related adverse events in both treatment groups and as might be expected there was a lower incidence of diarrhoea and rash in the placebo group (13% and 9% respectively) compared with the lapatinib group (53% and 38% respectively). Nausea was also less prevalent in the letrozole plus placebo group (11% compared with the letrozole plus lapatinib group 20%). The incidences of grade III and IV events were generally lower in the placebo compared to the lapatinib group (6% compared with 22% respectively). Two patients in the letrozole plus lapatinib group had grade IV diarrhoea.

In the letrozole plus placebo group two patients had fatal SAEs that were considered to be treatment-related by the investigator, one being myocardial infarction and the other dyspnoea. In the letrozole plus lapatinib group one patient had a fatal treatment-related SAE (abnormal hepatic function).

Table 10: Treatment-Related Adverse Events in Study EGF30008

Table 13 Incidence of the Five Most Common Treatment-Related Adverse Events by Maximum Toxicity CTCAE Grade (Safety Population): Study EGF30008

MedDRA preferred term	Number (%) of subjects						Total
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	NA/ Unknown ^a	
Letrozole 2.5 mg + Placebo (N=624)							
Any treatment-related AE	182 (29)	122 (20)	35 (6)	2 (<1)	2 (<1)	0	343 (55)
Diarrhoea	62 (10)	13 (2)	4 (<1)	0	0	0	79 (13)
Rash ^b	49 (8)	8 (1)	0	0	0	0	57 (9)
Nausea	51 (8)	16 (3)	2 (<1)	0	0	0	69 (11)
Fatigue	30 (5)	15 (2)	1 (<1)	0	0	0	46 (7)
Pruritus	25 (4)	9 (1)	1 (<1)	0	0	0	35 (6)
Letrozole 2.5 mg + Lapatinib 1500 mg (N=654)							
Any treatment-related AE	155 (24)	248 (38)	134 (20)	11 (2)	0	0	548 (84)
Diarrhoea	174 (27)	116 (18)	55 (8)	2 (<1)	0	1 (<1)	348 (53)
Rash ^b	155 (24)	87 (13)	7 (1)	0	0	0	249 (38)
Nausea	92 (14)	33 (5)	4 (<1)	0	0	0	129 (20)
Fatigue	38 (6)	28 (4)	4 (<1)	0	0	0	70 (11)
Pruritus	44 (7)	19 (3)	1 (<1)	0	0	0	64 (10)

Source data: Study EGF30008, Table 8.17.

a. The grade for these subjects was unknown; no subjects had AEs included in the NA category.

b. Rash reported under "Skin and subcutaneous tissue disorders" and "Infections and infestations".

Note: If case report form data were missing, it was assumed that AEs were related to study treatment.

Reviewing deaths in study EGF30008, 474 patients had died by the cut-off date with 37% of patients in each treatment group being involved. The primary cause of death in both treatment groups was disease progression.

Of the 13 fatal adverse events reported only three as described above were considered to be treatment related.

Review of SAEs revealed that patients in the letrozole plus placebo group had a lower incidence of SAEs (15%) compared to the letrozole plus lapatinib group (22%). SAEs indicative of cardiac injury, including decreased ejection fraction and left ventricular dysfunction, were present in 2% of patients in the letrozole plus placebo group and 4% of patients in the letrozole plus lapatinib group. Gastrointestinal serious adverse events were less frequent in the placebo group; 1% of patients developing diarrhoea and vomiting versus 2% of patients in the lapatinib group developing diarrhoea and vomiting.

A total of 54 (8%) patients and 27 (4%) patients had serious adverse events considered associated with the study treatment in the letrozole plus lapatinib and the letrozole plus placebo groups respectively. Decreased ejection fraction (1%) and vomiting (1%) were the most common treatment-related serious adverse events in the letrozole plus placebo group, and decreased ejection fraction (3%) and diarrhoea (2%) were the most common treatment related adverse events on the letrozole plus lapatinib group.

Review of discontinuation due to adverse events indicated that these were more frequent in the letrozole plus lapatinib group (15%) versus the letrozole plus placebo group (6%). Cardiac events including ejection fraction decreased (2 patients) and left ventricular dysfunction (2 patients) and four patients with gastrointestinal disorders were the most common adverse events leading to discontinuation in treatment of the letrozole plus placebo group, while the gastrointestinal disorders of diarrhoea (4% of patients) and vomiting (2%) were the most common adverse events leading to discontinuation of lapatinib. Two patients in the letrozole plus placebo group and eight patients in the letrozole plus lapatinib group discontinued therapy due to a hepatobiliary event. These were due to raised hepatic enzymes. The most common treatment-related adverse event leading to

permanent discontinuation of study treatment was diarrhoea in 24 patients and vomiting in 10 patients in the letrozole plus lapatinib group. In the letrozole plus placebo group the most common treatment-related adverse events were diarrhoea, decreased ejection fraction and left ventricular dysfunction in two patients each.

Review of adverse events of special interest in the study EGF30008 included cardiac events, hepatobiliary events, pneumonitis and rash (Table 11). These are known toxicities seen with therapeutic agents which target the HER2 receptors. As might be expected a lower percentage of special interest adverse events were reported for patients from the letrozole plus placebo group (37%) compared with the letrozole plus lapatinib group (81%).

Table 11: Number (%) of Subjects with Adverse Events of Interest in Study EGF30008

Table 19 Number (%) of Subjects with Adverse Events of Interest (Safety Population): Study EGF30008

	Number (%) of subjects	
	Letrozole 2.5 mg + Placebo (N=624)	Letrozole 2.5 mg + Lapatinib 1500 mg (N=654)
Any AE of interest ^a	228 (37)	533 (81)
Diarrhoea	124 (20)	419 (64)
Rash	93 (15)	328 (50)
Hepatobiliary events	50 (8)	98 (15)
Nail changes	6 (<1)	73 (11)
Left ventricular ejection fraction decreased	15 (2)	32 (5)
Pulmonary events	0	1 (<1)

a. Please refer to the Study EGF30008 CSR, Section 5.6.3.2 for the MedDRA preferred terms used in each special interest grouping.

Source data: Study EGF30008, Table 8.14.

A review of hepatobiliary events shows that in the letrozole plus placebo group, 50 patients (8%) had a total of 100 hepatobiliary events while in the letrozole plus lapatinib group 98 patients (15%) had 373 hepatobiliary events. These were most commonly related to hepatic enzyme elevations. The majority of these events resolved; 66% in the letrozole plus placebo group and 73% in the letrozole plus lapatinib group. Most of these events did not require any action to be taken with regards to study treatment; 93% of events in the letrozole plus placebo group and 81% in the letrozole plus lapatinib group. Two patients in the letrozole plus placebo group discontinued treatment because of hepatobiliary events while eight patients in the letrozole plus lapatinib group discontinued therapy. The one death in the letrozole plus lapatinib group of patients due to hepatotoxicity after review was considered possibly related to hepatic metastases or cholestatic drug induced liver injury. Two additional patients in the letrozole plus lapatinib group after review were considered to have probable drug induced liver injury, which were accentuated to disturbance of liver enzymes.

The majority of hepatobiliary events occurred within six months of the start of treatment with a median time to onset for the letrozole plus lapatinib group being nine weeks compared to 17 weeks for the placebo group. There did not appear to be any relationship of hepatobiliary events to age.

A total of 18 patients had abnormalities of liver dysfunction which were considered indicative of toxicity, 12 of these were reported as adverse events, 10 in the letrozole plus lapatinib group. The majority of patients 11/18 (61%) with hepatic laboratory abnormalities had liver metastases at baseline.

A review of cardiac events in study EGF30008 showed that 2% of patients in the letrozole plus placebo group and 5% of patients in the letrozole plus lapatinib developed cardiac events. One patient in the letrozole plus placebo group and six patients in the letrozole plus lapatinib group had

more than one cardiac event. Most cardiac events in both groups were grade I or grade II in toxicity. No action was taken with regards to study treatment for 44% of the events in the letrozole plus placebo group and 56% of the events in the letrozole plus lapatinib group. Twelve of the cardiac events were considered to be related to study treatment in the letrozole plus placebo group while 33 of the events in the letrozole plus lapatinib group were considered treatment-related. There were no fatal cardiac adverse events. Discontinuation of study treatment was required for 31% of the events in the letrozole plus placebo group and 15% of the events in the letrozole plus lapatinib group.

The majority of the cardiac events occurred within six months of start of treatment with a median time to event being 21.79 weeks for the letrozole plus lapatinib group versus 34.57 weeks for the letrozole plus placebo group. Overall a total of 47 patients had 51 cardiac events which were primarily decreased ejection fraction. A total of 28 patients had 33 events which met the protocol definition for a serious cardiac event. Eight of these were in the letrozole plus placebo group and 20 were in the letrozole plus lapatinib group giving overall incidences of 1.3% (8/624) and 3.1% (20/654), respectively, in the two treatment groups. Of the twenty lapatinib-treated patients, five patients had six symptomatic events and 15 experienced 18 asymptomatic events. 89% of these events resolved. Reports of symptoms included dyspnoea and tachycardia. Study treatment was discontinued in four patients with resolution of events in three patients while one patient had ongoing cardiac event at the time of death from disease progression. One patient had a reoccurrence of cardiac events after reintroduction of the study treatment. The fifth patient had a symptomatic cardiac event which resolved without treatment interruption. It appeared that prior anthracycline exposure did not predispose to a cardiac event in either treatment group.

A review of diarrhoea revealed that a lower percentage of patients in the letrozole plus placebo group had diarrhoea adverse events compared with the letrozole plus lapatinib group. Most diarrhoea events in both groups were grade I or II in toxicity (95% in the letrozole plus placebo group and 85% in the letrozole plus lapatinib group). Most events in both treatment groups resolved (93% in the letrozole plus placebo and 94% in the letrozole plus lapatinib groups). For the majority of events no action was taken with regards to study treatment (90% of the events in the letrozole plus placebo group and 85% of the events in the letrozole plus lapatinib group). One hundred and ten of the events (65%) in the letrozole plus placebo group seemed to be related to study treatment compared to 811 of the events (81%) in the letrozole plus lapatinib group. The median time to onset of the first occurrence of diarrhoea was two weeks in the letrozole plus lapatinib group versus 8.36 weeks in the letrozole plus placebo group. The median duration of diarrhoea was shorter in the letrozole plus placebo group (eight days) compared to the letrozole plus lapatinib group (25 days). Ten of the patients in the letrozole plus lapatinib group with Grade 3 or 4 diarrhoea required discontinuation of study treatment. A further 11 required dose reduction and 22 had dose interruption with resumption of therapy subsequently.

A review of rash and nail disorders included dermatitis acneiform, eczema, exfoliative rash, photosensitivity reaction, erythematous and generalised rashes and various other forms of rashes and skin ulcers. Fewer patients in the letrozole plus placebo group had events of rash (15%) compared to the letrozole plus lapatinib group (50%). Most events in the letrozole plus lapatinib group of patients were grade I or II in toxicity, whereas all of the events in the letrozole plus placebo group were grade I and II in toxicity. Three per cent of patients receiving letrozole plus lapatinib developed grade III skin toxicity. The majority of the rash events resolved without need for dose adjustment, temporary interruption or permanent discontinuation of study treatment. A lower percentage (59%) of the rashes reported in the subjects in the letrozole plus placebo group was considered by the investigator to be related to study treatment compared with the letrozole plus lapatinib group (83%). The median time to onset of first incidence of rash was 10.14 weeks in the letrozole plus placebo group compared to 2.86 weeks in the letrozole plus lapatinib group.

There were a few patients with nail disorder adverse events; fewer in the letrozole plus placebo group (<1%) versus the letrozole plus lapatinib group (11%). Most of these were grade I or II in toxicity and resolved without the need for dose adjustments, temporary interruption or permanent discontinuation of study treatment. No serious adverse events of rash or nail disorders were reported. The median time to onset of nail disorders was 111 days in the letrozole plus placebo group versus 197 days in the letrozole plus lapatinib group.

A review of interstitial pneumonitis revealed that one patient in each treatment group developed pneumonitis or interstitial lung disease. The patient who developed pneumonitis on lapatinib was considered to have this related to study treatment.

A review of clinical laboratory evaluation in study EGF30008 revealed that haematological abnormalities were uncommon in both treatment groups. The incidence of neutropenia was 2% of patients in both treatment groups, with a small incidence of grade III or IV neutropenia. Febrile neutropenia was reported for three patients in the letrozole plus lapatinib group.

A review of other clinical chemistry assessments revealed uncommon changes in both treatment groups other than those associated with liver abnormalities. The clinical chemistry data was generally considered representative of post-menopausal women with locally advanced or metastatic breast cancer.

A review of vital sign changes and ECGs performed during study EGF30008 revealed no consistent abnormalities in either treatment group and a generally low incidence.

A review of the influence of age on adverse events failed to reveal any significant differences in those patients with ages <65 years versus those >65 years in terms of incidence, severity or potential discontinuation of therapy.

Supportive Study EGF10030

The Phase I study EGF10030 had 39 patients enrolled including 12 patients on the dose finding cohort, seven in the expansion cohort and 20 in the pharmacokinetic cohort. The median treatment duration was 9 weeks for the dose finding cohort which involved lapatinib, letrozole plus lapatinib 1250 mg, 17.1 weeks for those who received letrozole 2.5 mg plus lapatinib 1500 mg and for the expanded group lapatinib 1500 mg the treatment duration was 18.8 weeks. Among the PK cohort the duration was 13.3 weeks.

No patients in the lapatinib 1250 mg group discontinued study treatment due to an adverse event. Two patients who received lapatinib 1500 mg discontinued study due to a single adverse event which included respiratory failure in one patient and grade III rash in another.

A review of overall adverse events in study EGF10030 revealed that there were 37 patients who developed an adverse event with 394 adverse events reported (Table 12). These were most frequently gastrointestinal disorders (35 patients) and skin and subcutaneous tissue disorders (28 patients). The most commonly reported adverse events were diarrhoea (30 patients), rash (25), nausea (19) and vomiting (14). Most of the adverse events reported were grade I in intensity. There was no grade III or IV adverse events reported for patients receiving 1250 mg of lapatinib. A total of 21 patients had grade III adverse events and two grade IV with lapatinib at 1500 mg. This included diarrhoea in six patients, anaemia in three patients and hypokalaemia in two patients. The two grade IV adverse events were femur fracture and respiratory failure, but neither seemed to be treated-related.

A total of 34 patients had 213 adverse events that were considered to be treatment related by the investigators, the most common being diarrhoea (30 patients), rash (24), nausea (18) and vomiting (9).

One patient died in the study EGF10030 after developing grade IV respiratory failure. The death was not considered by the investigator to be due to study treatment.

A total of 11 patients had 41 non-fatal SAEs. The most frequent were dyspnoea (3 patients), anaemia (3), asthenia (2), hypokalaemia (2), nausea (2) and pleural effusion (2). Only three of these were considered to be treatment-related including grade III anaemia in one patient and grade III diarrhoea in another. Two patients who received lapatinib 1500 mg discontinued study treatment, one due to respiratory failure and the other rash.

A review of hepatic toxicities in study EGF10030 revealed that five patients developed adverse events, four due to raised hepatoenzymes and one hyperbilirubinanaemia. All five events resolved without dose modification, were grade I in toxicity and were considered to be treatment related by the investigator.

Table 12: Summary of Adverse Events from Study EGF10030

Table 14 Summary of All Adverse Events Experienced by 10% or More of All Subjects by Treatment Combination (Safety Population): Study EGF10030

	Number (%) of subjects			
	Letrozole 2.5 mg + Lapatinib 1250 mg (N=4)	Letrozole 2.5 mg + Lapatinib 1500 mg (N=34)	Letrozole 2.5 mg ^a (N=1)	All Subjects (N=39)
Any Event	4 (100)	32 (94)	1 (100)	37 (95)
Diarrhoea	4 (100)	26 (76)	0	30 (77)
Rash	3 (75)	22 (65)	0	25 (64)
Nausea	3 (75)	16 (47)	0	19 (49)
Vomiting	3 (75)	11 (32)	0	14 (36)
Fatigue	1 (25)	11 (32)	0	12 (31)
Anorexia	3 (75)	9 (26)	0	12 (31)
Dyspnoea	1 (25)	6 (18)	0	7 (18)
Cough	3 (75)	3 (9)	0	6 (15)
Hot flush	0	6 (18)	0	6 (15)
Weight decreased	1 (25)	5 (15)	0	6 (15)
Anaemia	0	5 (15)	0	5 (13)
Back pain	1 (25)	3 (9)	1 (100)	5 (13)
Dry skin	1 (25)	4 (12)	0	5 (13)
Pyrexia	1 (25)	4 (12)	0	5 (13)
Arthralgia	0	4 (12)	0	4 (10)
Chills	0	4 (12)	0	4 (10)
Headache	0	4 (12)	0	4 (10)
Urinary tract infection	0	4 (12)	0	4 (10)

Source data: Study EGF10030, Table 8.2.

a. This subject received letrozole for 2.7 weeks and discontinued treatment (and the study) before receiving lapatinib.

A review of cardiac events revealed that four patients developed a decrease in LVEF by at least 20% from baseline. Only one of these was considered to be treatment-related by the investigator. It was grade II in intensity and resolved without dose modification.

A review of diarrhoea revealed that 30 patients developed diarrhoea during the study, four on lapatinib 1250 mg and 26 on lapatinib 1500 mg. The majority of these events were considered to be treatment-related and most were grade I or II in intensity. Six patients had grade III diarrhoea although none led to discontinuation of study treatment. One of these patients had diarrhoea that was considered to be serious. Four patients required dose interruption and subsequent dose reduction.

A review of the incidence of rash in study EGF10030 revealed that 25 patients had 36 events of rash, three of whom were on lapatinib 1250 mg and 22 on lapatinib 1500 mg. Most of the events reported were considered to be treatment-related and were grade I and II in intensity. No serious adverse events of rash were reported but one patient developed grade III rash which led to

discontinuation of study treatment. Two patients developed nail disorders which were grade I in intensity and considered to be treatment-related.

No patients developed interstitial pneumonitis on this study.

A review of laboratory changes revealed that among the haematological assessments anaemia was reported in five patients who received lapatinib 1500 mg, three of which were grade III in intensity. Leukopenia was reported in one patient. Only one of these was considered to be treatment related, namely a grade III event of anaemia. This apparently resolved without dose modification.

A review of clinical chemistry changes revealed that four events of hypokalaemia were reported, three of which were considered serious adverse events and one grade III in intensity. All four events of hypokalaemia resolved without the need for dose modification. Grade II hypocalcaemia and hypomagnesaemia were reported in one patient each. These resolved without dose modification. None of these events were considered to be related to treatment by the investigator.

Evaluator's Comments

These data, particularly those from the pivotal trial EGF30008, essentially confirm the known safety profile for lapatinib. Those adverse effects most commonly related to lapatinib, namely diarrhoea, skin rash, nausea and vomiting had been well described previously. The incidence and severity of these adverse events in study EGF30008 were essentially similar to those previously reported. There was clearly an incidence of more significant adverse events, namely hepatic function disturbance, cardiac events and interstitial pneumonitis. All of these were relatively uncommon but potentially serious. Clearly these will require appropriate monitoring in any administration of lapatinib.

It is noteworthy that there were no new adverse events reported in this trial and those even associated with potential serious sequelae are well recognised as toxicities associated with the general class of tyrosine kinase inhibitors.

Post-Marketing Experience

There were no formal post-marketing surveillance studies for lapatinib. Routine pharmacovigilance monitoring has been undertaken in relation to the initial approval of lapatinib in combination with capecitabine for metastatic breast cancer. An individual usage programme in France has enrolled a total of 1385 patients as of August 2008 and review of serious adverse events in this programme has revealed a total of 1554 adverse events of which 498 were serious among 555 patients. The most frequently reported were diarrhoea and general health deterioration. Among the serious adverse events reported the most frequent treatment-related events were diarrhoea, vomiting and nausea. Of the 167 deaths reported, six were assessed as related to study medication. One patient had developed hepatocellular dysfunction, another cardiac tamponade, a third disseminated intravascular coagulation, a fourth an acute cardiac event, a fifth septic shock and the last patient internal haemorrhage.

A total of 39 hepatobiliary events have been reported of which twenty are considered possibly related to lapatinib. This gives an overall incidence of approximately 1.4%. Two of these were fatal.

A total of 23 cardiac events have been reported all of which were decreased LVEF events. This is an incidence of 1.7%. The majority (78%) were asymptomatic and most events resolved on discontinuation of lapatinib. One patient developed congestive cardiac failure which resolved on discontinuation of lapatinib. There have been two cases of pneumonitis reported one of which involved lapatinib as a monotherapy.

Evaluator's Comments

This data again essentially confirms the known safety profile for lapatinib and no new toxicities have been reported. However, the evaluator emphasised the need for appropriate monitoring in relation to hepatic, cardiac and pulmonary events.

Clinical Summary and Conclusions

The Phase I study EGF10030 involved enrolment of a total of 39 patients with advanced stage malignancies of whom 18 had advanced and metastatic breast cancer and 16 had advanced and metastatic ovarian cancer. These patients had been heavily previously treated and were enrolled into the study in three cohorts. Data revealed that there was no evidence with concurrent administration of lapatinib and letrozole of a statistically significant alteration in the PK of either drug. Although there was a tendency towards lower plasma concentrations of lapatinib in the presence of letrozole no statistically significant or clinically meaningful difference was found.

The pivotal study EGF30008 was a randomised double-blind placebo-controlled parallel group multi-centre Phase III study to evaluate the efficacy and tolerability of lapatinib and letrozole (letrozole 2.5 mg plus lapatinib 1500 mg) compared with letrozole 2.5 mg and placebo. A total of 1286 patients were enrolled and 644 receiving placebo and 642 lapatinib with all patients being hormone receptor positive and having advanced or metastatic breast cancer who had not received prior therapy for advanced or metastatic disease. All patients received continuing therapy until disease progression or withdrawal from treatment. All patients were followed for survival information until lost to follow up.

The study was conducted in 29 countries at 212 centres. The majority (57%) of patients were enrolled in Europe. The two treatment groups were generally well balanced in terms of their baseline disease characteristics in the HER2+, ITT and HER2-negative populations.

In these patients with HER2+ tumours a statistically significant improvement in investigator-evaluated progression free survival in patients treated with letrozole plus lapatinib compared with letrozole plus placebo was observed - HR 0.71, $p = 0.019$. Results of PFS assessed by the independent review committee supported these findings. The median PFS for patients receiving lapatinib was 60 weeks vs 35.4 weeks for patients receiving placebo - $p = 0.022$.

There was a statistically significantly longer PFS in the letrozole plus lapatinib group compared with the letrozole plus placebo group in the ITT population by Kaplan-Meier and Cox regression analyses. However the 4.7 week PFS prolongation in the letrozole plus lapatinib group compared with the letrozole plus placebo group may not be clinically relevant. In the ITT population there is no significant difference between the two treatment groups in relation to overall survival and overall response rates.

For the HER2-patient population investigator-evaluated PFS as examined by Kaplan-Meier demonstrated an insignificant treatment effect - HR 0.9, $p = 0.188$. A step wise Cox regression analysis showed an adjusted treatment HR of 0.77, $p = 0.01$. These data however need to be considered with reservation.

A review of efficacy data for study EGF10030 showed that of a total of 34 patients, who were assessed for response, no patients had a complete response and two patients had a partial response. One patient with breast cancer in the dose finding phase of trial involving 1250mg of lapatinib had an unconfirmed partial response. It is noteworthy that all of these patients had been heavily treated previously.

In EGF30008, the incidence of adverse events was greater in the letrozole plus lapatinib group occurring in 96% of patients compared to the letrozole plus placebo group who had an adverse event incidence of 86%. The most frequently reported treatment related adverse events for patients receiving letrozole plus lapatinib were diarrhoea (53%), rash (38%) and nausea (20%). Most

adverse events were of grade I and II and resolved. Diarrhoea, nausea and rash are well recognised in association with tyrosine kinase inhibitors. The incidence of adverse events did not appear to be influenced by age.

The percentage of patients with serious adverse events and adverse events leading to permanent discontinuation of study treatment were higher in the letrozole plus lapatinib group (22% and 15% respectively) compared to letrozole plus placebo group (15% and 6% respectively).

As at the data cut-off date 3 June 2008, 474 patients had died (37%) with the primary cause of death in both treatment groups being disease progression. Fatal serious adverse events were reported in 16 patients, eight in each treatment group. It was considered that three of these were related to study treatment, two patients in the letrozole plus placebo group dying from myocardial infarction and dyspnoea and one in the letrozole plus lapatinib group dying of abnormal hepatic function.

Review of significant individual toxicities confirmed the relatively high incidence of diarrhoea being reported in 64% of patients receiving letrozole plus lapatinib compared to 20% receiving letrozole plus placebo. Most adverse events were grade I or II in severity. The first occurrence of diarrhoea for the majority of patients receiving letrozole plus lapatinib was within four weeks of initiating treatment. Two patients actually had diarrhoea as a serious adverse event (<2%) or permanently discontinued study treatment because of diarrhoea (<4%).

Incidence of rash was more frequent in the letrozole plus lapatinib patients occurring in 50% compared to 15% of patients receiving letrozole plus placebo. The majority were grade I or II in intensity. The first occurrence of rash was generally within four weeks. Rash was predictable and the majority of events (>90%) resolved without action being taken regarding study treatment or the need for treatment of the rash.

Hepatobiliary events were reported less frequently in the letrozole plus placebo group (8%) compared with the letrozole plus lapatinib group (15%). The majority of these occurred within six months from the start of treatment. Most did not require any action being taken with regards to study treatment. There was one fatal event of hepatic dysfunction which was assessed as possible cholestatic drug induced liver injury or associated with disseminated liver metastases. Two additional cases of elevated liver function tests were assessed as probable drug induced liver injury.

Among cardiac events assessed, a total of 47 patients had 51 cardiac events which were predominantly decreased left ventricular ejection fraction. Thirty-nine of these patients were receiving letrozole plus lapatinib and 16 were receiving letrozole plus placebo. Twenty of these events in the patients receiving letrozole plus lapatinib were considered serious adverse events compared to eight in the letrozole plus placebo group. Five of these patients had symptomatic events.

Pneumonitis was reported in one patient receiving letrozole plus placebo and another patient receiving letrozole plus lapatinib. It was considered that the patient receiving lapatinib had pneumonitis secondary to treatment.

Assessment of haematological and clinical chemistry parameters revealed only minor variations throughout the course of study in both treatment groups.

Review of safety data from Phase I trial EGF10030 revealed that a total of 37 patients had 394 adverse events during study. Of these 213 events in 34 patients were considered to be related to treatment the most common being diarrhoea (77%), rash (62%) and nausea (46%). Twenty one patients had grade III adverse events and two grade IV adverse events when receiving lapatinib 1500mg. Diarrhoea, anaemia and hyperkalaemia were the grade III adverse events. One patient had a decline of 31% in LVEF relative to baseline. A total of 41 non-fatal serious adverse events were reported for 11 patients (28%). Three of these were considered to be related to treatment including grade III anaemia and grade III diarrhoea. One patient died due to grade IV respiratory

failure but was not considered to be related to treatment. One other adverse event was a grade III rash which led to discontinuation of study treatment.

These data have therefore demonstrated that from the pivotal study EGF30008 that there is definite evidence of benefit from lapatinib in conjunction with letrozole in prolonging progression free survival for patients with previously untreated hormone receptor positive metastatic breast cancer. This result is quite robust in a relatively large study and confirmed by sensitivity analyses and sub-group assessments. Overall response rates were also significantly better for those patients receiving lapatinib compared to placebo. A secondary but very important parameter namely overall survival was not significantly different between the two treatment groups. It is recognised however that the data is still somewhat immature and further follow up is required.

It is also pertinent to note that in relation to PFS the response rates of this data was particularly related to those who are HER2+. The HER2-negative patient population in this trial failed to reveal significant differences in PFS or other parameters. Certainly sub-group analyses suggest that some potential benefit for the addition of lapatinib to letrozole for these patients but as the primary parameters of assessment were not significant one has to view these data with reservation.

In relation to toxicities the adverse effect profiles observed in the pivotal trial essentially confirm those already well recognised for lapatinib namely that diarrhoea, skin rash, nausea and vomiting are frequent. These however are generally manageable. Of some concern are the infrequent but nevertheless potentially severe adverse effects of hepatic dysfunction, cardiac dysfunction and pneumonitis. These would require careful monitoring to ensure safety in the context of long term patient administration of lapatinib. No new significant adverse effects were reported from the current pivotal trial.

The evaluator believed that the data from this pivotal study are robust and therefore indicative of an apparent clinical benefit for the addition of lapatinib to letrozole in the treatment of patients with hormone receptor positive previously untreated metastatic breast cancer. Further follow up is desirable to assess the potential benefit on overall survival. Being a single study does require some reservation about the overall validity of the data but in the context of a large robust study with a clear cut benefit, it is appropriate to make a recommendation for marketing of lapatinib in combination with letrozole for the proposed new indication, namely, lapatinib in combination with an aromatase inhibitor is indicated for the treatment of patients with hormone sensitive metastatic breast cancer whose tumours overexpress HER2 (ErbB2).

V. Pharmacovigilance Findings

Risk Management Plan

A Risk Management Plan (RMP) was submitted by the sponsor and reviewed by the TGA's Office of Medicines Safety Monitoring (OMSM). The following important safety concerns were identified by the sponsor:

Important identified risks	Hepatobiliary events Decreased LVEF Pneumonitis/ILD Diarrhoea Rash
Important potential risks	QTc changes Food effect/grapefruit
Important missing information	Children The Elderly Pregnant or lactating females Patients with hepatic disease Patients with renal disease Patients with low cardiac ejection fraction Patients of different racial and / or ethnic origin

The sponsor stated that there are no newly identified safety concerns for lapatinib based on the data from the lapatinib plus letrozole combination studies EGF30008 and EGF10030.

The proposed application of routine pharmacovigilance activities for all safety concerns as identified by the sponsor and the application of additional pharmacovigilance activities for some of these safety concerns were considered to be generally acceptable.

Nevertheless it would appear that the two planned clinical studies in the pharmacovigilance plan have now been cancelled for various reasons (LPT112513 and EGF111583). In particular the planned study LPT112513, which was to provide information on lapatinib use in breast cancer patients with left ventricular dysfunction, was cancelled due to insufficient numbers of patients with low LVEF. Therefore it was suggested that the sponsor make some provision to pro-actively gain such information by initiating an appropriate patient registry, the details of which should be submitted to the TGA for assessment.

In addition little detail has been provided regarding the 'targeted follow up questionnaire' to be employed for some of the safety concerns. Therefore the sponsor should provide copies of these documents to the TGA.

The sponsor responded by indicating that it had considered the feasibility of conducting an observational study using one or more external electronic medical records databases but it considered that at the present time, there are too few patients captured in population-based observational databases with both exposure to lapatinib and decreased LVEF to provide a meaningful sample size to study rare safety events. The sponsor provided details on the targeted follow-up questionnaires used to document reports of cardiac events, pneumonitis and hepatobiliary events. The sponsor also gave assurance that updates on targeted safety studies and other important studies would be provided in Periodic Safety Update Reports (PSURs).

The sponsor's response was generally considered acceptable by the OMSM except for the issue of a patient registry. The OMSM noted that it is in this situation that a patient registry, as suggested by the TGA, would be of most use to determine if lapatinib has a special impact in breast cancer patients with left ventricular dysfunction. Such a registry may collect a battery of information, including data on adverse events, using standardised questionnaires in a prospective fashion. Patients may be followed over time to further characterise risks.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There were no toxicological concerns with the proposed higher dose of lapatinib since lapatinib AUC and C_{max} were lower when lapatinib was co-administered with letrozole.

Pharmacokinetic interactions between lapatinib and the aromatase inhibitors letrozole or exemestane are considered unlikely based on information in the product information.

There were two carcinogenicity studies, one in mice and one in rats. The rat study showed an increased incidence of benign haemangiomas with lapatinib, but the incidence was within background range.

There were no nonclinical objections to approval.

Clinical

In the dose-finding cohort (n=12) of trial EGF10030 of letrozole in combination with lapatinib in cancer patients (mostly breast and ovarian cancer), the letrozole dose was held constant at 2.5 mg

once daily whilst the lapatinib dose was escalated from 1,250 mg to 1,500 mg once daily. The optimal lapatinib dose was 1,500 mg. An additional seven subjects confirmed the tolerability of this dose. In the pharmacokinetic cohort (n=18), interaction between lapatinib and letrozole was not clinically significant.

In a randomised, double-blind trial (EGF30008)⁴ in post-menopausal women with metastatic hormone-receptor positive breast cancer, the addition of lapatinib to letrozole significantly increased progression-free survival (PFS), the primary endpoint, by a small amount (median 1.1 months) (Table 13). In subgroup analysis, the increase in PFS was clinically significant (median 5.1 months) in subjects with HER2-positive tumours but there was no significant increase in those with HER2-negative tumours. Overall survival was not significantly increased, although there was a small trend in favour of the letrozole-lapatinib combination in those with HER2-positive tumours (Table 13). HER2 receptor status had been determined retrospectively and was done in 91% of subjects. The dose of letrozole was 2.5 mg once daily and lapatinib 1,500 mg once daily orally. Treatment was continued until disease progression or unacceptable toxicity. The median age of subjects was 60 years, range 44-87 years.

Table 13: Efficacy of Letrozole + Lapatinib in Metastatic HR+, HER2+ Breast Cancer

	Letrozole + Lapatinib	Letrozole + Placebo	Hazard Ratio¹ [95% CI]
<i>Intent-to-Treat</i>	<i>n=642</i>	<i>n=644</i>	
PFS <i>median mths</i>	11.9	10.8	0.86 [0.76, 0.98]
OS <i>median mths</i>	not stated	not stated	not stated
<i>HER2-Positive</i>	<i>n=111</i>	<i>n=108</i>	
PFS <i>median mths</i>	8.1	3.0	0.71 [0.53, 0.96]
OS <i>median mths</i>	33.3	32.3	0.74 [0.50, 1.10]
<i>HER2-Negative</i>	<i>n=478</i>	<i>n=474</i>	
PFS <i>median mths</i>	13.7	13.4	0.90 [0.77, 1.05]
OS <i>median mths</i>	40.1	45.5	1.15 [0.90, 1.40]

¹ Lapatinib/Placebo. Survival estimates are from Kaplan-Meier analysis.

⁴ Johnston S, Pippen J, Pivot X et al. Lapatinib Combined With Letrozole Versus Letrozole and Placebo As First-Line Therapy for Postmenopausal Hormone Receptor-Positive Metastatic Breast Cancer. J Clin Oncol 2009; 27: 5538-5546.

The major safety data was from the pivotal trial in which 654 subjects received the letrozole-lapatinib combination. The median duration of treatment in this trial was 9 months. There was a higher incidence of adverse events with the letrozole-lapatinib combination (96%) than with letrozole-placebo (86%), and also a higher incidence of serious adverse events (22% vs 15%) and adverse events leading to treatment discontinuation (15% vs 6%) (Table 8). Common adverse effects were anorexia, nausea, vomiting, diarrhoea, rash and fatigue (Table 9). Hepatobiliary events, mainly increases in liver enzymes, were also common.

Serious cardiac and gastrointestinal events were common and of higher incidence with the letrozole-lapatinib combination. Hepatic injury in 3 subjects was probably related to the letrozole-lapatinib combination. An instance of interstitial pneumonitis in a subject on letrozole-lapatinib was considered drug-related.

In the Phase I trial, 38 subjects received the letrozole-lapatinib combination. Adverse effects observed were consistent with those in the pivotal trial.

The evaluator recommended approval.

Risk Management Plan (RMP)

Important identified risks are hepatobiliary events, decreased left ventricular ejection fraction (LVEF), pneumonitis and interstitial lung disease, diarrhoea and rash. Regular review of reports of these events is proposed. Further, a targeted follow-up questionnaire is proposed for hepatobiliary events, decreased LVEF and pneumonitis.

The advice in the product information under Precautions, Adverse Events and Dosage and Administration is detailed with respect to risk minimisation. The sponsor will conduct a retrospective epidemiology study to evaluate physician compliance with liver function test monitoring. The sponsor is also investigating ways to evaluate the effectiveness of risk minimisation advice for the other identified risks.

In regard to cardiac risk, the OMSM evaluator requested the sponsor implement a patient registry of the experience of lapatinib in breast cancer patients with left ventricular dysfunction. The sponsor questioned the scientific benefit of a registry due to the rarity of patients with decreased LVEF and exposure to lapatinib. The RMP reviewer countered that a registry “would be of most use in this situation” and that it “may collect a battery of information, including data on adverse events using standardised questionnaires in a prospective fashion. Patients may be followed over time to further characterise risks”. The sponsor was invited to further respond in their pre-ACPM Response on the merit and feasibility of a patient registry. The sponsor considered that a patient registry or an observational study would not be feasible due to the rarity of patients exposed to lapatinib and also with baseline decreased LVEF.

There were some additional undertakings and requests.

Risk-Benefit Analysis

Concomitant administration of lapatinib and letrozole did not significantly alter the pharmacokinetics of either agent. This is also likely for concomitant administration of lapatinib and other aromatase inhibitors.

In post-menopausal women with metastatic hormone-receptor positive and HER2-positive breast cancer, the addition of lapatinib to letrozole increased progression-free survival by a clinically significant amount (median 5.1 months). There was also a trend to increase in overall survival; however, the effect appeared small (median 1.0 month).

Adverse effects with the letrozole-lapatinib combination were consistent with the known safety profiles of letrozole and lapatinib. Serious effects such as decreased cardiac ejection fraction, hepatotoxicity and interstitial lung disease were seen and are well known with lapatinib. There were

no new serious effects. The incidence of adverse events was increased with the letrozole-lapatinib combination. The incidence of serious adverse events and discontinuations due to adverse events was almost doubled with letrozole-lapatinib compared with letrozole-placebo.

Therefore, the increased efficacy of letrozole-lapatinib in HER2-positive subjects is at the cost of an increased incidence of adverse events, serious adverse events and discontinuations.

The benefit is likely to outweigh the risk and therefore, the Delegate recommended approval. However, more information is needed about the risks in the PI. The Delegate recommended a table of the incidence of serious adverse effects with the letrozole-lapatinib combination in the product information.

The proposed combination of an aromatase inhibitor and lapatinib has not been directly compared with the combination of chemotherapy and lapatinib in first line treatment of hormone receptor positive, HER2-receptor positive metastatic breast cancer. The latter combination is likely to have greater efficacy based on data for trastuzumab in combination with a taxane and in combination with anastrozole (see trastuzumab product information). A chemotherapy regimen is likely to remain the treatment of choice. However, in specific instances, an aromatase inhibitor-lapatinib or aromatase inhibitor-trastuzumab regimen may be advantageous since the chemotherapy regimen is likely to be more toxic. Both the taxane- and aromatase inhibitor-trastuzumab combinations are approved for first line metastatic breast cancer. A first line chemotherapy-lapatinib combination has not been evaluated.

In view of the trastuzumab approvals and the need for choice in the absence of additional information, the lack of a comparison between aromatase inhibitor-lapatinib and chemotherapy-lapatinib is not a barrier to approval. However, the sponsor is urged to clarify the relative benefits of the aromatase inhibitor-lapatinib and chemotherapy-lapatinib regimens and the optimal patient populations for each.

The indication should be restricted to post-menopausal women in line with the current registration for aromatase inhibitors and trastuzumab. There were no data in males or pre-menopausal women. The term “hormone receptor-positive” rather than “hormone sensitive” is preferred.

The anti-oestrogen effects of aromatase inhibitors are likely to be similar at the recommended dosage of one tablet daily. Therefore, the Delegate supported the general indication proposed of combination with an aromatase inhibitor rather than limiting the indication to combination with letrozole, the aromatase inhibitor used in the trials.

The proposed Risk Management Plan (RMP) is directed at the identified risks. The Delegate requested advice from the Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC) on the RMP evaluator’s recommendation for a patient registry to assess cardiac risk. The Delegate recommended that additional undertakings and requests be incorporated into the plan.

The Delegate recommended approval of the following indication:

In combination with an aromatase inhibitor, treatment of post-menopausal women with metastatic hormone receptor-positive breast cancer whose tumours overexpress HER2 (ErbB2),

The ACPM, having considered the evaluations and the Delegate’s overview, as well as the sponsor’s response to these documents, agreed with the Delegate’s proposal and recommended the following indication:

Lapatinib (TYKERB) in combination with an aromatase inhibitor is indicated for the treatment of post-menopausal women with hormone receptor-positive metastatic breast cancer whose tumours overexpress HER2 (ErbB2) and for whom hormonal therapy is indicated.

In making this recommendation the ACPM considered the merit of restricting access to post-menopausal women in line with the current registration for aromatase inhibitors and trastuzumab and advised that it would not be appropriate to approve the combination in premenopausal women and, while it is likely to work in men, it would also not be appropriate to approve use in men in the absence of data.

The ACPM advised that the important identified risks include hepatobiliary events, decreased LVEF and pneumonitis and supported the recommendation for a targeted follow up patient questionnaire. The ACPM advised that as the adverse effects with the letrozole-lapatinib combination were consistent with the known safety profiles of letrozole and lapatinib the risk benefit analysis favours this combination.

Outcome

Based on a review of quality, safety and efficacy, TGA approved registration of Tykerb tablet blister pack containing lapatinib (as ditosylate monohydrate) 250mg for the new indication:

Lapatinib (Tykerb) in combination with an aromatase inhibitor is indicated for the treatment of post-menopausal women with hormone receptor-positive metastatic breast cancer whose tumours overexpress HER2 (ErbB2) and for whom hormonal therapy is indicated.

In addition to standard conditions of registration, a further condition was that:

The revised Risk Management Plan submitted to the Office of Medicines Safety Monitoring on 11 May 2010 must be implemented.

Attachment 1. Product Information

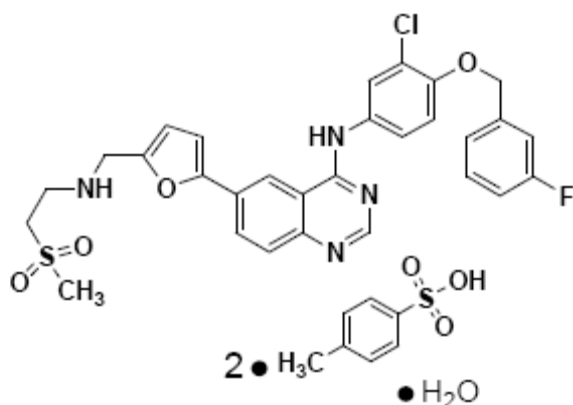
The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

TYKERB® PRODUCT INFORMATION
(Lapatinib Ditosylate)
250 mg tablets

NAME OF THE DRUG

TYKERB® film-coated tablets contain lapatinib ditosylate which is a member of 4-anilinoquinazoline class of kinase inhibitors. The chemical name for (IUPAC) lapatinib ditosylate is N-(3-chloro-4-[(3-fluorophenyl) methyl]oxy)phenyl)-6-[5-({[2-(methylsulfonyl)ethyl]amino}methyl)-2-furanyl]-4-quinazolinamine bis(4-methylbenzenesulfonate) monohydrate.

The structural formula is:



Molecular formula: C₂₉H₂₆ClFN₄O₄S(C₇H₈O₃S)₂H₂O

Molecular weight: 943.48 (ditosylate monohydrate)

CAS number : 388082-78-8

DESCRIPTION

Lapatinib ditosylate monohydrate is a yellow solid, and its solubility in water is 0.007 mg/mL and in 0.1N HCl is 0.001 mg/mL at 25 °C.

TYKERB® 250 mg film-coated tablets contain microcrystalline cellulose, povidone K30, sodium starch glycolate, magnesium stearate, hypromellose, titanium dioxide, macrogol 400, Polysorbate 80, Iron oxide red (CI77491) and Iron oxide yellow (CI77492).

PHARMACOLOGY

Lapatinib is a potent, reversible, and selective inhibitor of the intracellular tyrosine kinase domains of both ErbB1 (EGFR) and HER2 (ErbB2) receptors (estimated K_i^{app} values of 3nM and 13nM, respectively) with a slow off-rate from these receptors (half-life greater

than or equal to 300 minutes). This dissociation rate from ErbB1 (EGFR) was found to be slower for lapatinib than for erlotinib and gefitinib. Lapatinib inhibits tumour cell proliferation *in vitro*, and inhibits the growth of ErbB1 (EGFR) and HER2 over-expressing xenograft tumours in mice. Inhibition of tumour growth was associated with decreased phosphorylation of ErbB1 (EGFR) and HER2 in tumour tissue.

The growth inhibitory effects of lapatinib were evaluated in trastuzumab-conditioned cell lines. Lapatinib retained significant activity against breast cancer cell lines selected for resistance to trastuzumab by long-term growth in trastuzumab-containing medium *in vitro*. These findings suggest non-cross-resistance between these two HER2 directed agents.

Hormone sensitive breast cancer cells (oestrogen receptor [ER] positive and/or progesterone receptor [PgR] positive) that co-express HER2 tend to be resistant to established endocrine therapies. Hormone sensitive breast cancer cells that initially lack overexpression of EGFR or HER2 will up regulate these receptors as the tumour becomes resistant to endocrine therapy.

Pharmacokinetics

Absorption:

Absorption following oral administration of lapatinib is highly variable. Serum concentrations appear after a median lag time of 0.25 hours (range 0 to 1.5 hours). Peak plasma concentrations (C_{max}) of lapatinib are achieved approximately 4 hours after administration. Daily dosing of 1250 mg produces steady state geometric mean (95% confidence interval) C_{max} values of 2.43 (1.57 to 3.77) $\mu\text{g/mL}$ and AUC values of 36.2 (23.4 to 56) $\mu\text{g}\cdot\text{hr/mL}$. The absolute bioavailability of lapatinib has not been determined.

Systemic exposure to lapatinib is increased when administered with food (*See Dosage and Administration and Interactions*). Lapatinib AUC values were approximately 3- and 4-fold higher (C_{max} approximately 2.5 and 3-fold higher) when administered with a low fat (5% fat [500 calories]) or with a high fat (50% fat [1,000 calories]) meal, respectively.

Distribution:

Lapatinib is highly bound (greater than 99%) to plasma proteins.

Metabolism:

Lapatinib undergoes extensive metabolism, primarily by CYP3A4 and CYP3A5, with minor contributions from CYP2C19 and CYP2C8 to a variety of oxidated metabolites, none of which account for more than 14% of the dose recovered in the faeces or 10% of the lapatinib concentration in plasma. Furthermore, it is unlikely that any of these metabolites would contribute to the pharmacological activity of lapatinib.

Lapatinib significantly inhibited the metabolism of the substrates of the recombinant CYP enzymes, CYP3A4 and CYP2C8 *in vitro* at clinically relevant concentrations ($\sim 5 \mu\text{M}$ or 3 $\mu\text{g/mL}$). Lapatinib did not significantly inhibit the following enzymes in human liver

microsomes: CYP2C9, CYP2C19 and CYP2D6 or UGT enzymes (in vitro IC₅₀ values were greater than or equal to 6.9 µg/mL). Lapatinib was reported to inhibit the metabolism of substrates of recombinant CYP1A2, however it did not significantly inhibit CYP1A2 in human liver microsomes.

In healthy volunteers receiving ketoconazole, a CYP3A4 inhibitor, at 200 mg twice daily for 7 days, systemic exposure to lapatinib was increased approximately 3.6-fold, and half-life increased 1.7-fold.

In healthy volunteers receiving carbamazepine, a CYP3A4 inducer, at 100 mg twice daily for 3 days and 200 mg twice daily for 17 days, systemic exposure to lapatinib was decreased approximately 72%.

Excretion:

The half-life of lapatinib measured after single doses increases with increasing dose (range 6 to 14 hours). However, daily dosing of lapatinib results in achievement of steady state within 6 to 7 days, indicating an effective half-life of 24 hours. The primary route of elimination for lapatinib and its metabolites is in faeces, with less than 2% of the dose (as lapatinib and metabolites) excreted in urine. Recovery of unchanged lapatinib in faeces accounts for a median 27% (range 3 to 67%) of an oral dose.

Special Populations:

Renal Impairment

Lapatinib pharmacokinetics have not been specifically studied in patients with renal impairment or in patients undergoing haemodialysis. However, renal impairment is unlikely to affect the pharmacokinetics of lapatinib given that less than 2% of an administered dose (as unchanged lapatinib and metabolites) is eliminated by the kidneys.

Hepatic Impairment

The pharmacokinetics of lapatinib were examined in subjects with moderate (n = 8) or severe (n = 4) hepatic impairment and in 8 healthy control subjects. Systemic exposure (AUC) to lapatinib after a single oral 100 mg dose increased approximately 56% and 85% in subjects with moderate and severe hepatic impairment, respectively. Administration of lapatinib in patients with hepatic impairment should be undertaken with caution due to increased exposure to the drug. A dose reduction is recommended for patients with severe pre-existing hepatic impairment. In patients who develop severe hepatotoxicity while on therapy, lapatinib should be discontinued and patients should not be retreated with lapatinib (*see Dosage and Administration and Precautions*).

CLINICAL TRIALS

Combination treatment with TYKERB and capecitabine

The efficacy and safety of TYKERB in combination with capecitabine in breast cancer was evaluated in a randomised, phase III trial (EGF100151). Patients eligible for enrolment had HER2 over-expressing, locally advanced or metastatic breast cancer, after prior treatment that included taxanes, anthracyclines and trastuzumab. LVEF was evaluated in all patients (using echocardiogram or MUGA) prior to initiation of treatment with TYKERB to ensure baseline LVEF was within the institutions normal limits.

In clinical trials, LVEF was monitored at approximately 8-week intervals during treatment with TYKERB to ensure it did not decline to below the institutions lower limit of normal. The majority of LVEF decreases (greater than 60%) were observed during the first nine weeks of treatment, however limited data was available for long term exposure.

Patients were randomized to receive either TYKERB 1250 mg once daily (continuously) plus capecitabine (2000 mg/m²/day on days 1-14 every 21 days), or to receive capecitabine alone (2500 mg/m²/day on days 1-14 every 21 days). The primary efficacy endpoint was time to tumour progression (TTP) as assessed by an independent review panel. TTP was defined as the time from randomisation to tumour progression or death related to breast cancer.

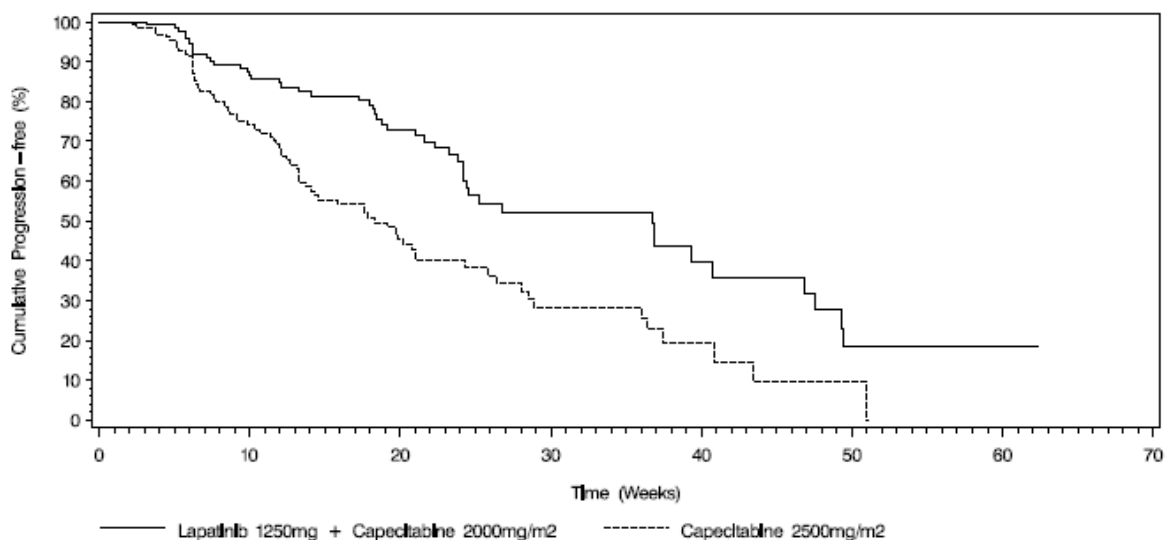
At the data cut-off date for the pre-specified interim analysis (November 15, 2005), 324 patients were enrolled (163 in the combination arm, 161 in the monotherapy arm). The efficacy results showed a statistically significant improvement in TTP (51% reduction in the hazard of disease progression) for patients receiving TYKERB plus capecitabine with a median TTP of 8.5 months in the combination arm versus 4.5 months in the monotherapy arm (p 0.00008). See Table 1.

Table 1: Efficacy results by Independent Review from EGF100151 clinical trial in locally advanced or metastatic breast cancer (Pre-specified Interim analysis)

Efficacy Outcome	TYKERB plus capecitabine (N=163)	Capecitabine alone (N=161)
Time to progression		
Progressed or died due to breast cancer	30%	45%
Median time to progression (months)	8.5	4.5
Hazard ratio, 95% CI (p value)	0.49 (0.34, 0.71) 0.00008	

The TTP data are represented graphically in Figure 1.

Figure 1: Kaplan-Meier Estimates of Time to Progression (TTP) by Independent review: TYKERB + capecitabine v capecitabine (Study EGF100151, pre-specified interim analysis)



Note: Four subjects who died due to causes other than breast cancer were censored.

Progression-free survival (PFS) is defined as time from randomisation until disease progression or death due to any cause. At the interim analysis, TYKERB, when given in combination with capecitabine significantly prolonged PFS compared to capecitabine alone (8.5 months v 4.1 months, $p=0.000023$).

The response rate (complete or partial response) independently assessed was 22% in the TYKERB plus capecitabine group compared with 14% in the capecitabine group ($p = 0.091$); similar results were observed for the clinical benefit response rate (complete response + partial response + stable disease for at least 6 months), which was 27% vs 18% ($p=0.069$) in the combination versus the monotherapy arm, respectively.

At the time of interim analysis, the survival data were not sufficiently mature to detect a difference in overall survival between the treatment groups, 36 subjects (22%) in the TYKERB plus capecitabine group and 35 subjects (22%) in the capecitabine group had died. An exploratory analysis of patients with central nervous system (CNS) metastases showed four (2%) patients in the combination-therapy group had symptomatic CNS progression as part of their first progression event as compared to 11 (7%) patients in the monotherapy group ($p=0.068$).

An independent data monitoring committee (IDMC) initially reviewed the results of the interim analysis (which included data from 321 of the 324 patients), and recommended that further enrolment into the study was halted due to a statistically significant and clinically relevant increase in TTP for the combination of TYKERB and capecitabine over

capecitabine alone, which crossed a pre-defined statistical stopping boundary for superiority. At the time enrolment was halted (April 03, 2006), a total of 399 patients had been randomised to study treatment.

A subsequent updated analysis was conducted with a data cut-off of April 03, 2006 when enrollment was halted. An additional 75 subjects had been enrolled into the study between the interim analysis clinical cut-off date and halting enrollment into the study (n=198 combination arm vs n= 201 control arm). This analysis revealed maintenance of a highly statistically significant improvement in TTP for subjects enrolled in the combination arm conferring a 43% reduction in hazard of disease progression (p=0.00013). The median TTP by independent review for the combination arm versus the control arm was 6.3 versus 4.3 months respectively. At this time, the overall survival data remained immature: 55 subjects (28%) in the TYKERB plus capecitabine group and 64 subjects (32%) in the capecitabine group had died. Four (2%) patients in the combination-therapy group had symptomatic CNS progression as part of their first progression event as compared to 13 (6%) patients in the monotherapy group (p=0.0445).

Combination treatment with TYKERB and letrozole

TYKERB has been studied in combination with the aromatase inhibitor letrozole for the treatment of advanced or metastatic breast cancer in hormone receptor positive (oestrogen receptor [ER] positive and/or progesterone receptor [PgR] positive) postmenopausal women.

EGF30008 was a Phase III, randomised, double-blind, controlled trial in patients with hormone receptor-positive locally advanced or metastatic breast cancer (MBC), who had not received prior systemic therapy for their metastatic disease. 1286 patients were randomised to letrozole 2.5 mg once daily plus TYKERB 1500 mg once daily or letrozole 2.5 mg with placebo. Randomisation was stratified by sites of disease and prior adjuvant anti-oestrogen therapy. HER2 receptor status was retrospectively determined by central laboratory testing.

Of all patients randomised to treatment, 219 patients had tumours over-expressing the HER2 receptor (the 'HER2-positive population'), which was the pre-specified primary population for the analysis of efficacy. There were 952 HER2 negative patients and a total of 115 patients whose HER2 status was unconfirmed.

In the HER2-positive population, investigator-determined progression-free survival (PFS) was significantly greater with letrozole plus TYKERB compared with letrozole plus placebo (see Table 2).

Table 2 Progression Free and Overall Survival data from Study EGF30008 (TYKERB / letrozole)

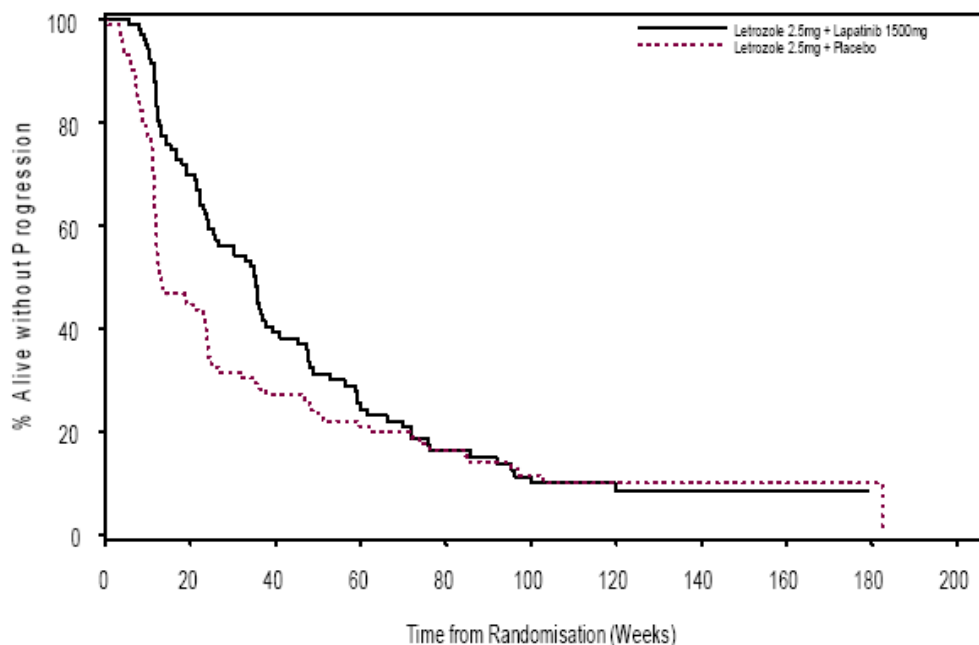
	Primary endpoint		Secondary endpoints			
	HER2-Positive Population		Intent-to-Treat Population		HER2-Negative Population	
	N = 111	N = 108	N = 642	N = 644	N = 478	N = 474
	TYKERB 1500 mg / day + Letrozole 2.5 mg / day	Letrozole 2.5 mg / day + placebo	TYKERB 1500 mg / day + Letrozole 2.5 mg / day	Letrozole 2.5 mg / day + placebo	TYKERB 1500 mg / day + Letrozole 2.5 mg / day	Letrozole 2.5 mg / day + placebo
Median PFS, months (95% CI)	8.2 (5.6, 9.1)	3.0 (2.8, 5.5)	11.9 (10.9, 13.7)	10.8 (8.5, 11.7)	13.7 (11.2, 16.0)	13.4 (11.0, 14.3)
Hazard Ratio	0.71 (0.53, 0.96)		0.86 (0.76, 0.98)		0.90 (0.77, 1.05)	
P-value	0.019		0.026		0.188	
Median OS, months (95% CI)	33.3 (22.0 – NE)	32.3 (21.2 – 36.7)	39.4 (36.3, 45.1)	40.5 (35.9, 43.6)	40.1 (37.1, NE)	41.3 (38.8, NE)
Hazard Ratio	0.74 (0.5, 1.1)		1.01 (0.8, 1.2)		1.15 (0.9, 1.4)	
P-value	0.113		0.915		0.193	

CI= confidence interval

NE = Non-evaluable

The PFS data in the HER2-positive population is represented graphically in Figure 2.

Figure 2: Kaplan-Meier Estimates for Investigator-Evaluated PFS (Study EGF30008, HER2 +ve Population)



The benefit of TYKERB + letrozole on PFS in the HER2-positive population was confirmed in a pre-planned Cox regression analysis (HR=0.65 (95 %CI 0.47-0.89) p=0.008). In addition to a PFS benefit seen in the HER2+ patient population, combination therapy of TYKERB and letrozole was associated with a significant improvement in objective response rate (27.9 % and 14.8 % respectively) (p=0.021) compared with treatment with letrozole plus placebo. Although not yet mature, a trend towards a survival benefit was noted for the TYKERB/letrozole combination, HR= 0.74 (95 % CI 0.50, 1.1) p=0.113 (see Table 2).

In the Intent-to-Treat (ITT) population, investigator-determined PFS was greater between the two treatment arms (see Table 2). Although statistically significant, the difference was not considered clinically relevant.

In the HER2-negative population (n=952), the Kaplan-Meier analyses for PFS did not show a significant difference between the two treatment arms (see Table 2).

INDICATIONS

TYKERB, in combination with an aromatase inhibitor, is indicated for the treatment of post-menopausal women with hormone receptor-positive metastatic breast cancer whose tumours overexpress HER2 (ErbB2) and for whom hormonal therapy is indicated.

TYKERB, in combination with capecitabine, is indicated for the treatment of patients with advanced /metastatic breast cancer whose tumours overexpress HER2 (ErbB2) and whose tumours have progressed after treatment with an anthracycline, a taxane and trastuzumab.

CONTRAINDICATIONS

TYKERB is contraindicated in patients with hypersensitivity to any of the ingredients (see *Description and Adverse Events*).

PRECAUTIONS

TYKERB has been associated with reports of decreases in left ventricular ejection fraction [LVEF] (see *Adverse Events*). Caution should be taken if TYKERB is to be administered to patients with conditions that could impair left ventricular function. LVEF should be evaluated in all patients prior to initiation of treatment with TYKERB to ensure that the patient has a baseline LVEF that is within the institutions normal limits. LVEF should be evaluated during treatment with TYKERB; this should be performed prior to the initiation of therapy and then approximately 8-12 week intervals to ensure that LVEF does not decline to an unacceptable level (see *Dosage and Administration — Dose delay and dose reduction — Cardiac events and Clinical Trials*).

TYKERB has been associated with reports of interstitial lung disease and pneumonitis (see *Adverse Events*). Patients should be monitored for pulmonary symptoms indicative of interstitial lung disease/pneumonitis (see *Dosage and Administration*).

Hepatotoxicity (ALT or AST >3 times the upper limit of normal and total bilirubin >1.5 times the upper limit of normal) has been observed in clinical trials (<1% of patients) and postmarketing experience. The hepatotoxicity may be severe and deaths have been reported, although the relationship to TYKERB is uncertain. The hepatotoxicity may occur days to several months after initiation of treatment. Liver function tests (transaminases, bilirubin, and alkaline phosphatase) should be monitored before initiation of treatment, every 4 to 6 weeks during treatment, and as clinically indicated. If changes in liver function are severe, therapy with TYKERB should be discontinued and patients should not be retreated with TYKERB (see *Adverse Events*).

Diarrhoea, including severe diarrhoea, has been reported with TYKERB treatment (see *Adverse Events*). 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 TYKERB therapy (see *Dosage and Administration — Dose delay and dose reduction — Other toxicities*).

Concomitant treatment with inhibitors or inducers of CYP3A4 should proceed with caution due to risk of increased or decreased exposure to TYKERB, respectively (see *Interactions*).

Co-administration of TYKERB with medications with narrow therapeutic windows that are substrates of CYP3A4 or CYP2C8 should be avoided (see *Interactions*).

Patients with renal impairment:

Refer to Pharmacokinetics.

Patients with Hepatic Impairment:

If TYKERB is to be administered to patients with severe pre-existing hepatic impairment, dose reduction is recommended. In patients who develop severe hepatotoxicity while on therapy, TYKERB should be discontinued and patients should not be retreated with TYKERB (see *Dosage and Administration and Pharmacokinetics – Hepatic Impairment*).

Elderly:

Refer to Dosage and Administration

Children:

Refer to Dosage and Administration

Genotoxicity:

Lapatinib was not mutagenic in the bacterial reverse mutation assay (Ames test), or clastogenic in Chinese hamster ovary cells or human lymphocytes *in vitro*, or an *in vivo* rat bone marrow chromosome aberration assay. Lapatinib contains an impurity that was genotoxic *in vitro* and *in vivo*, however the levels of this impurity in the drug are considered acceptable given the proposed indication.

Carcinogenicity:

In oral carcinogenicity studies with lapatinib, severe skin lesions were seen at the highest doses tested which produced exposures based on AUC up to 2-fold in mice and male rats, and up to 8-fold in female rats, the anticipated clinical AUC. There was no evidence of carcinogenicity in mice. In rats, the incidence of benign haemangioma of the mesenteric lymph nodes was higher in some groups than in concurrent controls, but was within background range. There was also an increase in renal infarcts and papillary necrosis in female rats at exposures 5 and 8-fold the anticipated clinical AUC. The relevance of these findings for humans is uncertain.

Effects on fertility:

Rat fertility was unaffected by lapatinib at doses (as free base) of up to 180 mg/kg/day (males) and 120 mg/kg/day (females), which correspond to exposures (AUC) that were approximately 2 and 8 times the expected clinical exposure, respectively. There was an increase in post implantation loss in the female fertility study at > 60 mg/kg/day (relative exposure approximately 4). The effect on human fertility is unknown.

Use in Pregnancy (Category C)

Lapatinib was studied in pregnant rats and rabbits given oral doses of 30, 60 and 120 mg/kg/day. There were no treatment-related malformations, however alterations (left-sided umbilical artery, cervical rib) were observed in rats in the presence of maternal toxicity at 120 mg/kg/day (approximately 6 times the clinical exposure based on AUC). An increased number of early post implantation losses were also seen in rats treated at 120 mg/kg/day, while precocious ossification was observed in rats in all treatment groups, independent of maternal toxicity or foetal body weight changes.

In rabbits, an increased incidence of fetuses and litters with minor skeletal variations was seen at ≥ 60 mg/kg/day, in the presence of decreased maternal body weight and clinical signs. Abortions were seen in doses treated at 120 mg/kg/day. Lapatinib exposures at 60 and 120 mg/kg/day in the rabbit study were approximately 10 and 20% respectively, the clinical exposure (based on AUC).

In the pre- and postnatal development study, a marked decrease in pup survival occurred between birth and postnatal day 21 at doses of ≥ 60 mg/kg/day (approximately 3 times the expected clinical exposure based on AUC). The highest no-effect dose for this study was 20 mg/kg/day, similar to the clinical exposure.

There are no adequate and well-controlled studies of TYKERB in pregnant women. The effect of TYKERB on human pregnancy is unknown. TYKERB should not be used in pregnancy. Women of childbearing potential must be advised to use adequate contraception and avoid becoming pregnant while receiving treatment with TYKERB. If the drug is used during pregnancy or if the patient becomes pregnant while receiving the drug, the patient should be notified that TYKERB may cause harmful effects to the human fetus or neonate.

Use in Lactation

It is not known whether TYKERB is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breast-feeding infants from TYKERB, women who are receiving therapy with TYKERB should not breastfeed.

Interactions

TYKERB is predominantly metabolised by CYP3A (see *Pharmacokinetics*). Therefore, inhibitors or inducers of these enzymes may alter the pharmacokinetics of TYKERB. Coadministration of TYKERB with known inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole or grapefruit juice) should proceed with caution and clinical response and adverse events should be carefully monitored (see *Precautions*). If patients must be coadministered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a dose reduction to 500 mg/day of TYKERB is predicted to adjust the TYKERB AUC to the range observed without inhibitors and should be considered. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors. If the strong inhibitor is discontinued, a washout period of approximately 1 week should be allowed before the TYKERB dose is adjusted upward to the indicated dose.

Coadministration of TYKERB with known inducers of CYP3A4 (e.g., rifampicin, carbamazepine, or phenytoin) should proceed with caution and clinical response and adverse events should be carefully monitored (see *Precautions*). If patients must be coadministered a strong CYP3A4 inducer, the dose of TYKERB should be titrated gradually, based on tolerability. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued the TYKERB dose should be reduced over approximately 2 weeks to the indicated dose.

TYKERB inhibits CYP3A4, and CYP2C8 *in vitro* at clinically relevant concentrations. Caution should be exercised when dosing TYKERB concurrently with medications with narrow therapeutic windows that are substrates of CYP3A4, and CYP2C8 (see *Precautions and Pharmacokinetics*).

TYKERB is a substrate for the transport proteins Pgp and BCRP. Inhibitors and inducers of these proteins may alter the exposure and/or distribution of TYKERB.

Lapatinib inhibits the transport proteins Pgp, BCRP and OATP1B1 in vitro. The clinical relevance of this effect has not been evaluated. It cannot be excluded that lapatinib will affect the pharmacokinetics of substrates of Pgp (e.g. digoxin), BCRP (e.g. topotecan) and OATP1B1 (e.g. rosuvastatin).

Concomitant administration of TYKERB with capecitabine, letrozole or trastuzumab did not meaningfully alter the pharmacokinetics of these agents (or the metabolites of capecitabine) or TYKERB.

The bioavailability of TYKERB is affected by food (*see Dosage and Administration and Pharmacokinetics*).

Driving or operating machinery

There have been no studies to investigate the effect of TYKERB on driving performance or the ability to operate machinery. A detrimental effect on such activities cannot be predicted from the pharmacology of TYKERB, although in clinical studies, fatigue is a very common adverse event associated with TYKERB treatment. If patients experience fatigue, weakness or tiredness, they should be advised not to drive or operate machinery (*see Adverse Events*).

ADVERSE EVENTS:

Safety of TYKERB has been evaluated as monotherapy or in combination with other chemotherapies for various cancers in more than 11,000 patients, including 164 patients who received TYKERB in combination with capecitabine and 654 patients who received TYKERB in combination with letrozole (*see Clinical Trials*).

The following convention has been utilised for the classification of frequency: Very common (greater than or equal to 1/10), common (greater than or equal to 1/100 and less than 1/10), uncommon (greater than or equal to 1/1000 and less than 1/100), rare (greater than or equal to 1/10,000 and less than 1/1000) and very rare (less than 1/10,000).

TYKERB monotherapy

The following adverse reactions have been reported to be associated with TYKERB:

Metabolism and nutrition disorders	
Very common	Anorexia.
Cardiac disorders	
Common	Decreased left ventricular ejection fraction ¹ (see <i>Dosage and Administration — dose delay and dose reduction — Cardiac events and Precautions</i>).
¹ Left ventricular ejection fraction (LVEF) decreases have been reported in approximately 1% of patients 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 TYKERB. Symptomatic LVEF decreases were observed in approximately 0.1% of patients who received TYKERB monotherapy. Observed symptoms included dyspnoea, cardiac failure and palpitations. All events resolved promptly on discontinuation of TYKERB.	
Respiratory, thoracic and mediastinal disorders:	
Uncommon	Interstitial lung disease / pneumonitis (see <i>Dosage and Administration and Precautions</i>)
Gastrointestinal disorders	
Very common	Diarrhoea ² , which may lead to dehydration ³ (see <i>Dosage and Administration — dose delay and dose reduction — Other toxicities and Precautions</i>). Nausea. Vomiting.
³ Most events of diarrhoea were grade 1 or 2.	
Hepatobiliary disorders	
Very common	Hyperbilirubinaemia ⁴ .
Common	Hepatotoxicity.
⁴ Elevated bilirubin may be due to TYKERB inhibition of hepatic uptake by OATP1B1 or inhibition of excretion into bile by Pgp or BCRP.	
Skin and subcutaneous tissue disorders	
Very common	Rash ² (including dermatitis acneform) (see <i>Dosage and Administration — dose delay and dose reduction — Other toxicities</i>).
Common	Nail disorders including paronychia
Immune System Disorders	
Rare	Hypersensitivity reactions including anaphylaxis (see <i>Contraindications</i>)
General disorders and administration site conditions	
Very common	Fatigue.

²Diarrhoea and rash were generally low grade and did not result in discontinuation of treatment with TYKERB. Diarrhoea responds well to proactive management (see *Precautions*). Rash was transient in the majority of cases.

TYKERB in combination with capecitabine

The following adverse reactions have been reported to be associated with TYKERB in combination with capecitabine with a frequency difference of greater than 5% compared to capecitabine alone. These data are based on exposure to this combination in 164 patients.

Gastrointestinal disorders	
Very common	Dyspepsia.
Skin and subcutaneous tissue disorders	
Very common	Dry skin.

In addition, the following adverse reactions were reported to be associated with TYKERB in combination with capecitabine but were seen at a similar frequency in the capecitabine alone arm.

Gastrointestinal disorders	
Very common	Stomatitis, constipation, abdominal pain.
Skin and subcutaneous tissue disorders	
Very common	Palmar-plantar erythrodysesthesia.
General disorders and administrative site conditions	
Very common	Mucosal inflammation.
Musculoskeletal and connective tissue disorders	
Very common	Pain in extremity, back pain.
Nervous system disorders	
Common	Headache.
Psychiatric disorders	
Very common	Insomnia.

Table 3 Most common study medication related adverse reactions (³5%) in studies of lapatinib ditosylate in combination with Capecitabine (EGF100151)

Preferred term	Lapatinib 1250mg + Capecitabine 2000mg/m ²	Capecitabine (2500 mg/m ²)
	(N = 164)	(N=152)
	%	%
Any related AEs	80	78
Diarrhoea	56	36
Palmar-plantar erythrodysesthesia syndrome	44	47
Nausea	40	38
Rash	26	14
Vomiting	21	20
Stomatitis	14	10
Fatigue	13	23
Anorexia	13	18
Mucosal inflammation	10	11
Dry skin	10	5
Dyspepsia	7	2
Pain in extremity	7	6
Abdominal pain	5	12
Anaemia	5	5
Epistaxis	5	(<1)
Asthenia	4	8
Headache	4	5

Table 4 Selected hepatic laboratory abnormalities* observed during study EGF 100151

	Lapatinib 1250mg + Capecitabine 2000mg/m ²			Capecitabine (2500 mg/m ²)		
	All Grades	Grade 3 (%)	Grade 4 (%)	All Grades	Grade 3 (%)	Grade 4 (%)
Total Bilirubin	45	3	0	30	2	0
AST	48	1	<1	42	2	0
ALT	36	2	0	31	2	0

*National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

An updated analysis inclusive of 75 subjects who were enrolled into the study between the interim analysis clinical cut-off date and halting enrollment into the study (n=198 combination arm vs n= 191 control arm) was performed. No difference in the safety profile was observed from that described previously. In this analysis 4% (7 subjects) treated with the combination arm and 1% (2 subjects) in the control arm experienced a decreased LVEF, although none were fatal and did not result in permanent discontinuation from the study.

TYKERB in combination with letrozole

The following additional adverse reactions have been reported to be associated with TYKERB in combination with letrozole with a frequency difference of greater than 5% compared to letrozole alone. These data are based on exposure to this combination in 654 patients.

Respiratory, thoracic and mediastinal disorders	
Very common	Epistaxis.
Skin and subcutaneous tissue disorders	
Very common	Alopecia, dry skin.

Table 5 Most common study medication related adverse reactions (³ 10%) in for TYKERB in combination with Letrozole (EGF30008)

Preferred term	Letrozole 2.5 mg + TYKERB 1500 mg	Letrozole 2.5 mg + Placebo
	(N = 654)	(N=624)
	%	%
Any related AEs	84	55
Diarrhoea	53	13
Rash	38	9
Nausea	20	11
Dry skin	11	3
Fatigue	11	7
Alopecia	10	5
Nail disorder	10	<1
Pruritus	10	6

In the TYKERB plus letrozole treatment group, the most commonly observed study medication related serious adverse events were decreased left ventricular ejection fraction (LVEF) (2% of patients, compared to 1% for letrozole plus placebo) and diarrhoea (2% of patients, compared to <1% for letrozole plus placebo). Other study medication related serious adverse events, including skin rash, hepatotoxicity and pneumonitis, were observed in <1% of patients. The most common adverse events leading to discontinuation of treatment in the TYKERB plus letrozole treatment group were diarrhoea (4%) and vomiting (2%).

DOSAGE AND ADMINISTRATION

TYKERB treatment should only be initiated by a physician experienced in the administration of anti-cancer agents.

Prior to the initiation of treatment, left ventricular ejection fraction (LVEF) must be evaluated to ensure that baseline LVEF is within the institutional limits of normal (see *Precautions*). LVEF must continue to be monitored during treatment with TYKERB to ensure that LVEF does not decline below the institutional lower limit of normal (see *Dose delay and dose reduction — Cardiac events*).

HER2 protein overexpression or gene amplification is necessary for the selection of patients for whom TYKERB therapy is appropriate. Evidence of a previous positive test result for HER2 overexpression or gene amplification should be confirmed before initiating therapy with TYKERB. If historical results are not available, repeat HER2 testing should be considered.

Assessment of HER2 overexpression and/or of HER2 gene amplification should be performed by laboratories with accreditation or demonstrated proficiency. HER2 overexpressing tumours are defined by a score of 3+ using an immunohistochemistry (IHC)-based assessment, or IHC2+ and gene amplification or gene amplification alone.

Treatment with TYKERB should be continued until disease progression or unacceptable toxicity occurs.

TYKERB should be taken at least one hour before, or at least one hour after food (see *Interactions and Pharmacokinetics — Absorption*). The recommended daily TYKERB dose should not be divided.

Missed doses should not be replaced and the dosing should resume with the next scheduled daily dose (see *Overdosage*).

Consult the product information of the co-administered medicinal product for relevant details of their dosage, contraindications and safety information.

HER2+ over expressing metastatic breast cancer

The recommended dose of TYKERB is 1250 mg (i.e. five tablets) once daily continuously when taken in combination with capecitabine.

The recommended dose of capecitabine is 2000 mg/m²/day taken in 2 doses 12 hours apart on days 1-14 in a 21 day cycle (see *Clinical Trials*). Capecitabine should be taken with food or within 30 minutes after food.

Hormone receptor + and HER2+ metastatic breast cancer

The recommended dose of TYKERB is 1500 mg (i.e. six tablets) once daily continuously when taken in combination with an aromatase inhibitor.

When TYKERB is co-administered with the aromatase inhibitor letrozole, the recommended dose of letrozole is 2.5 mg once daily. If TYKERB is co-administered with an alternative aromatase inhibitor, please refer to the product information of the medicinal product for dosing details.

Dose delay and dose reduction (all indications)

Cardiac events (see Precautions)

TYKERB should be discontinued in patients with symptoms associated with decreased LVEF that are National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade 3 or greater or if their LVEF drops below the institution's lower limit of normal. TYKERB may be restarted at a reduced dose (1000 mg/day when administered with capecitabine and 1250 mg/day when administered with an aromatase inhibitor) after a minimum of 2 weeks and if the LVEF recovers to normal and the patient is asymptomatic. Based on current data, the majority of LVEF decreases occur within the first 9 weeks of treatment, however, there is limited data on long term exposure.

Interstitial lung disease/pneumonitis (see Precautions and Adverse Events).

TYKERB should be discontinued in patients who experience pulmonary symptoms indicative of interstitial lung disease/pneumonitis which are NCI CTCAE grade 3 or greater.

Other toxicities

Discontinuation or interruption of dosing with TYKERB may be considered when a patient develops toxicity greater than or equal to grade 2 on the NCI CTCAE. Dosing can be restarted at either, 1250 mg/day when administered with capecitabine or 1500 mg/day when administered with an aromatase inhibitor, when the toxicity improves to grade 1 or less. If the toxicity recurs, then TYKERB should be restarted at a lower dose (1000 mg/day when administered with capecitabine and 1250 mg/day when administered with an aromatase inhibitor).

Children:

The safety and efficacy of TYKERB in paediatric patients has not been established.

Elderly:

Of the number of metastatic breast cancer patients in clinical studies of TYKERB in combination with capecitabine, approximately 15% were 65 and over and 1% were 75 and over. For single agent TYKERB, approximately 15% were 65 and over and 2% were 75 and over. No overall differences in safety of the combination of TYKERB and capecitabine or single agent TYKERB were observed between these subjects and younger subjects. Of the total number of hormone sensitive metastatic breast cancer patients in the clinical studies of TYKERB in combination with letrozole (N=642), 44% were 65 and over. No overall differences in safety of the combination of TYKERB and letrozole were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Similarly no differences in effectiveness for the combination of either TYKERB and capecitabine or TYKERB and letrozole on the basis of age were observed.

Hepatic Impairment:

Patients with severe hepatic impairment (Child-Pugh Class C) should have their dose of TYKERB reduced. A dose reduction from 1250 mg/day to 750 mg/day or from 1500 mg/day to 1000 mg/day in patients with severe hepatic impairment is predicted to adjust the area under the curve (AUC) to the normal range. However, there are no clinical data with this dose adjustment in patients with severe hepatic impairment (see Precautions and Pharmacokinetics – Hepatic Impairment).

OVERDOSAGE

There is no specific antidote for the inhibition of ErbB1 (EGFR) and/or HER2 tyrosine phosphorylation. The maximum oral dose of TYKERB that has been administered in clinical trials is 1800 mg once daily.

More frequent ingestion of TYKERB could result in serum concentrations exceeding those observed in clinical trials, therefore missed doses should not be replaced, and dosing should resume with the next scheduled daily dose (*see Dosage and Administration*).

There has been a report of one patient who took an overdose of 3000 mg of TYKERB for 10 days and suffered grade 3 diarrhoea and vomiting on day 10. The symptoms resolved following IV hydration and interruption of treatment with lapatinib and letrozole.

TYKERB is not significantly renally excreted and is highly bound to plasma proteins, therefore haemodialysis would not be expected to be an effective method to enhance the elimination of lapatinib.

STORAGE

Do not store above 30°C. Shelf life at this temperature is 2 years.

PRESENTATION

TYKERB (Lapatinib ditosylate monohydrate) tablets, 250 mg, are oval, biconvex, yellow film-coated tablets, with one side plain and the opposite side debossed with GS XJG.

TYKERB film-coated tablets are supplied in packs of 40 (sample pack), 70, 84 and 168*.

*not all pack sizes may be marketed.

POISON SCHEDULE

Schedule 4 – Prescription only medicine

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This document was approved by the Therapeutic Goods Administration on 26 May 2010.

Version 3.0