AUSTRALIAN PRODUCT INFORMATION - TYKERB® (LAPATINIB) TABLETS

1. NAME OF THE MEDICINE

Lapatinib (as ditosilate monohydrate)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance
Each TYKERB tablet contains 405 mg of lapatinib ditosilate monohydrate, which is equivalent to 250 mg of lapatinib free base. Lapatinib is a member of 4-anilinoquinazoline class of kinase inhibitors.

Excipients

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Yellow, oval, biconvex, film-coated tablet, with GS XJG debossed on one face of the tablet and a plain reverse face.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Human Epidermal Growth factor receptor 2 positive (HER2+) over expressing advanced or metastatic breast cancer

TYKERB is indicated in combination with:

- An aromatase inhibitor for the treatment of post-menopausal women with hormone receptor-positive metastatic breast cancer whose tumours overexpress HER2 (ErbB2) (epidermal growth factor receptor 2) and for whom hormonal therapy is indicated.
- 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 and a taxane, and who have progressed on prior trastuzumab therapy in the metastatic setting.
- Paclitaxel for the first-line treatment of patients with metastatic breast cancer whose tumours overexpress HER2 (ErbB2) and for whom trastuzumab is not appropriate (see section 5.1 Pharmacodynamic properties - Clinical trials).

4.2 Dose and method of administration

TYKERB 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 in all patients, using echocardiogram or multigated acquisition (MUGA),to ensure that baseline LVEF is within the institutional limits of normal (see section 4.4 Special warnings and precautions for use). LVEF must continue to be monitored during treatment with TYKERB to ensure that

LVEF does not decline below the institutional lower limit of normal (LLN) (see section 4.2 Dose and Method of Administration: 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.

Dosage

HER2+ over expressing advanced or metastatic breast cancer

General target population

TYKERB in combination with capecitabine
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/m^2/day taken in 2 doses 12 hours apart on days 1-14 in a 21 day cycle (see section 5.1 Pharmacodynamic properties - Clinical Trials). Capecitabine should be taken with food or within 30 minutes after food.

TYKERB in combination with paclitaxel
The recommended dose of TYKERB is 1500 mg (i.e. six tablets) once daily continuously in combination with paclitaxel. When co-administered with TYKERB, the recommended dose of paclitaxel is 80 mg/m^2 on days 1, 8, and 15 of a 28 day schedule. Alternatively, paclitaxel may be given at a dose of 175 mg/m^2 every 21 days (see section 5.1 Pharmacodynamic properties - Clinical Trials).

TYKERB in combination with an aromatase inhibitor
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.

Special Populations

Use in 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 section 4.4 Special warning and precautions for use and section 5.2 Pharmacokinetic properties: Special Populations - Hepatic Impairment).

Use in Renal Impairment
See section 5.2 Pharmacokinetic properties - Special Patient Populations.

Use in the Elderly

There are limited data on the use of lapatinib in patients aged 65 years and older. See Table 1.

Table 1 Exposure in Elderly Patients

	Patient age (years)	
	≥ 65	**≥ 75**
TYKERB + capecitabine (N=198) (EGF100151)	33 (17%)	2 (1%)
TYKERB + paclitaxel (N=222) (EGF104535)	16 (7%)	0
TYKERB + letrozole (N=642) (EGF30008)	285 (44%)	77 (12%)
Single agent TYKERB (N=599) (EGF20002, EGF20008, EGF20009, EGF103009)	101 (17%)	24 (4%)

No age based differences in the safety or efficacy of these regimens were observed. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Greater sensitivity of elderly individuals cannot be ruled out.

Paediatric Use

The safety and efficacy of TYKERB in patients below 18 years of age has not been established.

Dose delay and dose reduction (all indications)

Cardiac events
TYKERB should be interrupted 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 paclitaxel or 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 12 weeks of treatment, however, there is limited data on long term exposure. Also see section 4.4 Special warnings and precautions for use.

Interstitial lung disease/pneumonitis
TYKERB should be discontinued in patients who experience pulmonary symptoms indicative of interstitial lung disease/pneumonitis, which are NCI CTCAE grade 3 or greater. See section 4.4 Special warnings and precautions for use and section 4.8 Adverse effects (undesirable effects).

Diarrhoea
TYKERB dosing should be interrupted in patients with diarrhoea which is NCI CTCAE grade 3 or grade 1 or 2 with complicating features (moderate to severe abdominal cramping, nausea or vomiting greater than or equal to NCI CTCAE grade 2, decreased performance status, fever, sepsis, neutropenia, frank bleeding or dehydration). TYKERB may be reintroduced at a lower dose (reduced from 1000 mg/day to 750 mg/day, from 1250 mg/day to 1000 mg/day or from 1500 mg/day to 1250 mg/day) when diarrhoea resolves to grade 1 or less. TYKERB dosing should be permanently discontinued in patients with diarrhoea which is NCI CTCAE grade 4. See section 4.4 Special warnings and precautions for use and section 4.8 Adverse effects (undesirable effects).

Severe Cutaneous Reactions
Lapatinib should be discontinued in patients who experience severe progressive skin rash with blisters or mucosal lesions. See section 4.4 Special warning and precautions for use.

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

Dose delay and dose reduction (administration with paclitaxel)
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 1500 mg/day when toxicity improves to grade 1 or less. If the toxicity recurs, then TYKERB should be restarted at 1250 mg/day.

Taxanes are also associated with bone marrow suppression and other toxicities. The full prescribing information for paclitaxel should be referred to for advice on dose delay and dose reduction of paclitaxel.

Administration

TYKERB should be taken at least one hour before, or at least one hour after food (see section 4.5 Interactions with other medicines and other forms of interactions and section 5.2 Pharmacokinetic properties - 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 section 4.9 Overdose).

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

4.3 Contraindications

TYKERB is contraindicated in patients with hypersensitivity to any of the ingredients (see section 6.1 List of excipients and section 4.8 Adverse effects (undesirable effects)).

4.4 Special warnings and precautions for use

Cardiac Toxicity

Left ventricular ejection fraction (LVEF)
TYKERB has been associated with decreases in LVEF. In clinical studies cardiac events, including LVEF decreases, were observed in patients who received TYKERB (see section 4.8 Adverse effects (undesirable effects)). 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 it is within the institutions normal limits. LVEF should continue to be evaluated during treatment with TYKERB at approximately 8-12 week intervals to ensure that LVEF does not decline to an unacceptable level (see section 4.2 Dose and method of administration: Dose delay and dose reduction - Cardiac events, and section 5.1 Pharmacodynamic properties - Clinical Trials).

QT Prolongation
A concentration dependent QTc interval increase has been observed in a dedicated placebo-controlled crossover study in subjects with advanced solid tumours. Electrocardiograms with QT measurement should be considered prior to administration of TYKERB and throughout treatment.

Study EGF114271
The effect of lapatinib on the QT-interval was evaluated in a single-blind, placebo-controlled, single sequence (placebo and active treatment) crossover study in patients with advanced solid tumours (N=58). Patients with cardiac conduction abnormalities and abnormal baseline ECG findings (including of QTcF interval > 480 ms) were excluded from the study. During the 4-day treatment period, three doses of matching placebo were administered 12 hours apart in the morning and evening on Day 1 and in the morning on Day 2. This was followed by three doses of lapatinib 2000 mg administered in the same way. Measurements, including ECGs and pharmacokinetic samples were done at baseline and at the same time points on Day 2 and Day 4.

In the evaluable population (N=37), the maximum mean ΔΔQTcF (90% CI) of 8.75 ms (4.08, 13.42) was observed 10 hours after ingestion of the third dose of lapatinib 2000 mg. The ΔΔQTcF exceeded the 5 ms threshold and the upper bound 90% CIs exceeded the 10 ms threshold at multiple time points. The results for the PD population (n=52) were consistent with those from the evaluable population (maximum ΔΔQTcF (90% CI) of 7.91 ms (4.13, 11.68) observed 10 hours after ingestion of the third dose of lapatinib. The PK/PD analyses confirmed the presence of a positive relationship between lapatinib plasma concentrations and ΔΔQTcF.

Caution should be taken if TYKERB is administered to patients who have or may develop prolongation of QTc. These conditions include patients with hypokalaemia or hypomagnesemia, congenital long QT syndrome, patients taking anti-arrhythmic medicines or other medicinal products that lead to QT prolongation. Hypokalaemia, hypocalcaemia or hypomagnesemia should be corrected prior to TYKERB administration.

Interstitial lung disease and pneumonitis
TYKERB has been associated with reports of interstitial lung disease and pneumonitis (see section 4.8 Adverse Effects (undesirable effects)). Patients should be monitored for pulmonary symptoms indicative of interstitial lung disease/pneumonitis (see section 4.2 Dose and method of administration).

Hepatotoxicity
Hepatotoxicity (ALT or AST > 3 times the upper limit of normal (ULN) and total bilirubin > 1.5 times the ULN) has been observed in clinical trials (< 1 % of patients) and post marketing 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 permanently (see section 4.8 Adverse Effects (undesirable effects)).

Patients who carry the HLA alleles DQA1*02:01 and DRB1*07:01 have increased risk of TYKERB-associated hepatotoxicity. In a large, randomised clinical trial of TYKERB monotherapy (n=1,194), the overall risk of severe liver injury (ALT > 5 times the upper limit of normal, NCI CTCAE grade 3) was 2% (1:50), the risk in DQA1*02:01 and DRB1*07:01 allele carriers was 8% (1:12) and the risk in non-carriers was 0.5 % (1:200). Carriage of the HLA risk alleles is common (15 % to 25%) in Caucasian, Asian, African and Hispanic populations but lower (1 %) in Japanese populations.

Diarrhoea

Diarrhoea, including severe diarrhoea, has been reported with TYKERB treatment (see section 4.8 Adverse effects (undesirable effects)). Diarrhoea may be severe, and deaths have been reported. Diarrhoea generally occurs early during TYKERB treatment, with almost half of those patients with diarrhoea first experiencing it within 6 days. This usually lasts 4-5 days. TYKERB-induced diarrhoea is usually low-grade, with severe diarrhoea of NCI CTCAE grades 3 and 4 occurring in < 10 % and < 1 % of patients, respectively. Early identification and intervention is critical for the optimal management of diarrhoea. Patients should be instructed to report any change in bowel patterns immediately. Prompt treatment of diarrhoea with anti-diarrhoeal agents (such as loperamide) after the first unformed stool is recommended. Severe cases of diarrhoea may require administration of oral or intravenous electrolytes and fluids, use of antibiotics such as fluoroquinolones (especially if diarrhoea is persistent beyond 24 hours, there is fever, or grade 3 or 4 neutropenia) and interruption or discontinuation of TYKERB therapy (see section 4.2 Dose and method of administration - Dose delay and dose reduction - Diarrhoea).

Neutropenia

Neutropenia has been reported with TYKERB administered in combination with paclitaxel (see section 4.8 Adverse Effects (undesirable effects) and section 4.5 Interactions with other medicines and other forms of interactions). Complete blood counts should be monitored regularly during treatment with this combination (see section 4.2 Dose and method of administration: Dose delay and dose reduction – administration with paclitaxel).

Severe cutaneous reactions

Severe cutaneous reactions have been reported with lapatinib. If erythema multiforme or life-threatening reactions such as, Stevens-Johnson syndrome, or toxic epidermal necrolysis (e.g. progressive skin rash often with blisters or mucosal lesions) are suspected, discontinue treatment with lapatinib (see section 4.2 Dose and method of administration).

Concomitant Treatment with Inhibitors or Inducers of CYP3A4

Concomitant treatment with inhibitors or inducers of CYP3A4 should proceed with caution due to risk of increased or decreased exposure to TYKERB, respectively (see section 4.5 Interactions with other medicines and other forms of interactions).

Special Populations

Use in 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 section 4.2 Dose and method of administration and section 5.2 Pharmacokinetic properties – Hepatic Impairment).

Use in Renal impairment

Less than 2 % of an administered dose is eliminated by the kidneys as unchanged lapatinib and metabolites. Lapatinib pharmacokinetics have not been specifically studied in patients with renal impairment or in patients undergoing haemodialysis. Please refer to section 5.2 Pharmacokinetic properties.

Use in the Elderly

Refer to section 4.2 Dose and method of administration.

Paediatric Use

Refer to section 4.2 Dose and method of administration.

Use in patients for whom trastuzumab is not appropriate
Limited data suggest that TYKERB in combination with paclitaxel is less effective and not as tolerable as trastuzumab in combination with paclitaxel for the first-line treatment of patients with metastatic breast cancer whose tumours overexpress HER2 (ErbB2). Therefore lapatinib-paclitaxel should be used in patients for whom trastuzumab is not appropriate (see section 5.1 Pharmacodynamic properties - Clinical Trials).

Effects on laboratory tests

Please refer to section 4.8 Adverse effects (undesirable effects).

4.5 Interactions with other medicines and other forms of interactions

TYKERB is predominantly metabolised by CYP3A (see section 5.2 Pharmacokinetic properties). Therefore, inhibitors or inducers of these enzymes may alter the pharmacokinetics of TYKERB.

Interactions with CYP3A4-inhibitors
Co-administration 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 section 4.4 Special warnings and precautions for use).

If patients must be co-administered 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.

Interactions with CYP3A4-inducers
Co-administration of TYKERB with known inducers of CYP3A4 (e.g., rifampicin, carbamazepine, phenytoin or *Hypericum perforatum* (St. John's wort)) should proceed with caution and clinical response and adverse events should be carefully monitored (see section 4.4 Special warnings and precautions for use). If patients must be co-administered 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.

Drugs that affect gastric pH
The solubility of TYKERB is pH-dependent. Concomitant treatment with substances that increase gastric pH should be avoided since TYKERB solubility and absorption may decrease. Pre-treatment with a proton pump inhibitor (esomeprazole) decreased TYKERB exposure by an average of 27% (range: 6% to 49 %). This effect decreases with increasing age from approximately 40 to 60 years. Therefore, caution should be used when TYKERB is used in patients pre-treated with a proton pump inhibitor.

Effect of TYKERB on other drugs
TYKERB inhibits CYP3A4 *in vitro* at clinically relevant concentrations. Co-administration of lapatinib with orally administered midazolam resulted in an approximate 45% increase in the

AUC of midazolam. There was no clinically meaningful increase in AUC when midazolam was dosed intravenously. Caution should be exercised when dosing TYKERB concurrently with orally administered medications with narrow therapeutic windows that are substrates of CYP3A4 (see section 5.2 Pharmacokinetic properties).

TYKERB inhibits CYP2C8 at clinically relevant concentrations. Caution should be exercised (see section 5.2 Pharmacokinetic properties) when dosing lapatinib concurrently with medications with narrow therapeutic windows that are substrates of CYP2C8 (see section 5.2 Pharmacokinetic properties).

Combination therapy and non-fixed dose combination therapy

Co-administration of lapatinib with intravenous paclitaxel increased the exposure of paclitaxel by 23%, due to lapatinib inhibition of CYP2C8 and/or P-glycoprotein (Pgp). An increase in the incidence and severity of diarrhoea and neutropenia has been observed with this combination in clinical trials. Caution is advised when lapatinib is co-administered with paclitaxel.

Effect of TYKERB on transport proteins

TYKERB is a substrate for the transport proteins P-glycoprotein and BCRP (Breast Cancer Resistance Protein). Inhibitors and inducers of these proteins may alter the exposure and/or distribution of lapatinib.

TYKERB inhibits the transport protein P-glycoprotein *in vitro* at clinically relevant concentrations. Co-administration of lapatinib with orally administered digoxin resulted in an approximate 98% increase in the AUC of digoxin. Caution should be exercised when dosing lapatinib concurrently with medications with narrow therapeutic windows that are substrates of Pgp.

Lapatinib inhibits the transport proteins 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 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.

Drug-food/drink interactions

The bioavailability of TYKERB is affected by food (see section 4.2 Dose and method of administration and section 5.2 Pharmacokinetic properties). Grapefruit juice may increase the bioavailability of lapatinib and should be avoided during treatment with TYKERB (see earlier section: Interactions with CYP3A4-inhibitors above).

4.6 Fertility, pregnancy, and lactation

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)

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.

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 post-natal 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.

Contraception
Based on findings in animal studies, lapatinib can cause fetal harm. Females of reproductive potential must be advised to use effective contraception using methods that result in less than 1 % pregnancy rates to avoid becoming pregnant while receiving treatment with TYKERB and for at least 5 days after the last dose. 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

There are no data on the presence of lapatinib in human milk, or the effect of lapatinib on the breastfed infant, or on milk production. As many drugs are transferred into human milk and due to the potential for serious ADRs in breast-fed infants from lapatinib, it is advised that women should not breastfeed while receiving therapy with TYKERB and for at least 5 days after the last dose.

4.7 Effects on ability to drive and use machines

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 section 4.8 Adverse Effects (undesirable effects)).

4.8 Adverse effects (undesirable effects)

The safety of TYKERB has been evaluated as monotherapy or in combination with other chemotherapies for various cancers in more than 19,000 patients. These included 198 patients who received TYKERB in combination with capecitabine, 222 patients who received TYKERB in combination with paclitaxel (80mg/m^2 weekly), 293 patients who received TYKERB in combination with paclitaxel (175mg/m^2 every 3 weeks), and 654 patients who received TYKERB in combination with letrozole (also see section 5.1 Pharmacodynamic properties - Clinical Trials).

Adverse effects (undesirable effects) are listed by MedDRA system organ class (SOC) in Tables 2 to 11. The following convention has been utilised for the classification of frequency in all of the AE tables:

Very common	≥ 1/10)
Common	≥1/100 and < 1/10)
Uncommon	≥ 1/1000 and < 1/100)
Rare	≥ 1/10,000 and < 1/1000) and
Very rare	< 1/10,000).

TYKERB monotherapy

The following adverse reactions have been reported to be associated with TYKERB (Table 2).

Table 2 Adverse reactions occurring with TYKERB monotherapy

Immune System Disorders	
Rare	Hypersensitivity reactions including anaphylaxis[1]
Metabolism and nutrition disorders	
Very common	Anorexia
Cardiac disorders	
Common	Decreased left ventricular ejection fraction[2]
Respiratory, thoracic and mediastinal disorders	
Uncommon	Interstitial lung disease/pneumonitis[3]
Gastrointestinal disorders	
Very common	Diarrhoea, which may lead to dehydration[4], Nausea, Vomiting.
Hepatobiliary disorders	
Very common	Hyperbilirubinaemia[5].
Common	Hepatotoxicity[6].
Skin and subcutaneous tissue disorders	
Very common	Rash[4] (including dermatitis acneform)
Common	Nail disorders including paronychia.
General disorders and administration site conditions	
Very common	Fatigue.

[1] See section 4.3 Contraindications

[2] LVEF decreases have been reported in approximately 1% of patients and were asymptomatic in > 70% of cases. LVEF decreases resolved or improved in > 60% of cases on discontinuation of treatment with TYKERB. Symptomatic LVEF decreases were observed in approximately 0.3% of patients who received TYKERB. Observed symptoms included dyspnoea, cardiac failure and palpitations. See section 4.2 Dose and method of administration - dose delay and dose reduction - Cardiac events and section 4.4 Special warnings and precautions for use.

[3] See section 4.2 Dose and method of administration and section 4.4 Special warnings and precautions for use

[4] Diarrhoea and rash were generally low grade (most events of diarrhoea were grade 1 or 2) and did not result in discontinuation of treatment with TYKERB. Diarrhoea responds well to proactive management (see section 4.2 Dose and method of administration - Dose delay and dose reduction (all indications) - Diarrhoea). Rash was transient in the majority of cases. See section 4.2 Dose and method of administration - Dose delay and dose reduction (all indications) – Other toxicities.

[5] Elevated bilirubin may be due to TYKERB inhibition of hepatic uptake by OATP1B1 or inhibition of excretion into bile by Pgp or BCRP.

[6] ALT or AST >3 times ULN and total bilirubin >1.5 times ULN or serious hepatobiliary events associated with lapatinib or Hy's law cases.

TYKERB in combination with capecitabine

In addition to the adverse reactions observed with TYKERB monotherapy, 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 (Table 3). These data are based on exposure to this combination in 198 patients.

Table 3 Adverse reactions reported to be associated with TYKERB in combination with capecitabine at a frequency difference of > 5% compared to capecitabine alone

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

Table 4 Adverse reactions reported to be associated with TYKERB in combination with capecitabine (seen at a similar frequency to the capecitabine alone arm)

Gastrointestinal disorders	
Very common	Stomatitis, constipation, abdominal pain
Skin and subcutaneous tissue disorders	
Very common	Palmar-plantar erythrodysaesthesia
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 5 Most common study medication related adverse reactions (≥ 5 %) in studies of TYKERB in combination with capecitabine (EGF100151: 03 April 2006 Cut Off)

Preferred term	**Lapatinib 1250 mg + Capecitabine 2000 mg/m^2** **(N = 198)** **%**	**Capecitabine 2500 mg/m^2** **(N=191)** **%**
Any related AEs	87	82
Diarrhoea	60	37

Preferred term	Lapatinib 1250 mg + Capecitabine 2000 mg/m^2 (N = 198) %	Capecitabine 2500 mg/m^2 (N=191) %
Palmar-plantar erythrodysaesthesia syndrome	49	49
Nausea	40	39
Rash	25	12
Vomiting	20	17
Stomatitis	13	9
Fatigue	18	21
Anorexia	11	18
Mucosal inflammation	14	11
Dry skin	9	6
Dyspepsia	8	2
Pain in extremity	6	5
Abdominal pain	6	12
Anaemia	5	5
Epistaxis	7	(<1)
Asthenia	7	9
Headache	4	5
Neutropenia	3	6
Nail Disorder	5	2
Peripheral sensory neuropathy	1	5

Table 6 Selected hepatic laboratory abnormalities* observed during study EGF100151

	Lapatinib 1250 mg + Capecitabine 2000 mg/m^2			Capecitabine 2500 mg/m^2		
	All Grades	Grade 3 (%)	Grade 4 (%)	All Grades	Grade 3 (%)	Grade 4 (%)
Total Bilirubin	45	4	0	30	3	0
AST	49	2	<1	43	2	0
ALT	37	2	0	33	2	0

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

TYKERB in combination with paclitaxel

The following additional adverse reactions have been reported to be associated with TYKERB in combination with paclitaxel (80 mg/m^2 weekly) with a frequency of greater than 5 % compared to paclitaxel alone. These data are based on exposure to this combination in 222 patients.

Table 7 Adverse reactions reported to be associated with TYKERB in combination with paclitaxel at a frequency difference of > 5 % compared to paclitaxel alone

Blood and lymphatic system disorders	
Very common	Leucopenia, Anaemia, Neutropenia (see section 4.4 Special warnings and precautions for use)
Nervous system disorders	
Very common	Peripheral neuropathy.*
Musculoskeletal and connective tissue disorders	
Very common	Myalgia.*

* additional adverse reactions report in 293 patients on TYKERB in combination with paclitaxel (175 mg/m^2 every 3 weeks) with a frequency difference of greater than 5% compared to paclitaxel alone.

Table 8 Adverse Reactions Occurring in ≥ 10% of Patients in a study of TYKERB in combination with paclitaxel (EGF 104535)

	TYKERB 1,500 mg/day + Paclitaxel 80 mg/m^2 IV weekly (N = 222)			**Paclitaxel 80 mg/m^2 IV weekly (N = 221)**		
Adverse Reactions	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Blood and Lymphatic System Disorder						
Neutropenia	77	35	16	47	15	5
Leucopenia	53	23	3	33	8	<1
Anaemia	23	4	0	10	1	0
Skin and subcutaneous tissue disorders						
Rash	59	4	<1	24	0	0
Nail disorder	11	0	0	1	0	0
Gastrointestinal disorders						
Diarrhoea	77	20	0	29	<1	<1
Nausea	30	<1	0	19	0	0
Vomiting	22	2	0	12	1	0
General disorders and administrative site conditions						
Fatigue	22	2	0	16	<1	0
Investigations						
ALT increased	11	2	0	8	<1	0
Haemoglobin decreased	10	3	0	2	<1	0
Metabolism and nutrition disorders						
Decreased appetite	32	<1	0	19	0	0
Musculoskeletal and connective tissue disorders						
Myalgia	14	<1	0	10	0	0
Respiratory, thoracic, and mediastinal disorders						
Cough	10	0	0	9	<1	0

TYKERB in combination with letrozole

In addition to the adverse reactions observed with TYKERB monotherapy, the following 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.

Table 9 Adverse reactions reported to be associated with TYKERB in combination with letrozole at a frequency difference of > 5 % compared to letrozole alone

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

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

Preferred term	Letrozole 2.5 mg + TYKERB 1500 mg (N = 654) %	Letrozole 2.5 mg + Placebo (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 %).

Post Marketing Data

The following adverse drug reactions have been derived from post-marketing experience with TYKERB via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 11 Adverse reactions reported to be associated with TYKERB in spontaneous case reports and literature

Cardiac disorders
Ventricular arrhythmias/Torsades de Pointes (TdP), Electrocardiogram QT prolonged
Skin and subcutaneous tissue disorders
Severe cutaneous adverse reactions, including Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).
Skin Fissures[1]
[1] Frequency of skin fissures in pooled clinical trials data set was 4.9% (common)

Reporting suspected adverse events

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http:www.tga.gov.au/reporting-problems.

4.9 Overdose

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 section 4.2 Dose and method of administration).

Symptoms and Signs

Asymptomatic and symptomatic cases of overdose have been reported in patients being treated with lapatinib. Symptoms observed include known lapatinib associated events (see section 4.8 Adverse effects (undesirable effects)) and in some cases sore scalp, sinus tachycardia (with otherwise normal ECG) and/or mucosal inflammation.

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.

Treatment

There is no specific antidote for the inhibition of ErbB1 (EGFR) and/or HER2 tyrosine phosphorylation.

Further management should be as clinically indicated. For information on the management of overdose contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antineoplastic agent, other antineoplastic agents, human epidermal growth factor receptor 2 (HER)2 tyrosine kinase inhibitor. ATC code: L01EH01.

5.1 Pharmacodynamic properties

Mechanism of action

Lapatinib is a potent, reversible, and selective inhibitor of the intracellular tyrosine kinase domains of both ErbB1 (EGFR) and HER2 (ErbB2) receptors (estimated K_{iapp} 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 (estrogen 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.

Clinical Trials

Data in two randomised metastatic settings have shown that TYKERB combined with chemotherapy is less effective than trastuzumab when combined with chemotherapy (see studies EGF111438 and EGF108919 in this section). Lapatinib is not indicated in the adjuvant setting.

Combination treatment with TYKERB and capecitabine

Open label studies

Phase III Study EGF100151

The efficacy and safety of TYKERB in combination with capecitabine in breast cancer was evaluated in this randomised, open label, multicentre phase III trial. Patients eligible for enrolment had HER2 over-expressing, locally advanced or metastatic breast cancer, after prior treatment that included taxanes, anthracyclines and trastuzumab. Left ventricular ejection fraction (LVEF) was evaluated in all patients (using echocardiogram or multigated acquisition (MUGA) scans) 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 randomised to receive either TYKERB 1250 mg once daily (continuously) plus capecitabine (2000 mg/m^2/day on days 1-14 every 21 days), or to receive capecitabine alone (2500 mg/m^2/day on days 1-14 every 21 days). The primary 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 (15 November, 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 12. The TTP data are represented graphically in Figure 1.

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 versus 4.1 months, p = 0.000023).

Table 12 Interim analysis efficacy data (Independent Review) from TYKERB and capecitabine clinical study EGF100151 in locally advanced or metastatic breast cancer (15 November 2006 data cut off)

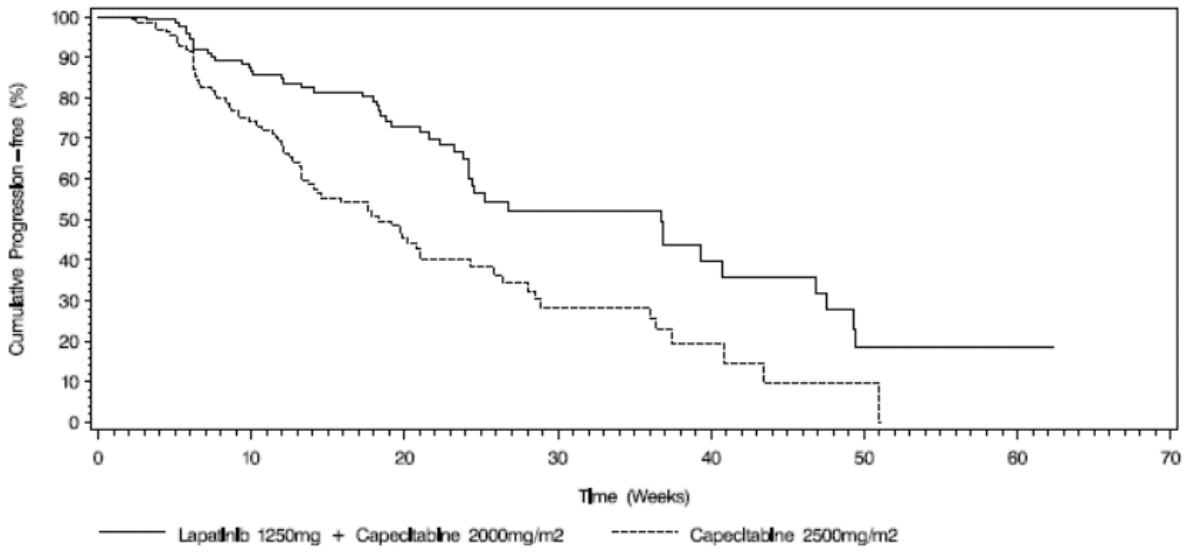
Efficacy Outcome	TYKERB plus capecitabine (N = 163)	Capecitabine alone (N = 161)
Time to progression		
Progressed or died due to breast cancer	30 %	45 %
Median time to progression	8.5 months	4.5 months
Hazard ratio, 95 % CI	0.49 (0.34, 0.71)	
p-value	0.00008	

CI = confidence interval

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).

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.

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 be 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 (3 April, 2006), a total of 399 patients had been randomised to study treatment.

A subsequent updated analysis was conducted with a data cut-off of 3 April, 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.

The overall response rate, as assessed by an independent review panel was 23.7 % for patients receiving lapatinib plus capecitabine and 13.9 % for patients receiving capecitabine (p=0.017). Median duration of response was 7.4 months and 7 months respectively. On the combination arm, there were 4 (2 %) progressions in the central nervous system as compared with the 13 (6 %) progressions on the capecitabine alone arm, as assessed by an independent review panel (p = 0.045).

At the time that enrolment into Study EGF100151 was halted, 399 patients were randomised to study therapy and 9 other patients were being screened. All 9 patients in screening, and all those already receiving capecitabine monotherapy, were offered combination treatment. In total, 207 patients were assigned to the combination therapy and 201 patients were assigned to capecitabine monotherapy. An analysis of overall survival (OS) data to 1 October 2008 is summarised in Table 13.

After the study was halted, 36 patients crossed over from capecitabine to TYKERB + capecitabine, of whom 26 crossed over prior to disease progression while on capecitabine alone.

To isolate the treatment effect in the presence of cross-over, Cox regression analysis considering crossover as a time-dependent covariate and treatment effect was performed. The results from this analysis suggest a clinically relevant reduction in risk of death by 20 %, with a treatment effect hazard ratio of 0.80 (95% confidence interval [CI]: 0.64, 0.99; p = 0.043).

Table 13 OS data from lapatinib and capecitabine combination Study EGF100151 (to 1 October 2008)

	TYKERB plus capecitabine (N=207)	Capecitabine alone (N=201)
Overall Survival		
Died	81 %	86 %
Median overall survival (months)	17.3	14.9
Hazard ratio, 95% CI	0.87 (0.71, 1.08)	
(p value)	0.210	

CI = confidence interval

Phase III Study EGF111438

A randomised Phase III open label study (EGF111438) (N=540) compared the effect of TYKERB in combination with capecitabine relative to trastuzumab in combination with capecitabine on the incidence of CNS as site of first relapse in women with HER2 overexpressing metastatic breast cancer. Patients were randomised to either TYKERB 1250 mg once daily (continuously) plus capecitabine (2000 mg/m^2/day on days 1-14 every 21 days), or trastuzumab (loading dose of 8 mg/kg followed by 6mg/kg infusions every 3 weeks) plus capecitabine (2500 mg/m^2/day, days 1-14, every 21 days). Randomisation was stratified by prior trastuzumab treatment and number of prior treatments for metastatic disease (none versus ≥ 1st line). The study was stopped early when a pre-planned interim analysis (N=475) showed superior efficacy of the trastuzumab plus capecitabine arm and a low incidence of CNS events.

The final analysis confirmed that the results of the primary endpoint were inconclusive due to a low number of CNS events [8 patients (3.2 %) in the TYKERB plus capecitabine arm experienced CNS metastasis as site of first progression, compared with 12 patients (4.8 %) in the trastuzumab plus capecitabine arm]. The final results of progression free survival and overall survival (the key secondary endpoints) are shown in Table 14, as well as the subgroup analyses based on the stratification factors. At the time of final analysis the median overall survival (OS) was not reached. The final analysis confirmed the superior efficacy of trastuzumab plus capecitabine arm.

Table 14 Analyses of Investigator-Assessed PFS and OS in Study EGF111438

	Investigator-Assessed PFS		OS	
	TYKERB + capecitabine	**Trastuzumab + capecitabine**	**TYKERB + capecitabine**	**Trastuzumab + capecitabine**
All patients, N	271	269	271	269
Number (%) with Event[1]	59%	50%	26%	22%
Kaplan-Meier estimate, months [a]				
Median (95% CI)	6.6 (5.7, 8.1)	8.0 (6.1, 8.9)	22.7 (19.5, -)	27.3 (23.7, -)
Stratified Hazard ratio [b]				
HR (95% CI)	1.30 (1.04, 1.64)		1.34 (0.95, 1.90)	
p-value	0.021		0.095	
Patients who had received prior trastuzumab				
N	167	159	167	159
Number (%) with Event[1]	103 (62)	86 (54)	43 (26)	38 (24)
Median (95% CI)	6.6 (5.7, 8.3)	6.1 (5.7, 8.0)	22.7 (20.1,-)	27.3 (22.5, 33.6)
HR (95% CI)	1.13 (0.85, 1.50)		1.18 (0.76, 1.83)	
Patients who had not received prior trastuzumab				

	Investigator-Assessed PFS		OS	
	TYKERB + capecitabine	**Trastuzumab + capecitabine**	**TYKERB + capecitabine**	**Trastuzumab + capecitabine**
N	104	110	104	110
Number (%) with Event[1]	57 (55)	48 (44)	27 (26)	20 (18)
Median (95% CI)	6.3 (5.6, 8.1)	10.9 (8.3, 15.0)	NE[2] (14.6, -)	NE[2] (21.6, -)
HR (95% CI)	1.70 (1.15, 2.50)		1.67 (0.94, 2.96)	

CI = confidence interval

a. PFS was defined as the time from randomisation to the earliest date of disease progression or death from any cause, or to the date of censor.

b. Pike estimate of the treatment hazard ratio, >1 indicates a higher risk for TYKERB plus capecitabine compared with Trastuzumab plus capecitabine.

[1] PFS event is Progressed or Died and OS event is Died due to any cause.

[2] NE = Median was not reached

Combination treatment with TYKERB and paclitaxel

Double-Blind, placebo-controlled studies

Phase III study EGF104535

The efficacy and safety of TYKERB in combination with paclitaxel in breast cancer were evaluated in a randomised double-blind, placebo-controlled trial, EGF104535. Patients had histologically confirmed invasive breast cancer (Stage IV disease) that overexpressed HER2, and had not received prior therapy for metastatic disease.

Patients were randomly assigned to paclitaxel (80 mg/m^2 intravenous on days 1, 8, and 15 of a 28 day schedule) and either TYKERB 1500 mg/day or placebo once daily. Patients received a minimum of 6 cycles of TYKERB or placebo plus paclitaxel. After the 6 cycles of combination with paclitaxel were completed, patients continued on TYKERB or placebo until disease progression or an unacceptable toxicity occurred. The primary endpoint was overall survival (OS). Four hundred forty four (444) patients were enrolled in this study. Of the 222 patients who were on paclitaxel plus placebo, 149 patients (67%) with disease progression entered the open-label extension phase of the study and received TYKERB monotherapy. The median age was 50 years and 7% were older than 65 years. Eighty-six percent (86%) were Asian, 8% Hispanic, and 5% Caucasian. The overall survival data are summarised in Table 15 and represented graphically in Figure 2. A summary of other key efficacy endpoints are provided in Table 16.

Table 15 TYKERB in combination with paclitaxel - Overall Survival Data in Phase III study EGF104535

	TYKERB plus Paclitaxel (N = 222)	**Placebo plus Paclitaxel (N = 222)**
Died	54%	64%
Median overall survival (months)[1]	27.8	20.5
(95% CI)	(23.2, 32.2)	(17.9, 24.3)
Hazard ratio[2], 95% CI	0.74 (0.58, 0.94)	
(Two-sided P value)	0.0124	
Cox Regression[3] Hazard Ratio	0.64 (0.49, 0.82)	
95% CI (Two-sided P value)	0.0005	

CI = confidence interval

[1] Kaplan-Meier estimates

[2] Pike estimator of hazard ratio

[3] Adjusted for hormonal status, metastatic disease sites, stage at initial diagnosis, ECOG Performance Status, number of metastatic sites, age and disease-free interval.

Figure 2 Kaplan-Meier Estimates of Overall Survival (ITT Population) in Phase III study EGF104535

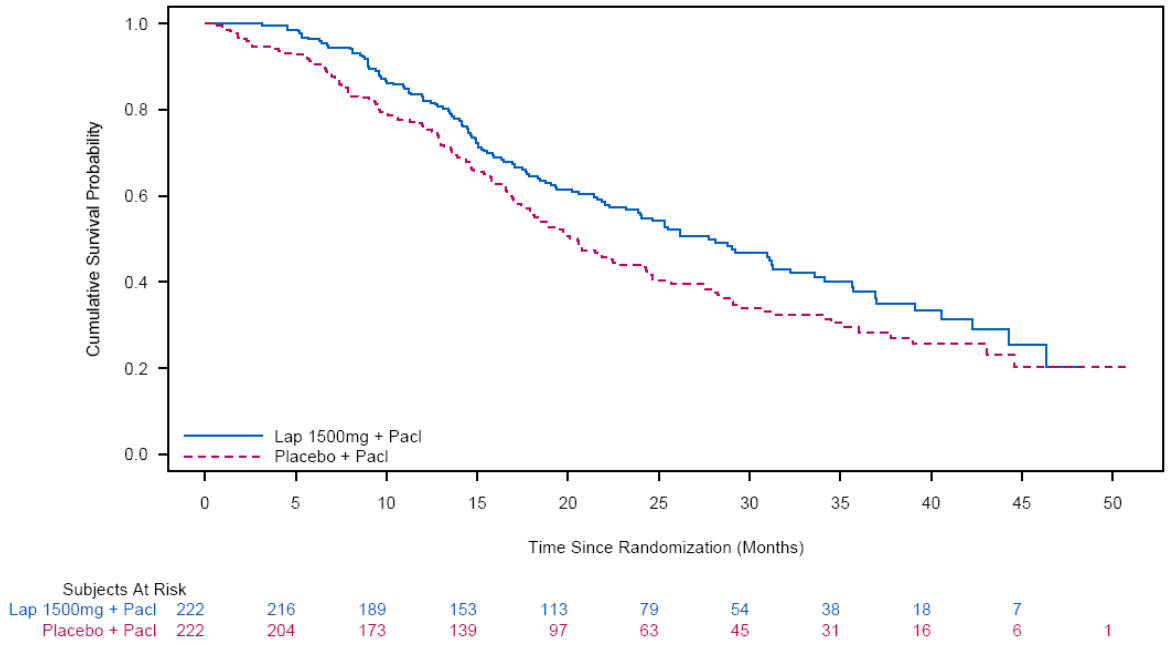


Table 16 TYKERB in combination with paclitaxel - Efficacy Data in Phase III study EGF104535

	TYKERB plus Paclitaxel (N = 222)	Placebo plus Paclitaxel (N = 222)
Median PFS[1], months	9.7	6.5
(95% CI)	(9.2, 11.1)	(5.5, 7.3)
Hazard Ratio (95% CI)	0.52 (0.42, 0.64)	
P value	<0.0001	
Response Rate (%)	69	50
(95% CI)	(62.9, 75.4)	(42.8, 56.3)
Duration of Response, months	9.3	5.8
(95% CI)	(7.7, 10.7)	(5.6, 7.4)

PFS = progression-free survival; CI = confidence interval.

[1] Kaplan-Meier estimate

Phase III Study EGF30001

Another randomised, double-blind, placebo controlled study evaluated TYKERB and paclitaxel as first-line therapy for metastatic breast cancer in patients with negative or untested HER2 status and previously untreated in the metastatic setting (EGF30001). Patients (N= 579) were randomly assigned 1:1 to paclitaxel (175mg/m^2 intravenously over 3 hours on day 1, every 3 weeks) and either TYKERB 1500mg/day or placebo once daily. Sixty-four percent (64%) were Caucasian,

18% Hispanic, and 11% Asian. There were 91 patients (16%) with HER2 positive disease.
The primary endpoint was time-to-progression (TTP); secondary endpoints included PFS, tumour response rate (RR), clinical benefit rate (CBR), OS and safety. No significant differences in TTP or PFS were observed between treatment arms in the unselected ITT population. In the HER2 positive subgroup, statistically significant and clinically relevant benefit was observed in TTP and PFS in favour of the TYKERB plus paclitaxel group. The median TTP in the HER2 positive subgroup was 35.1 weeks in the TYKERB plus paclitaxel group compared to 23.1 weeks in the paclitaxel plus placebo group (hazard ratio of 0.57; 95% CI: 0.34, 0.93; p = 0.011). The median PFS in the HER2 positive subgroup was 34.4 weeks (95% CI: 32.1, 41.6) in the TYKERB plus paclitaxel combination compared to 22.6 weeks (95% CI: 20.1, 32.9) in the paclitaxel plus placebo group (hazard ratio of 0.56; 95% CI: 0.34, 0.90; p = 0.007). The overall survival analysis of the ITT population and HER2 positive subgroup are presented in Table 17.

Table 17 Overall Survival data from Study EGF30001 (TYKERB/paclitaxel 175mg/m^2)

Overall Survival (HER2+ Population)	**TYKERB plus paclitaxel** (N=52)	**Paclitaxel alone** (N=39)
Died	71%	74%
Median overall survival (months)	24.3	19.2
Hazard ratio, 95% CI	0.77 (0.5, 1.3)	
(p value)	0.281	

CI = confidence interval

Open label studies

Phase III Study EGF108919

A randomised Phase III open label study (EGF108919) (N=652) compared the efficacy and safety of TYKERB plus a taxane followed by TYKERB alone versus trastuzumab plus a taxane followed by trastuzumab alone as first line therapy for women with HER2 positive metastatic breast cancer. Patients were randomised to either TYKERB 1250 mg once daily plus paclitaxel: 80 mg/m2 once weekly (Days 1, 8 and 15 of a 4-week cycle) or docetaxel 75 mg/m2 once every 3 weeks (Days 1 of a 3 week cycle) for 24 weeks followed by TYKERB 1500mg once daily, or trastuzumab once weekly (loading dose 4 mg/kg followed by 2 mg/kg weekly infusions) plus paclitaxel: 80 mg/m2 once weekly (Days 1, 8 and 15 of a 4-week cycle) or docetaxel 75 mg/m2 once every 3 weeks (Days 1 of a 3 week cycle) for 24 weeks followed by trastuzumab: 6 mg/kg once every 3 weeks. The study was stopped early when a pre-planned interim analysis showed superior efficacy of the combination trastuzumab plus taxane arm in terms of progression-free survival (primary endpoint). This was confirmed by the final analysis. At the clinical cut-off date for final analysis, 28 % of subjects had died, and therefore the median OS for this study was not reached (see Table 18).

The TTax/T regimen was better tolerated than the LTax/L regimen with the exception of slightly higher incidence of LV dysfunction observed in the trastuzumab arm. Across both the combination and monotherapy study phases, the incidences of AEs leading to permanent discontinuation of study treatment, SAEs, and drug-related SAEs were higher in the LTax/L treatment arm.

Table 18 Summary of PFS and OS in Study EGF108919

	TYKERB plus taxane	trastuzumab plus taxane
Progression Free Survival (ITT Population)	(N=326)	(N=326)
Median PFS[1], months	8.9	11.3
(95% CI)	(0.30 - 32.69)	(0.30 - 38.54)
Hazard Ratio (95% CI)	1.367 (1.133, 1.648)	
P value	0.0010	
Overall Survival (ITT Population)	(N=326)	(N=326)
Died	31%	25%
Hazard ratio, 95% CI	1.227 (0.946, 1.722)	
(p value)	0.1093	

Abbreviations: CI=confidence interval.
a. Stratified HR for LTax/L versus TTax/T

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 (estrogen receptor [ER] positive and/or progesterone receptor [PgR] positive) postmenopausal women.

Double-blind controlled trial

Phase III Study EGF30008
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-estrogen 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 PFS was significantly greater with letrozole plus TYKERB compared with letrozole plus placebo (see Table 18). The PFS data in the HER2-positive population is represented graphically in Figure 3.

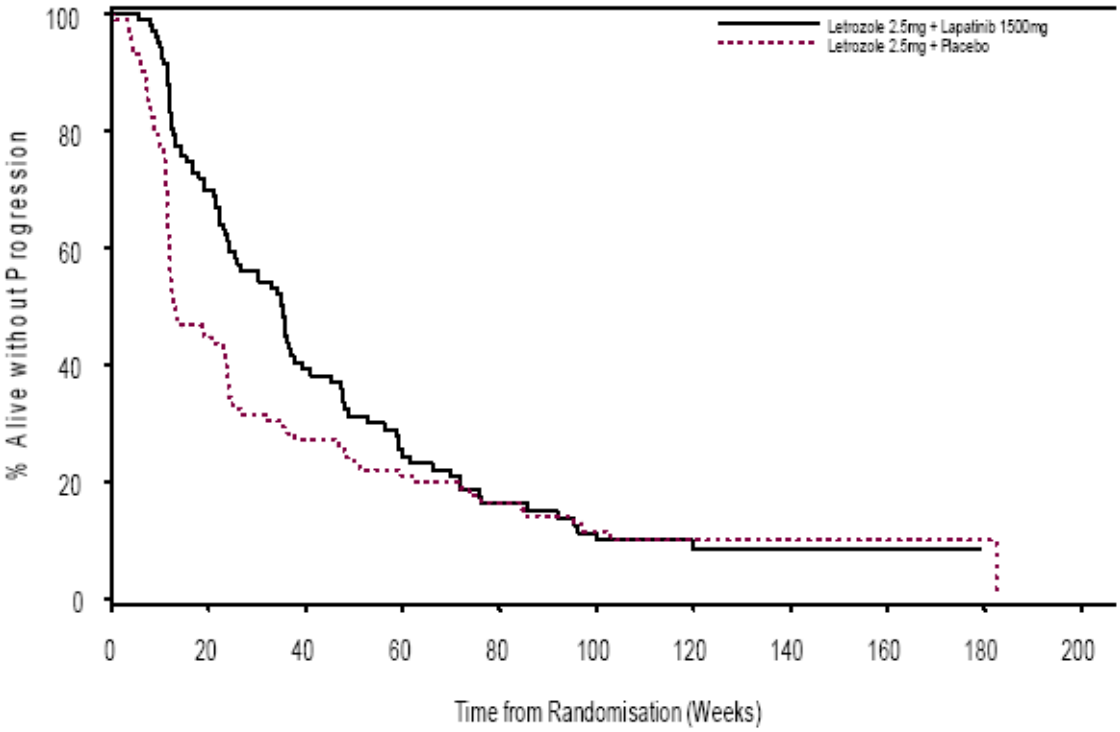
The benefit of TYKERB + letrozole on PFS in the HER2-positive population was confirmed in a pre-planned Cox regression analysis (HR = 0.65 (95 % CI 0.47 - 0.89), p = 0.008). In addition to a PFS benefit seen in the HER2+ patient population, combination therapy of TYKERB and letrozole was associated with 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 19).

Table 19 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 TYKERB 1500 mg/day + letrozole 2.5 mg/day	N = 108 letrozole 2.5 mg/day + placebo	N = 642 TYKERB 1500 mg/ day + letrozole 2.5 mg/day	N = 644 letrozole 2.5 mg/day + placebo	N = 478 TYKERB 1500 mg/day + letrozole 2.5 mg/day	N = 474 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

Figure 3 Kaplan-Meier Estimates for Investigator-Evaluated PFS (Study EGF30008, HER2 +ve Population)



In the Intent-to-Treat (ITT) population, investigator-determined PFS was greater between the two treatment arms (see Table 19). 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 19).

5.2 Pharmacokinetic properties

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) μg/mL and AUC values of 36.2 (23.4 to 56) μg*hr/mL. The absolute bioavailability of lapatinib has not been determined.

Daily dosing of 1500 mg lapatinib in combination with paclitaxel 175 mg/m^2 every three weeks produces steady state geometric mean (95% confidence interval) C_{max} values of 5.31 (3.54 to 7.97) μg/mL and AUC values of 64.5 (43.3 to 96.2) μg*hr/mL.

Systemic exposure to lapatinib is increased when administered with food (see section 4.2 Dose and method of administration and section 4.5 Interactions with other medicines and other forms of 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 albumin and alpha-1 acid glycoprotein. *In vitro* studies indicate that lapatinib is a substrate for the transporters BCRP (ABCG2) and P-glycoprotein (ABCB1). Lapatinib has also been shown to inhibit P-glycoprotein (IC_{50} 2.3 μg/mL), BCRP (IC_{50} 0.015 μg/mL) and the hepatic uptake transporter OATP1B1(IC_{50} 2.3 μg/mL), *in vitro* at clinically relevant concentrations. The clinical significance of these effects on the pharmacokinetics of other drugs or the pharmacological activity of other anti-cancer agents is not known. Limited inhibition of the OAT and OCT renal transporters was seen with 17 μg/mL lapatinib.

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 (approximately 5 μM or 3 μg/mL). Lapatinib did not significantly inhibit the following enzymes in human liver microsomes: CYP2C9, CYP2C19 and CYP2D6 or UGT enzymes (*in vitro* IC_{50} 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 section 4.2 Dose and method of administration and section 4.4. Special warnings and precautions for use).

5.3 Preclinical Safety Data

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

TYKERB tablet contains microcrystalline cellulose, povidone, sodium starch glycollate type A, magnesium stearate, hypromellose, titanium dioxide, macrogol 400, polysorbate 80, iron oxide red (CI77491) and iron oxide yellow (CI77492) as therapeutically inactive ingredients.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of the container

Packs available
TYKERB tablets are supplied in HDPE bottles with child resistant closure packs containing 70 tablets in Australia.

Other packs registered
Bottle packs (HDPE) containing 30*, 84*, 105*, and 140* tablets.
Blister packs (PA/Al/PVC/Al) containing 40*, 70*, 84* and 168* tablets are also registered (not supplied).

*Not all pack sizes may be distributed.

6.6 Special precautions for disposal

Any unused product should be returned to a pharmacist for safe disposal. Unused tablets should not be disposed in domestic waste or waste water.

6.7 Physicochemical properties

Lapatinib ditosilate (monohydrate) has the chemical name: N-(3-chloro-4-{[(3-fluoro phenyl) methyl] oxy}phenyl)-6-[5-({[2-(methyl sulfonyl)ethyl]amino}methyl)-2-furanyl]-4-quinazolin amine bis(4-methyl benzene sulfonate) monohydrate.

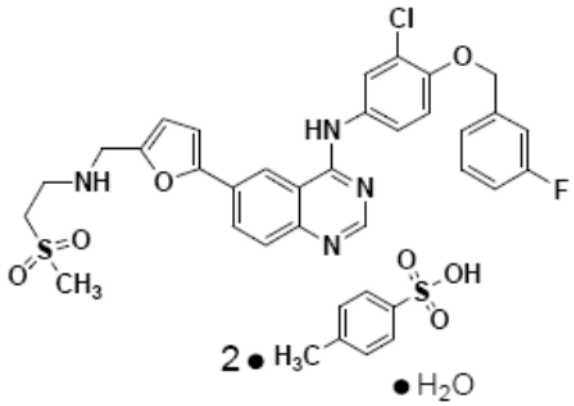
It is a yellow crystalline powder at room temperature.

Lapatinib ditosilate (monohydrate) has the molecular formula: $C_{29}H_{26}ClFN_4O_4S(C_7H_8O_3S)_2H_2O$.

The molecular weights are 943.48 g/mole and 581.06 g/mole for the ditosilate and free base respectively.

Lapatinib ditosilate solubility in water and 0.1N HCl are 0.007 g/L and 0.001 g/L at 25°C respectively.

Chemical structure



CAS number

388082-78-8

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription only medicine

8. SPONSOR

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9. DATE OF FIRST APPROVAL

28 June 2007

10. DATE OF REVISION

27 May 2022

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Addition of post-market AE “skin fissures” with frequency “common” based on pooled trial data
5.1	Revision of ATC code and Pharmacotherapeutic group

Internal document code (tyk270522i) is based on CDS dated 18 August 2021