

DATA SHEET

TYKERB[®] Tablets

Lapatinib ditosylate film coated tablets 250mg

Presentation

250mg: Yellow, oval, biconvex, film-coated tablets, with one side plain and the opposite side debossed with GS XJG.

Clinical particulars

Therapeutic Indications

HER2-positive overexpressing metastatic breast cancer

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.

Hormone receptor-positive metastatic breast cancer

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 (see *Clinical Studies*).

Posology and Method of 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*).

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-positive overexpressing metastatic breast cancer

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

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

Hormone receptor-positive metastatic breast cancer

The recommended dose of TYKERB is 1500mg (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 2.5mg 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 (HER2-positive overexpressing/Hormone receptor-positive metastatic breast cancer)

Cardiac events (see Special Warnings and Special 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 (1000mg/day when administered with capecitabine and 1250mg/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 12 weeks of treatment, however, there is limited data on long term exposure.

Interstitial lung disease/pneumonitis (see Special Warnings and Special Precautions and Undesirable Effects)

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 1250mg/day when administered with capecitabine or 1500mg/day when administered with an aromatase inhibitor, when the toxicity improves to grade 1 or less. If the toxicity recurs, then lapatinib should be restarted at a lower dose (1000mg/day when administered with capecitabine and 1250mg/day when administered with an aromatase inhibitor).

Hepatic Impairment

Patients with severe hepatic impairment (Child-Pugh Class C) should have their dose of TYKERB reduced. A dose reduction from 1250mg/day to 750 mg/day or from 1500mg/day to 1000mg/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 Special Warnings and Precautions for Use and Pharmacokinetics – Hepatic Impairment*).

Contra-indications

TYKERB is contraindicated in patients with hypersensitivity to any of the ingredients (*see Pharmaceutical Particulars and Undesirable effects*).

Special Warnings and Special Precautions for Use

Lapatinib has been associated with reports of decreases in left ventricular ejection fraction [LVEF] (*see Undesirable Effects*). Caution should be taken if lapatinib 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 lapatinib to ensure that the patient has a baseline LVEF that is within the institutions normal limits. LVEF should continue to be evaluated during treatment with lapatinib to ensure that LVEF does not decline to an unacceptable level (*see Posology and Method of Administration — dose delay and dose reduction — cardiac events and Further Information -Clinical Studies*).

Lapatinib has been associated with reports of interstitial lung disease and pneumonitis (*see Undesirable Effects*). Patients should be monitored for pulmonary symptoms indicative of interstitial lung disease/pneumonitis (*see Posology and Method of 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 lapatinib 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

lapatinib should be discontinued and patients should not be retreated with lapatinib (see Undesirable Effects).

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 Posology and Method of Administration and Pharmacokinetics – Special patient Populations).

Diarrhoea, including severe diarrhoea, has been reported with lapatinib treatment (see *Undesirable effects*). Proactive management of diarrhoea with anti-diarrhoeal agents is important. Severe cases of diarrhoea may require administration of oral or intravenous electrolytes and fluids, and interruption or discontinuation of lapatinib therapy (see *Posology and Method of 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 lapatinib, respectively (see *Interactions*).

Use During Pregnancy and Lactation

Pregnancy:-

There are no adequate and well-controlled studies of TYKERB in pregnant women. The effect of TYKERB on human pregnancy is unknown. TYKERB should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus. Women of childbearing potential should be advised to use adequate contraception and avoid becoming pregnant while receiving treatment with TYKERB.

TYKERB was not teratogenic when studied in pregnant rats and rabbits but caused minor abnormalities at doses which were maternally toxic (see *Non-clinical Information*).

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, it is recommended that breast-feeding be discontinued in women who are receiving therapy with TYKERB.

Non-clinical information

Lapatinib was studied in pregnant rats and rabbits given oral doses of 30, 60, and 120 mg/kg/day. There were no teratogenic effects; however, minor anomalies (left-sided umbilical artery, cervical rib and precocious ossification) occurred in rats at the maternally toxic dose of 120mg/kg/day (6.4 times the expected clinical exposure in humans given 1250mg lapatinib and 2000 mg/m² capecitabine). In rabbits, lapatinib was associated with maternal toxicity at 60 and 120mg/kg/day (6.5 % and 19 % of the expected clinical exposure in humans given 1250mg

lapatinib and 2000mg/m² capecitabine, respectively) and abortions at 120mg/kg/day. Maternal toxicity was associated with decreased foetal body weights, and minor skeletal variations. In the rat pre- and postnatal development study, a decrease in pup survival occurred between birth and postnatal day 21 at doses of 60 mg/kg/day or higher (3.3 times the expected clinical exposure in humans given 1250mg lapatinib and 2000mg/m² capecitabine). The highest no-effect dose for this study was 20mg/kg/day.

There were no effects on male or female rat gonadal function, mating, or fertility at doses up to 120 mg/kg/day (females) and up to 180mg/kg/day (males) (6.4 and 2.3 times the expected clinical exposure in humans given 1250mg lapatinib and 2000mg/m² capecitabine, respectively). The effect on human fertility is unknown.

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

In oral carcinogenicity studies with lapatinib, severe skin lesions were seen at the highest doses tested which produced exposures based on AUC up to 1.7-fold in mice and male rats, and up to 12-fold in female rats, compared to humans given 1250mg of lapatinib and 2000mg/m² capecitabine. 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 6 and 8-fold compared to humans given 1250mg of lapatinib and 2000mg/m² capecitabine. The relevance of these findings for humans is uncertain.

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 the TYKERB. The clinical status of the patient and the adverse event profile of TYKERB should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills.

Interaction with Other Medicinal Products and Other Forms of Interaction

Lapatinib is predominantly metabolised by CYP3A (see *Pharmacokinetics*). Therefore, inhibitors or inducers of these enzymes may alter the pharmacokinetics of lapatinib.

Coadministration of lapatinib 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 *Warnings and Precautions*). If patients must be coadministered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a dose reduction to 500 mg/day of lapatinib is predicted to adjust the lapatinib 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 lapatinib dose is adjusted upward to the indicated dose.

Co-administration of lapatinib with known inducers of CYP3A4 (e.g., rifampin, carbamazepine, or phenytoin) should proceed with caution and clinical response and adverse events should be carefully monitored (see *Special Warnings and Special Precautions*). If patients must be co-administered a strong CYP3A4 inducer, based on pharmacokinetic studies, the dose of lapatinib should be titrated gradually from 1,250mg/day up to 4,500mg/day or from 1,500mg/day up to 5,500mg/day, based on tolerability. This dose of lapatinib is predicted to adjust the lapatinib AUC to the range observed without inducers and should be considered. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued the lapatinib dose should be reduced over approximately 2 weeks to the indicated dose.

Lapatinib inhibits CYP3A4 *in vitro* at clinically relevant concentrations. Coadministration 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 lapatinib concurrently with orally administered medications with narrow therapeutic windows that are substrates of CYP3A4 (see *Pharmacodynamic properties*).

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

Coadministration 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 if lapatinib is coadministered with paclitaxel.

Coadministration of lapatinib with intravenously administered docetaxel did not significantly affect the AUC or Cmax of either active substance. However, the occurrence of docetaxel-induced neutropenia was increased.

Coadministration of lapatinib with irinotecan (when administered as part of the FOLFIRI regimen) resulted in an approximate 40% increase in the AUC of SN-38, the active metabolite of irinotecan. The precise mechanism of this interaction is unknown. Caution is advised if lapatinib is coadministered with irinotecan.

Lapatinib is a substrate for the transport proteins Pgp and BCRP (Breast Cancer Resistance Protein). Inhibitors and inducers of these proteins may alter the exposure and/or distribution of lapatinib (see Pharmacodynamic properties).

Lapatinib inhibits the transport protein Pgp *in vitro* at clinically relevant concentrations. Coadministration 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) (see *Pharmacodynamic properties*)

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

The bioavailability of lapatinib is affected by food (see *Posology and Method of Administration and Pharmacokinetics*).

Undesirable Effects

Safety of TYKERB has been evaluated as monotherapy or in combination with other chemotherapies for various cancers in more than 15,000 patients, including 198 patients who received lapatinib in combination with capecitabine and 654 patients who received TYKERB in combination with letrozole (see *Further Information - Clinical Studies*).

The incidence of adverse events in the pivotal Phase III study (EGF100151) considered by the investigator to be related to study medication was similar in both groups (80% combination arm v 78% control arm).

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 Warnings and Precautions</i>).
¹ Left ventricular ejection fraction (LVEF) decreases have been reported in approximately 1% of patients and were asymptomatic in more than 75% of cases. LVEF decreases resolved or improved in more than 60% of cases on discontinuation of treatment with lapatinib. Symptomatic LVEF decreases were observed in approximately 0.2% of patients who received lapatinib. Observed symptoms included dyspnoea, cardiac failure and palpitations.	
<u>Respiratory, thoracic and mediastinal disorders:</u>	
Uncommon	Interstitial lung disease / pneumonitis
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 Warnings and Precautions</i>). Nausea. Vomiting.
³ Most events of diarrhoea were grade 1 or 2.	
Hepatobiliary disorders	
Uncommon	Hyperbilirubinaemia ⁴ , hepatotoxicity.
⁴ Elevated bilirubin may be due to lapatinib 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 lapatinib. Diarrhoea responds well to proactive management (see *Special Warnings and Special 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 198 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.

A subsequent post-hoc 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.

The following additional adverse reactions have been reported to be associated with lapatinib 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

Overdose

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 *Posology 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 Adverse Reactions) and in some cases sore scalp, sinus tachycardia (with otherwise normal ECG) and/or mucosal inflammation.

Treatment:-

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.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

Pharmacological properties

Pharmacodynamic properties

Mode of action:-

Lapatinib is a novel 4-anilinoquinazoline kinase inhibitor with a unique mechanism of action, since it is a potent, reversible, and selective inhibitor of the intracellular tyrosine kinase domains of both ErbB1 (EGFR) and HER2 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 was found to be slower than other 4-anilinoquinazoline kinase inhibitors studied. Lapatinib inhibits ErbB-driven tumour cell growth *in vitro* and in various animal models.

In addition to its activity as a single agent, an additive effect was demonstrated in an *in vitro* study when lapatinib and 5-FU (the active metabolite of capecitabine) were used in combination in the four tumour cell lines tested. The clinical significance of these *in vitro* data is unknown.

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

Hormone receptor-positive 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 receptor-positive breast cancer cells that initially lack overexpression of EGFR or HER2 will up regulate these receptors as the tumour becomes resistant to endocrine therapy.

Randomized trials in hormone receptor-positive metastatic breast cancer indicate that a HER2 or EGFR tyrosine kinase inhibitor may improve PFS when added to endocrine therapy.

Pharmacokinetic properties

Absorption

Absorption following oral administration of lapatinib results in approximately 50 to 100% coefficient of variation in AUC. 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) $\mu\text{g}\cdot\text{hr/mL}$.

Systemic exposure to lapatinib is increased when administered with food. 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 Pgp (ABCB1). Lapatinib has also been shown to inhibit Pgp (IC_{50} 2.3 $\mu\text{g/mL}$), BCRP (IC_{50} 0.014 $\mu\text{g/mL}$) and the hepatic uptake transporter OATP 1B1 (IC_{50} 2.3 $\mu\text{g/mL}$), *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. Lapatinib does not significantly inhibit the OAT or OCT renal transporters (*in vitro* IC_{50} values were greater than or equal to 6.9 $\mu\text{g/mL}$).

Metabolism

Lapatinib undergoes extensive metabolism, primarily by CYP3A4 and CYP3A5, with minor contributions from CYP2C19 and CYP2C8 to variety of oxidated metabolites, none of which account for more than 14% of the dose recovered in the faeces or 10% of lapatinib concentration in plasma.

Lapatinib inhibits CYP3A (K_i 0.6 to 2.3 $\mu\text{g/mL}$) and CYP2C8 (0.3 $\mu\text{g/mL}$) *in vitro* at clinically relevant concentrations. Lapatinib did not significantly inhibit the following enzymes in human liver microsomes: CYP1A2, CYP2C9, CYP2C19, and CYP2D6 or UGT enzymes (*in vitro* IC_{50} values were greater than or equal to 6.9 $\mu\text{g/mL}$).

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%.

Elimination

The half-life of lapatinib measured after single doses increases with increasing dose. However, daily dosing of lapatinib results in achievement of steady state within 6 to 7 days, indicating an effective half-life of 24 hours. Lapatinib is predominantly eliminated through metabolism by CYP3A4/5. 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 lapatinib in faeces accounts for a median 27% (range 3 to 67%) of an oral dose.

Children:-

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

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
Lapatinib + capecitabine (N=198) (EGF100151)	33 (17%)	2 (1%)
Lapatinib + letrozole (N=642) (EGF30008)	285 (44%)	77 (12%)
Single agent lapatinib (N=599) (EGF20002, EGF20008, EGF20009, EGF103009)	101 (17%)	24 (4%)

No overall differences in the safety or efficacy of these regimens on the basis of age 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.

Patients with 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.

Patients with 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, TYKERB should be discontinued and patients should not be retreated with TYKERB (see *Posology and Method of Administration and Special Warnings and Special Precautions*).

Further information

Clinical Studies

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 (ICH 3+ or ICH 2+ and FISH positive), 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 lapatinib to ensure baseline LVEF was within the institutions normal limits.

In clinical trials, LVEF was monitored at approximately 8-week intervals during treatment with lapatinib 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 1250mg once daily (continuously) plus capecitabine (2000mg/m²/day on days 1-14 every 21 days), or to receive capecitabine alone (2500mg/m²/day on days 1-14 every 21 days). Study treatment was given until disease progression, or withdrawal for another reason. The primary endpoint was time to progression (TTP) as assessed by an independent review panel. Results presented below are based on both the investigators assessment and review by an independent review panel.

The results at the data cut-off date of 03 April 2006 (the date at which further enrolment to the study was halted), showed a significant increase in TTP for patients receiving lapatinib plus capecitabine (representing a 43% reduction in the risk of disease progression or death due to breast cancer compared with capecitabine monotherapy, as assessed by the independent review panel). See Table 2.

Table 2 Key efficacy data from Study EGF100151 (lapatinib / capecitabine)

Efficacy Outcome	<i>Independent Assessment</i>		<i>Investigator Assessment</i>	
	Lapatinib plus capecitabine (N=198)	Capecitabine alone (N=201)	Lapatinib plus capecitabine (N=198)	Capecitabine alone (N=201)
Time to progression				
- Progressed or died due to breast cancer	41%	51%	61%	63%
- Median time to progression (weeks)	27.1	18.6	23.9	18.3
- Hazard ratio, 95% CI - (p value)	0.57 (0.43, 0.77) 0.00013		0.72 (0.56, 0.92) 0.00762	
Overall Response Rate, 95% CI	23.7% (18.0, 30.3)	13.9% (9.5, 19.5)	31.8% (25.4, 38.8)	17.4% (12.4, 23.4)

CI = confidence interval

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. Median duration of response was 32.1 weeks and 30.6 weeks 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.

At the time enrolment was halted to EGF100151 (03 April 2006), 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 survival data to 01 October 2008 is summarised in Table 3.

Table 3 Overall Survival data from Study EGF100151 (lapatinib / capecitabine)

	Lapatinib plus capecitabine (N=207)	Capecitabine alone (N=201)
Overall Survival		
- Died	81%	86%
- Median overall survival (weeks)	75.0	64.7
- Hazard ratio, 95% CI	0.87 (0.71, 1.08)	
- (p value)	0.210	

CI = confidence interval

After the study was halted, 36 patients crossed over from capecitabine to lapatinib + 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).

Combination treatment with TYKERB and letrozole

TYKERB has been studied in combination with 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 randomised, double-blind, controlled trial in patients with hormone-sensitive (HS) locally advanced or metastatic breast cancer (MBC), who had not received prior therapy for their metastatic disease. A total of 1286 patients were randomised to letrozole 2.5mg once daily plus TYKERB 1500mg once daily or letrozole 2.5mg 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 overexpressing 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 4).

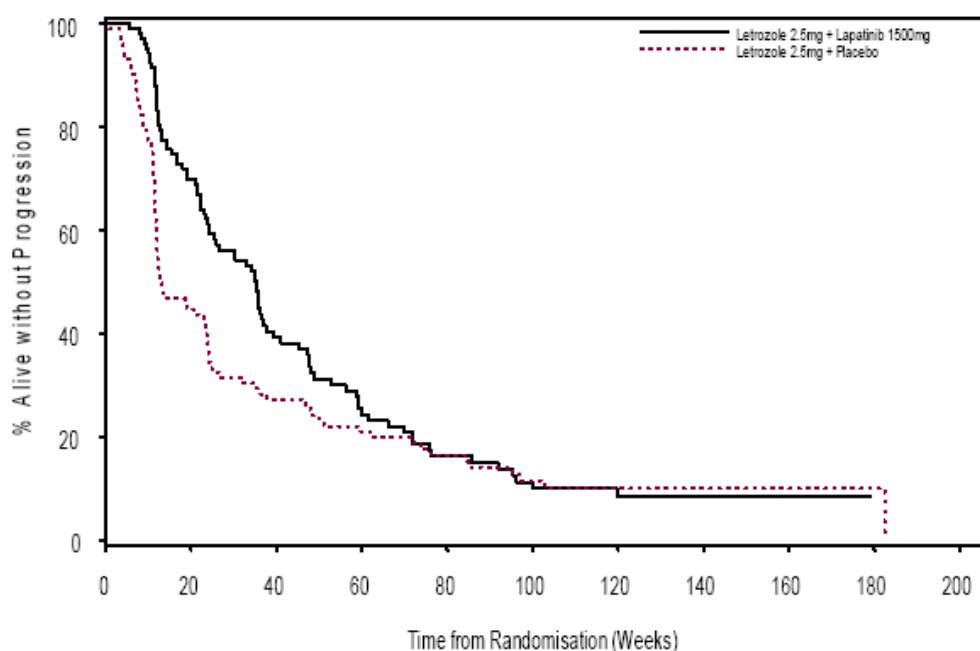
Table 4 Progression Free Survival data from Study EGF30008 (TYKERB / letrozole)

	Primary population		Secondary Populations			
	HER2-Positive Population		Intent-to-Treat Population		HER2-Negative Population	
	N = 111	N = 108	N = 642	N = 644	N = 478	N = 474
	TYKERB 1500mg / day + Letrozole 2.5 mg / day	Letrozole 2.5mg / day + placebo	TYKERB 1500mg / day + Letrozole 2.5mg / day	Letrozole 2.5mg / day + placebo	TYKERB 1500mg / day + Letrozole 2.5mg / day	Letrozole 2.5mg / day + placebo
Median PFS, weeks (95% CI)	35.4 (24.1, 39.4)	13.0 (12.0, 23.7)	51.7 (47.6, 59.6)	47.0 (36.9, 50.9)	59.7 (48.6, 69.7)	58.3 (47.9, 62.0)
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	

CI= confidence interval

The PFS data in the HER2-positive population is represented graphically in Figure 1.

Figure 1: Kaplan-Meier Estimates for Investigator-Evaluated PFS (Study EGF30008, HER2-positive 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) and in Clinical Benefit rate (CBR; complete plus partial response plus stable disease for >6 months) (47.7% and 28.7% respectively) (p=0.003) 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= 0.77 (95%CI 0.52-1.14) p=0.185.

In the Intent-to-Treat (ITT) population, investigator-determined PFS was greater between the two treatment arms (see Table 4). 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 4). However, the pre-planned Cox regression model taking into account a number of baseline covariates for PFS did show an improvement with the TYKERB plus letrozole combination. (HR=0.77 (95%CI 0.64-0.94) p=0.010). In addition, age (younger), performance status (0), baseline serum HER2 ECD (<15ng/ml), number of metastatic sites (<3) and prior adjuvant anti-oestrogen stratification (<6 months since discontinuation) were identified as being significant prognostic factors.

Growth factor upregulation occurs with anti-oestrogen or endocrine therapy resistance. Therefore, the treatment effect in the pre-defined trial strata of prior

endocrine therapy was further analyzed (<6 months since discontinuation of endocrine therapy and ≥6 months since discontinuation of endocrine therapy / never having received endocrine therapy). Table 5 below describes the PFS in these two subgroups of the HER2 negative population. In addition to the PFS benefit of TYKERB/letrozole therapy in the <6 months stratum, a benefit in CBR was also noted when compared with letrozole plus placebo (43.8% and 31.7% respectively).

Table 5 Efficacy Results for Two Subgroups of HER2-negative Population

	<6 months since prior endocrine therapy ¹		≥6 months since prior endocrine therapy/never received ²	
	N=200		N = 752	
	TYKERB 1500mg/ day + Letrozole 2.5mg/ day	Letrozole 2.5mg/ day + placebo	TYKERB 1500mg/ day + Letrozole 2.5mg / day	Letrozole 2.5mg/ day + placebo
	N = 96	N =104	N = 382	N = 370
Median PFS, weeks (95% CI)	36.3 (21.9, 55.3)	13.3 (12.1, 23.7)	64.0 (58.3, 73.1)	65.3 (59.1, 74.3)
Hazard Ratio	0.78 (0.57, 1.07)		0.94 (0.79, 1.13)	
P-value	0.117		0.522	

CI= confidence interval

¹ months since discontinuation of endocrine therapy

² months since discontinuation of endocrine therapy/never received

Pharmaceutical particulars

List of Excipients

TYKERB contains:-

Microcrystalline cellulose, Macrogol 400, Polysorbate 80, Sodium starch glycollate, Povidone K30, Titanium dioxide, Hypromellose, Magnesium stearate, Iron oxide yellow (C177492), Iron oxide red (C177491)

Incompatibilities

None Reported

