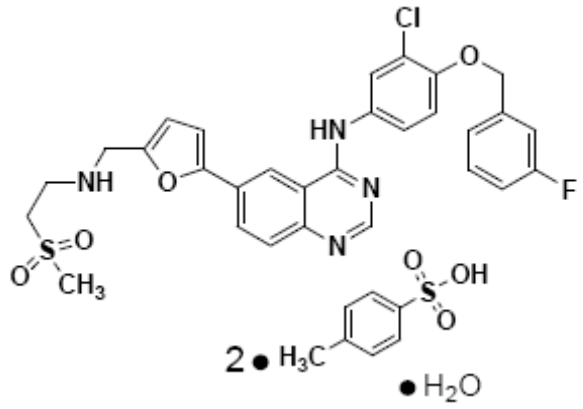
TYKERB® PRODUCT INFORMATION
(Lapatinib Ditosylate)
250 mg tablets

NAME OF THE DRUG

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

The structural formula is:



Molecular formula: $C_{29}H_{26}ClFN_4O_4S(C_7H_8O_3S)_2H_2O$
Molecular weight: 943.48 (ditosylate monohydrate)
CAS number : 388082-78-8

DESCRIPTION

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

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

PHARMACOLOGY

Lapatinib is a potent, reversible, and selective inhibitor of the intracellular tyrosine kinase domains of both ErbB1 (EGFR) and HER2 (ErbB2) receptors (estimated Ki^{app} values of 3nM and 13nM, respectively) with a slow off-rate from these receptors (half-life greater than or equal to 300 minutes). This dissociation rate from ErbB1

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

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

Pharmacokinetics

Absorption:

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

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

Distribution:

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

Metabolism:

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

Lapatinib significantly inhibited the metabolism of the substrates of the recombinant CYP enzymes, CYP3A4 and CYP2C8 in vitro at clinically relevant concentrations (~ 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 (Child-Pugh scores of 7-9, or greater than 9, respectively) 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 (*see Precautions*).

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

initiation of treatment with TYKERB to ensure baseline LVEF was within the institutions normal limits.

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

Patients were randomized to receive either TYKERB 1250 mg once daily (continuously) plus capecitabine (2000 mg/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.

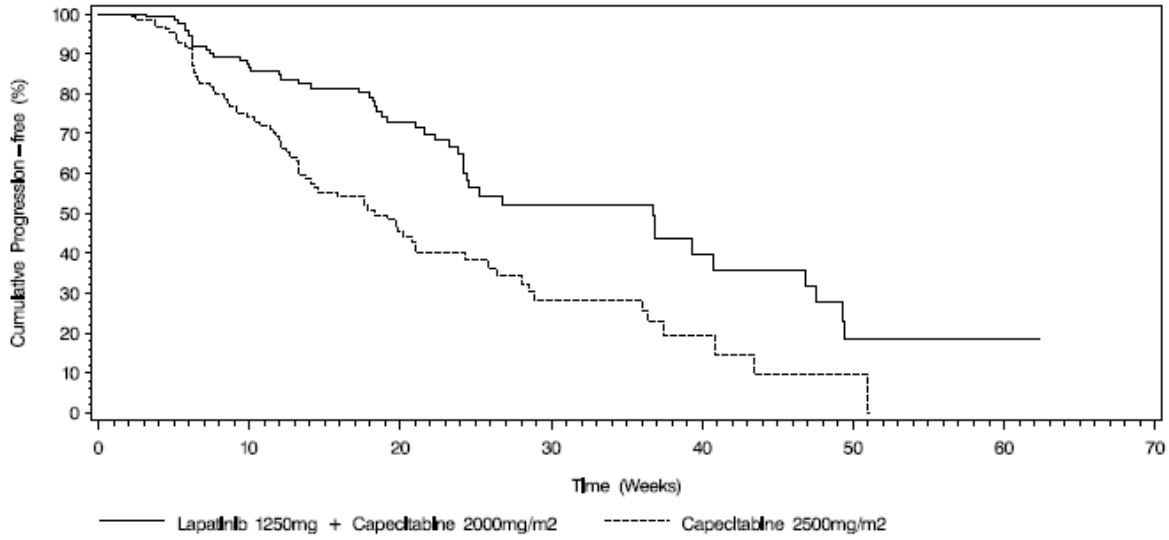
At the data cut-off date for the pre-specified interim analysis (November 15, 2005), 324 patients were enrolled (163 in the combination arm, 161 in the monotherapy arm). The efficacy results showed a statistically significant improvement in TTP (51% reduction in the hazard of disease progression) for patients receiving TYKERB plus capecitabine with a median TTP of 36.7 weeks in the combination arm versus 19.7 weeks in the monotherapy arm (p 0.00008). See Table 1.

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

Efficacy Outcome	TYKERB plus capecitabine (N=163)	Capecitabine alone (N=161)
Time to progression		
Progressed or died due to breast cancer	30%	45%
Median time to progression (weeks)	36.7	19.1
Hazard ratio, 95% CI (p value)	0.49 (0.34, 0.71) 0.00008	

The TTP data are represented graphically in Figure 1.

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



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

Progression-free survival (PFS) is defined as time from randomisation until disease progression or death due to any cause. At the interim analysis, TYKERB, when given in combination with capecitabine significantly prolonged PFS compared to capecitabine alone (36.7 weeks v 17.9 weeks, p=0.000023).

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

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

An independent data monitoring committee (IDMC) initially reviewed the results of the interim analysis (which included data from 321 of the 324 patients), and recommended that further enrolment into the study was halted due to a statistically significant and clinically relevant increase in TTP for the combination of TYKERB and capecitabine over capecitabine alone, which crossed a pre-defined statistical stopping boundary for superiority. At the time enrolment was halted (April 03, 2006), a total of 399 patients had been randomised to study treatment.

A subsequent updated analysis was conducted with a data cut-off of April 03, 2006 when enrollment was halted. An additional 75 subjects had been enrolled into the study between the interim analysis clinical cut-off date and halting enrollment into the study (n=198 combination arm vs n= 201 control arm). This analysis revealed maintenance of a highly statistically significant improvement in TTP for subjects enrolled in the combination arm conferring a 43% reduction in hazard of disease progression (p=0.00013). The median TTP by independent review for the combination arm versus the control arm was 27.1 versus 18.6 weeks respectively. At this time, the overall survival data remained immature: 55 subjects (28%) in the TYKERB plus capecitabine group and 64 subjects (32%) in the capecitabine group had died. Four (2%) patients in the combination-therapy group had symptomatic CNS progression as part of their first progression event as compared to 13 (6%) patients in the monotherapy group (p=0.0445).

INDICATIONS

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

CONTRAINDICATIONS

There are no known contraindications associated with TYKERB. Please refer to the capecitabine prescribing information for relevant contraindications and safety information when administering TYKERB in combination with capecitabine.

PRECAUTIONS

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

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

Diarrhoea, including severe diarrhoea, has been reported with TYKERB treatment (*see Adverse Events*). Proactive management of diarrhoea with anti-diarrhoeal agents

is important. Severe cases of diarrhoea may require administration of oral or intravenous electrolytes and fluids, and interruption or discontinuation of TYKERB therapy (*see Dosage and Administration — Dose delay and dose reduction — Other toxicities*).

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

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

Patients with renal impairment:
Refer to Pharmacokinetics.

Patients with Hepatic Impairment:
Caution is warranted if TYKERB is prescribed to patients with moderate or severe hepatic impairment (*Refer to Pharmacokinetics-Hepatic impairment*).

Elderly:
Refer to Dosage and Administration

Children:
Refer to Dosage and Administration

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

Carcinogenicity:
Two year carcinogenicity studies with lapatinib in rats and mice are ongoing.

Effect 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 human value with the recommended daily dose of 1250mg, respectively. There was an increase in post implantation loss in female fertility study at > 60 mg/kg/day (relative exposure approximately 4). The effect on human fertility is unknown.

Use in Pregnancy (Category C)
Lapatinib was studied in pregnant rats and rabbits given oral doses of 30, 60 and 120 mg/kg/day. There were no treatment-related malformations, however alterations (left-sided umbilical artery, cervical rib) were observed in rats in the presence of maternal toxicity at 120 mg/kg/day (approximately 7 times the human 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 foetuses 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, of those anticipated in humans following the recommended daily dose of 1250mg.

In the pre- and postnatal development study, a marked decrease in pup survival occurred between birth and postnatal day 21 at doses of ≥ 60 mg/kg/day (approximately 3 times the human exposure based on AUC). The highest no-effect dose for this study was 20 mg/kg/day, which may be expected to result in an exposure (AUC) similar to that seen in humans following a dose of 1250mg.

There are no adequate and well-controlled studies of TYKERB in pregnant women. The effect of TYKERB on human pregnancy is unknown. TYKERB should not be used in pregnancy. Women of childbearing potential must be advised to use adequate contraception and avoid becoming pregnant while receiving treatment with TYKERB. If the drug is used during pregnancy or if the patient becomes pregnant while receiving the drug, the patient should be notified that TYKERB may cause harmful effects to the human foetus or neonate without causing malformations.

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

Interactions
TYKERB is predominantly metabolised by CYP3A (*see Pharmacokinetics*). Therefore, inhibitors or inducers of these enzymes may alter the pharmacokinetics of TYKERB. Coadministration of TYKERB with known inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole or grapefruit juice) should proceed with caution and clinical response and adverse events should be carefully monitored (*see Precautions*). If patients must be coadministered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a dose reduction to 500 mg/day of TYKERB is predicted to

adjust the TYKERB AUC to the range observed without inhibitors and should be considered. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors. If the strong inhibitor is discontinued, a washout period of approximately 1 week should be allowed before the TYKERB dose is adjusted upward to the indicated dose.

Coadministration of TYKERB with known inducers of CYP3A4 (e.g., rifampin, carbamazepine, or phenytoin) should proceed with caution and clinical response and adverse events should be carefully monitored (*see Precautions*). If patients must be coadministered a strong CYP3A4 inducer, based on pharmacokinetic studies, the dose of TYKERB should be titrated gradually from 1,250 mg/day up to 4,500 mg/day based on tolerability. This dose of TYKERB is predicted to adjust the TYKERB 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 TYKERB dose should be reduced over approximately 2 weeks to the indicated dose.

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

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

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

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

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

Driving or operating machinery

There have been no studies to investigate the effect of TYKERB on driving performance or the ability to operate machinery. A detrimental effect on such activities cannot be predicted from the pharmacology of 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.

ADVERSE EVENTS:

Safety of TYKERB has been evaluated as monotherapy or in combination with other chemotherapies for various cancers in more than 3,000 patients, including 164 patients who received TYKERB in combination with capecitabine (*see Clinical Trials*).

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† (*see Dosage and Administration — dose delay and dose reduction — Cardiac events and Precautions*).
†Left ventricular ejection fraction (LVEF) decreases have been reported in approximately 1% of patients and were asymptomatic in more than 90% of cases. LVEF decreases resolved or improved in more than 60% of cases on discontinuation of treatment with TYKERB. Symptomatic LVEF decreases were observed in approximately 0.1% of patients who received TYKERB monotherapy. Observed symptoms included dyspnoea, cardiac failure and palpitations. All events resolved promptly on discontinuation of TYKERB.	
Respiratory, thoracic and mediastinal disorders:	
Uncommon	Interstitial lung disease / pneumonitis (*see Dosage and Administration and Precautions*)
Gastrointestinal disorders	
Very common	Diarrhoea*, which may lead to dehydration ‡(*see Dosage and Administration — dose delay and dose reduction — Other toxicities and Precautions*). Nausea. Vomiting.
‡Most events of diarrhoea were grade 1 or 2.	
Hepatobiliary disorders	
Very common	Hyperbilirubinaemia.

Skin and subcutaneous tissue disorders	
Very common	Rash* (including dermatitis acneform) (*see Dosage and Administration — dose delay and dose reduction — Other toxicities*).
General disorders and administration site conditions	
Very common	Fatigue.

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

TYKERB in combination with capecitabine

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

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

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

Gastrointestinal disorders	
Very common	Stomatitis, constipation, abdominal pain.
Skin and subcutaneous tissue disorders	
Very common	Palmar-plantar 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 2 Most common study medication related adverse reactions (≥5%) in studies of lapatinib ditosylate in combination with Capecitabine (EGF100151)

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

Table 3 Selected hepatic laboratory abnormalities* observed during study EGF 100151

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

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

An updated analysis inclusive of 75 subjects who were enrolled into the study between the interim analysis clinical cut-off date and halting enrollment into the study (n=198 combination arm vs n= 191 control arm) was performed. No difference in the safety profile was observed from that described previously. In this analysis 4% (7

subjects) treated with the combination arm and 1% (2 subjects) in the control arm experienced a decreased LVEF, although none were fatal and did not result in permanent discontinuation from the study.

DOSAGE AND ADMINISTRATION

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

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

TYKERB is taken in combination with capecitabine.

The recommended dose of TYKERB is 1250 mg (i.e. five tablets) once daily continuously. TYKERB should be taken at least one hour before, or at least one hour after food (*see Interactions and Pharmacokinetics — Absorption*).

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

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 Clinical Trials*). Capecitabine should be taken with food or within 30 minutes after food.

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.

Dose delay and dose reduction

Cardiac events (see Precautions)

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

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

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

Other toxicities

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

The prescribing information for capecitabine must be consulted for guidance on dose delay and dose reduction recommendations for capecitabine.

Children:

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

Elderly:

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

OVERDOSAGE

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

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

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

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

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

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

TYKERB film-coated tablets are supplied in packs of 70.

POISON SCHEDULE
Schedule 4 – Prescription only medicine

NAME AND ADDRESS OF THE SPONSOR
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