NOVARTIS

LAPATINIB

TYKERB®

250 mg Film-Coated Tablet

Antineoplastic (Protein Kinase Inhibitor)

DESCRIPTION AND COMPOSITION

Pharmaceutical form

Film-coated tablets

Oval, biconvex, yellow film-coated tablets, with one side plain and the opposite side debossed with GS XJG.

Active substance

Lapatinib ditosylate monohydrate.

The 250 mg film-coated tablet contains 405 mg of lapatinib ditosylate monohydrate, equivalent to 250 mg lapatinib free base.

Excipients

Microcrystalline cellulose

Povidone

Sodium starch glycolate

Magnesium stearate

Yellow tablet film-coat

Hypromellose

Titanium dioxide

Macrogol/PEG 400

Polysorbate 80

Iron oxide yellow

Iron oxide red

Pharmaceutical formulations may vary between countries.

INDICATIONS

HER2 overexpressing metastatic breast cancer

Lapatinib (Tykerb®), in combination with capecitabine, is indicated for the treatment of patients with advanced or metastatic breast cancer, whose tumors overexpress HER2/neu (ErbB2) and who have progressed on prior trastuzumab therapy in the metastatic setting (see section CLINICAL STUDIES).

Lapatinib (Tykerb®), in combination with trastuzumab, is indicated for the treatment of patients with hormone receptor-negative metastatic breast cancer whose tumors overexpress HER2/neu (ErbB2) and who have progressed on prior trastuzumab therapy in combination with chemotherapy in the metastatic setting (see section CLINICAL STUDIES).

Lapatinib (Tykerb®), in combination with paclitaxel, is indicated for the first line treatment of patients with metastatic breast cancer whose tumors overexpress HER2/neu (ErbB2) and for whom trastuzumab is not appropriate (see section CLINICAL STUDIES).

Lapatinib (Tykerb®), in combination with an aromatase inhibitor, is indicated for the treatment of postmenopausal women with hormone receptor-positive, HER2/neu (ErbB2) overexpressing advanced or metastatic breast cancer, and for whom endocrine therapy is indicated (see section CLINICAL STUDIES).

No data are available on the efficacy of this combination relative to trastuzumab in combination with an aromatase inhibitor or chemotherapy in this patient population.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen and method of administration

Lapatinib (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 to ensure that baseline LVEF is within the institutional limits of normal (see section WARNINGS AND PRECAUTIONS). LVEF must continue to be monitored during treatment with lapatinib (Tykerb®) to ensure that it does not fall below the institutional lower limit of normal (LLN) (see the sub heading *Dose delay and dose reduction*).

Lapatinib (Tykerb®) should be taken at least 1 hour before, or at least 1 hour after food (see sections INTERACTIONS and CLINICAL PHARMACOLOGY). The recommended daily Lapatinib (Tykerb®) dose should not be divided.

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

The full prescribing information of the co-administered medicinal product should be consulted for details of its posology and safety information.

General target population

HER2 overexpressing metastatic breast cancer

Lapatinib (Tykerb®) in combination with capecitabine

The recommended dose of lapatinib (Tykerb®) is 1250 mg (e.g. 5 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 to 14 in a 21 day cycle (see section CLINICAL STUDIES). Capecitabine should be taken with food or within 30 minutes after food.

Lapatinib (Tykerb®) in combination with trastuzumab

The recommended dose of lapatinib (Tykerb®) is 1000 mg (e.g. 4 tablets) once daily continuously when taken in combination with trastuzumab.

The recommended dose of trastuzumab is 4 mg/kg as an IVloading dose, followed by 2 mg/kg IV weekly (see section CLINICAL STUDIES).

Lapatinib (Tykerb®) in combination with paclitaxel

The recommended dose of lapatinib (Tykerb®) is 1500 mg (e.g. 6 tablets) once daily continuously in combination with paclitaxel.

The recommended dose of paclitaxel is 80 mg/m^2 IV on days 1, 8, and 15 of a 28 day schedule. Alternatively, paclitaxel may be given at a dose of 175 mg/m^2 IV every 21 days (see section CLINICAL STUDIES).

Lapatinib (Tykerb®) in combination with an aromatase inhibitor

The recommended dose of lapatinib (Tykerb®) is 1500 mg (e.g. 6 tablets) once daily continuously when taken in combination with an aromatase inhibitor.

When lapatinib (Tykerb®) is co-administered with the aromatase inhibitor letrozole, the recommended dose of letrozole is 2.5 mg once daily. If lapatinib (Tykerb®) is co-administered with an alternative aromatase inhibitor, refer to the full prescribing information of the medicinal product for dosing details.

Dose delay and dose reduction (all indications)

Cardiac events (see section WARNINGS AND PRECAUTIONS)

Lapatinib (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 institutionals lower limit of normal (LLN). Lapatinib (Tykerb®) may be restarted 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) after a minimum of 2 weeks and if 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 sections WARNINGS AND PRECAUTIONS and ADVERSE DRUG REACTIONS)

Lapatinib (Tykerb®) should be discontinued in patients who experience pulmonary symptoms indicative of interstitial lung disease/pneumonitis which are NCI CTCAE grade 3 or higher.

Diarrhea (see sections WARNINGS AND PRECAUTIONS and ADVERSE DRUG REACTIONS)

Lapatinib (Tykerb®) should be interrupted in patients with diarrhea 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). Lapatinib (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) if diarrhea resolves to grade 1 or less. Lapatinib (Tykerb®) should be permanently discontinued in patients with NCI CTCAE grade 4 diarrhea.

Severe cutaneous reactions (see section WARNINGS AND PRECAUTIONS)

Lapatinib (Tykerb®) should be discontinued in patients who experience severe progressive skin rash with blisters or mucosal lesions.

Other toxicities

Discontinuation or interruption with lapatinib (Tykerb®) may be considered if a patient develops toxicity greater than or equal to NCI CTCAE grade 2. Dosing can be restarted at the standard dose of 1000 mg/day, 1250 mg/day, or 1500 mg/day, if the toxicity improves to grade 1 or lower. If the toxicity recurs, lapatinib (Tykerb®) should be restarted 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).

Special populations

Renal impairment

There is no experience of lapatinib (Tykerb®) in patients with severe renal impairment. However, patients with renal impairment are unlikely to require dose modification of lapatinib (Tykerb®) given that under 2% of an administered dose (lapatinib and metabolites) is eliminated renally (see section CLINICAL PHARMACOLOGY).

Hepatic impairment

Lapatinib is metabolized in the liver. Moderate and severe hepatic impairment have been associated with 56% and 85% increases in systemic exposure, respectively. Administration of lapatinib (Tykerb®) to patients with hepatic impairment requires caution due to increased exposure to the drug (see sections WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY).

Patients with severe hepatic impairment (Child-Pugh Class C) should have their dose 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 sections WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY).

Pediatric patients (below 18 years)

The safety and efficacy of lapatinib (Tykerb®) in pediatric patients has not been established.

Geriatric patients (65 years or above)

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

Table-1 Number of geriatric patients

Patient age (years)	**≥65**	**≥75**
Lapatinib (Tykerb®) plus capecitabine (N=198) (EGF100151)	33 (17%)	2 (1%)
Lapatinib (Tykerb®) plus trastuzumab (N=148) (EGF 104900)	23 (16%)	6 (4%)
Lapatinib (Tykerb®) plus paclitaxel (N=222) (EGF 104535)	16 (7%)	0
Lapatinib (Tykerb®) plus letrozole (N=642) (EGF30008)	285 (44%)	77 (12%)
Single agent Lapatinib (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 geriatric and younger patients. Greater sensitivity of geriatric patients cannot be ruled out.

CONTRAINDICATIONS

Lapatinib (Tykerb®) is contraindicated in patients with hypersensitivity to any of the ingredients (see section ADVERSE DRUG REACTIONS).

WARNINGS AND PRECAUTIONS

Cardiac toxicity: Lapatinib (Tykerb®) has been associated with decreases in left ventricular ejection fraction (LVEF) (see section ADVERSE DRUG REACTIONS). Caution should be taken if lapatinib (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 lapatinib (Tykerb®) to ensure it is within the institutionals normal limits. LVEF should continue to be evaluated during treatment with lapatinib (Tykerb®) to ensure that it does not decline to an unacceptable level (see sections DOSAGE REGIMEN AND ADMINISTRATION and CLINICAL STUDIES).

In studies across the clinical development program for lapatinib (Tykerb®), cardiac events including LVEF decreases were reported in approximately 1% of patients. Symptomatic

LVEF decreases were observed in approximately 0.3% of patients who received lapatinib (Tykerb®). However, when lapatinib (Tykerb®) was administered in combination with trastuzumab in the metastatic setting, the incidence of cardiac events including LVEF decreases was higher (7%) versus the lapatinib (Tykerb®) monotherapy arm (2%) in the pivotal study. The cardiac events observed in this study were comparable in nature and severity to those previously seen with lapatinib (Tykerb®).

A concentration dependent QTc interval increase was observed in a dedicated placebo-controlled crossover study in patients with advanced solid tumors (see section CLINICAL PHARMACOLOGY). Caution should be taken if lapatinib (Tykerb®) is administered to patients who have or may develop QTc interval prolongation. This may include patients with hypokalemia or hypomagnesemia, congenital long QTc syndrome and patients taking anti-arrhythmics or other medicinal products that cause QTc prolongation. Hypokalemia, hypocalcemia or hypomagnesemia should be corrected prior to lapatinib (Tykerb®) administration.

Interstitial lung disease and pneumonitis: Lapatinib (Tykerb®) has been associated with interstitial lung disease and pneumonitis (see section ADVERSE DRUG REACTIONS). Patients should be monitored for pulmonary symptoms indicative of interstitial lung disease /pneumonitis (see section DOSAGE REGIMEN AND 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. Hepatotoxicity may be severe and deaths have been reported, although the relationship with lapatinib (Tykerb®) is uncertain. The hepatotoxicity may occur days to 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, lapatinib (Tykerb®) should be discontinued permanently (see section ADVERSE DRUG REACTIONS). Patients carryingthe HLA alleles DQA1*02:01 and DRB1*07:01 have an increased risk of lapatinib-associated hepatotoxicity. In a large, randomized clinical study of lapatinib (Tykerb®) monotherapy (EGF114471; n=1,194), the overall risk of severe liver injury (ALT >5 times theULN, 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.

If lapatinib (Tykerb®) is to be administered to patients with severe hepatic impairment, dose reduction is recommended. In patients who develop severe hepatotoxicity on therapy, lapatinib (Tykerb®) should be discontinued permanently (see sections DOSAGE REGIMEN AND ADMINISTRATION and CLINICAL PHARMACOLOGY).

Diarrhea: Diarrhea, including severe diarrhea, has been reported with lapatinib (Tykerb®) (see section ADVERSE DRUG REACTIONS). Diarrhea may be severe, and deaths have been reported. Diarrhea generally occurs early during lapatinib (Tykerb®) treatment, with almost half of patients with diarrhea first experiencing it within 6 days. This usually lasts 4 to 5 days. Lapatinib (Tykerb®)-induced diarrhea is usually low-grade, with severe diarrhea of NCI CTCAE grades 3 and 4 occurring in <10% and <1% of patients, respectively. Early identification and intervention is critical for the optimal diarrhea management. Patients should

be instructed to report any change in bowel patterns immediately. Prompt treatment of diarrhea with anti-diarrheals such as loperamide after the first unformed stool is recommended. Severe cases of diarrhea may require oral or intravenous electrolytes and fluids, antibiotics such as fluoroquinolones (especially if diarrhea persists beyond 24 hours, there is fever, or grade 3 or 4 neutropenia) or interruption or discontinuation of lapatinib (Tykerb®) (see section DOSAGE REGIMEN AND ADMINISTRATION).

Severe cutaneous reactions: Severe cutaneous reactions have been reported with lapatinib (Tykerb®). 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, treatment with lapatinib (Tykerb®) should be discontinued (see Dosage and Administration).

Concomitant Treatment with Inhibitors or Inducers of CYP3A4: Co-administration of CYP3A4 inhibitors or inducers requires caution due to risk of increased or decreased exposure to lapatinib (Tykerb®), respectively (see section INTERACTIONS).

ADVERSE DRUG REACTIONS

Clinical trial data

Safety of lapatinib (Tykerb®) has been evaluated as monotherapy or in combination with other chemotherapies for various cancers in > 20,000 patients including 198 patients in combination with capecitabine, 149 patients in combination with trastuzumab, 222 patients in combination with 80 mg/m^2 paclitaxel weekly, 293 patients in combination with 175 mg/m2 paclitaxel every 3 weeks, and 654 patients in combination with letrozole (see section CLINICAL STUDIES).

Tabulated summary of adverse drug reactions (ADRs) from clinical trials

ADRs from clinical trials are listed by MedDRA system organ class (SOC) in Tables 2 to 6. Within each SOC, the ADRs are ranked by frequency, with the most frequent first. The corresponding frequency category for each ADRs is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

ADRs with lapatinib (Tykerb®) monotherapy

The following ADRs have been reported to be associated with lapatinib (Tykerb®):

Table 2 ADRs reported to be associated with Lapatinib (Tykerb®)

ADR	Frequency category
Immune system disorders	
Hypersensitivity reactions including anaphylaxis[1]	Rare
Metabolism and nutrition disorders	
Anorexia	Very common
Cardiac disorders	
Decreased left ventricular ejection fraction[2]	Common

Respiratory, thoracic and mediastinal disorders	
Interstitial lung disease/pneumonitis	Uncommon
Gastrointestinal disorders	
Diarrhea, which may lead to dehydration[3]	Very common
Nausea	Very common
Vomiting	Very common
Hepatobiliary disorders	
Hepatotoxicity[4]	Uncommon
Hyperbilirubinemia[5]	Uncommon
Skin and subcutaneous tissue disorders	
Rash[3] (including acneiform dermatitis)	Very common
Nail disorders including paronychia	Common
General disorders and administration site conditions	
Fatigue	Very common

[1] See section Contraindications.

[2] LVEF decreases have been reported in approx. 1% of patients and were asymptomatic in >70% of cases. LVEF decreases resolved or improved in >70% of cases on discontinuation of lapatinib. Symptomatic LVEF decreases were observed in approx. 0.3% of patients on lapatinib. Observed adverse events included dyspnea, cardiac failure and palpitations (see sections DOSAGE REGIMEN AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

[3] Diarrhea and rash were generally low grade (most diarrhea events were grade 1 or 2) and did not result in discontinuation of lapatinib. Diarrhea responds well to proactive management (see section 6 Warnings and precautions). Rash was mostly transient (see section 4 Dosage regimen and administration - Dose delay and dose reduction - Other toxicities).

[4] 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.

[5] Elevated bilirubin may be due to lapatinib inhibition of hepatic uptake by OATPB1B1 or inhibition of excretion into bile by Pgp or BCRP.

ADRs with lapatinib (Tykerb®) in combination with capecitabine

In addition to the ADRs observed with lapatinib (Tykerb®) monotherapy, the following additional ADRs were reported to be associated with lapatinib (Tykerb®) in combination with capecitabine in study EGF100151 with a frequency difference of > 5% versus capecitabine alone. These data are based on exposure to this combination in 198 patients.

Table 3 ADRs occurring in EGF100151 with a frequency difference of >5% versus capecitabine alone

ADR	Frequency category
Gastrointestinal disorders	
Dyspepsia	Very common
Skin and subcutaneous tissue disorders	
Dry skin	Very common

The following ADRs listed in Table 4 below were reported to be associated with lapatinib (Tykerb®) in combination with capecitabine but were seen at a similar frequency in the capecitabine monotherapy arm.

ADR	Frequency category
Psychiatric disorders	
Insomnia	Very common
Nervous system disorders	
Headache	Common
Gastrointestinal disorders	
Stomatitis	Very common
Constipation	Very common
Abdominal pain	Very common
Skin and subcutaneous tissue disorders	
Palmar-plantar erythrodysaesthesia	Very common
Musculoskeletal and connective tissue disorders	
Pain in extremity	Very common
Back pain	Very common
General disorders and administrative site conditions	
Mucosal inflammation	Very common

ADRs with lapatinib (Tykerb®) in combination with trastuzumab

No additional ADRs were reported to be associated with lapatinib (Tykerb®) in combination with trastuzumab. There was an increased incidence of cardiac toxicity, but these events were comparable in nature and severity to those reported from the lapatinib (Tykerb®) clinical program (see section WARNINGS AND PRECAUTIONS). These data are based on exposure to this combination in 149 patients in the phase III study EGF104900.

ADRs with lapatinib (Tykerb®) in combination with paclitaxel

In addition to the ADRs observed with lapatinib (Tykerb®) monotherapy, the following ADRs were reported to be associated with lapatinib (Tykerb®) in combination with paclitaxel (80 mg/m^2 weekly) with a frequency difference of >5% versus paclitaxel alone. These data are based on exposure to this combination in 222 patients in study EGF104535.

Table 5 Additional ADRs occurring in EGF104535 with a frequency difference of >5% compared to paclitaxel

ADR	Frequency category
Blood and lymphatic system disorders	
Neutropenia	Very common
Leukopenia	Very common
Anaemia	Very common
Nervous system disorders	
Peripheral neuropathy	Very common
Musculoskeletal and connective tissue disorders	

Myalgia*	Very common

* Additional ADRs reported in 293 patients on lapatinib in combination with paclitaxel (175 mg/m^2 every 3 weeks) in study EGF30001 with a frequency difference of >5% versus paclitaxel alone.

Adverse reactions with lapatinib (Tykerb®) in combination with letrozole

In addition to the ADRs observed with lapatinib (Tykerb®)monotherapy, the following ADRs were reported to be associated with lapatinib (Tykerb®) in combination with letrozole in study EGF30008 with a frequency difference of >5% versus letrozole alone. These data are based on exposure to this combination in 654 patients.

Table 6 ADRs occurring with a frequency difference of >5% versus letrozole alone in study EGF30008

ADR	Frequency category
Respiratory, thoracic and mediastinal disorders	
Epistaxis	Very common
Skin and subcutaneous tissue disorders	
Alopecia	Very common
Dry skin	Very common

Post marketing data

The following ADRs are from post-marketing experience with lapatinib (Tykerb®) via spontaneous case reports and literature cases. As these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. ADRs are listed according to MedDRA SOCs. Within each SOC, ADRs are presented in order of decreasing seriousness.

Table 7 ADRs from spontaneous reports and literature (frequency not known)

ADR
Cardiac disorders
Ventricular arrhythmias/Torsades de Pointes
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)

INTERACTIONS

Lapatinib is predominantly metabolized by CYP3A (see section CLINICAL PHARMACOLOGY). Therefore, inhibitors or inducers of these enzymes may alter the pharmacokinetics of lapatinib.

Interactions with CYP3A4-inhibitors

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

Co-administration of lapatinib (Tykerb®) with known CYP3A4 inhibitors (e.g. erythromycin, telithromycin, ketoconazole, itraconazole, posaconazole, voriconazole or grapefruit juice, ritonavir, saquinavir, cisapride, verapamil, pimozide, nefazodone, Hypericum perforatum (St. John's wort), cyclosporine) requires caution clinical response and adverse events should be carefully monitored (see section WARNINGS AND PRECAUTIONS).

If patients must be co-administered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a dose reduction to 500 mg/day 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 (Tykerb®) dose is increased to the indicated dose.

Interactions with CYP3A4-inducers

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 approx. 72%.

Co-administration of lapatinib (Tykerb®) with known CYP3A4 inducers (e.g. rifampin, rifabutin, phenytoin, or carbamazepine) requires caution clinical response and adverse events should be carefully monitored (see section WARNINGS AND PRECAUTIONS).

If patients must be co-administered a strong CYP3A4 inducer, based on pharmacokinetic studies, the lapatinib (Tykerb®) dose should be titrated gradually from 1250 mg/day to 4500 mg/day or from 1500 mg/day to 5500 mg/day based on tolerability. This dose of lapatinib (Tykerb®) 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 (Tykerb®) dose should be reduced over approximately 2 weeks to the indicated dose.

Drugs that affect gastric pH

Pre-treatment with proton pump inhibitor (e.g. esomeprazole) decreased lapatinib exposure by an average of 27% (range: 6% to 49%). This effect decreases with increasing age from approximately 40 to 60 years. Therefore, caution is required when lapatinib (Tykerb®) is used in patients pre-treated with a proton pump inhibitor.

Effect of lapatinib (Tykerb®) on other drugs

Lapatinib inhibits CYP3A4 in vitro at clinically relevant concentrations. Co-administration of lapatinib (Tykerb®) with oral midazolam resulted in an approximate 45% increase in midazolam AUC. There was no clinically meaningful increase in AUC with IV midazolam. Caution is required when co-administering lapatinib (Tykerb®) with orally administered

medications with narrow therapeutic windows that are substrates of CYP3A4 (see section CLINICAL PHARMACOLOGY).

Lapatinib inhibits CYP2C8 in vitro at clinically relevant concentrations. Caution is required when co-administering lapatinib (Tykerb®) with medications with narrow therapeutic windows that are substrates of CYP2C8 such as repaglinide (see section CLINICAL PHARMACOLOGY).

Combination therapy and non-fixed dose combination therapy

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

Co-administration of lapatinib (Tykerb®) with IV docetaxel did not significantly affect the AUC or Cmax of either active substance. However, the occurrence of docetaxel-induced neutropenia increased.

Co-administration of lapatinib (Tykerb®) 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 (Tykerb®) is co-administered with irinotecan.

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.

Effect of lapatinib (Tykerb®) on transport proteins

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

Lapatinib inhibits the transport protein Pgp in vitro at clinically relevant concentrations. Co-administration of lapatinib (Tykerb®) with oral digoxin resulted in an approximate 98% increase in digoxin AUC. Caution is required when co-administering lapatinib (Tykerb®) concurrently with medications with narrow therapeutic windows that are substrates of Pgp (e.g. quinidine).

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, quinidine) and OATP1B1 (e.g. rosuvastatin) (see section CLINICAL PHARMACOLOGY).

Drug-food/drink interactions

The bioavailability of lapatinib is affected by food (see sections DOSAGE REGIMEN AND ADMINISTRATION and CLINICAL PHARMACOLOGY).

Grapefruit juice may inhibit CYP3A4 and Pgp in the gut wall, thereby it may increase the bioavailability of lapatinib and should therefore be avoided during treatment with Lapatinib (Tykerb®) (see sections INTERACTIONS and CLINICAL PHARMACOLOGY).

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

There are insufficient data in pregnant women exposed to lapatinib to assess the risks. Pregnant women should be advised of the potential risk to the fetus and lapatinib (Tykerb®) should be used during pregnancy only if the expected benefit for the patients justifies the potential risk to the fetus.

Lapatinib (Tykerb®) was not teratogenic when studied in pregnant rats and rabbits but caused minor abnormalities at doses which were maternally toxic (see section Animal data).

Animal data

In embryofetal development studies, pregnant animals received oral doses of lapatinib at 30, 60, and 120 mg/kg/day during organogenesis. 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 120 mg/kg/day (approx. 6.5 times the human clinical exposure based on AUC following a 1250 mg dose of lapatinib plus capecitabine).

In rabbits, lapatinib was associated with maternal toxicity at 60 and 120 mg/kg/day (approx. 0.07 and 0.2 times the human clinical exposure respectively, based on AUC following a 1250 mg dose of lapatinib plus capecitabine) and abortions at 120 mg/kg/day. Maternal toxicity was associated with decreased fetal body weights, and minor skeletal variations.

In a pre- and postnatal development study, rats were given oral doses of 20, 60, and 120 mg/kg/day from gestation up to weaning. Doses of 60 and 120 mg/kg/day (approx. 3.3 and 6.4 times the human clinical exposure, respectively, based on AUC following a 1250 mg dose of lapatinib plus capecitabine) led to a decrease in F1 postnatal survival (91% and 34% of the pups died by the fourth day after birth, at 60 and 120 mg/kg/day, respectively). The highest no-effect dose for this study was 20 mg/kg/day (approx. equal to the human clinical exposure based on AUC).

Lactation

Risk summary

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 breast-feed while receiving lapatinib (Tykerb®) and for at least 5 days after the last dose.

Females and males of reproductive potential

Contraception

Based on findings in animal studies, lapatinib can cause fetal harm. Females of reproductive potential should be advised to use effective contraception (methods that result in less than 1% pregnancy rates) while receiving Lapatinib (Tykerb®) and for at least 5 days after the last dose.

Infertility

The effect of lapatinib on human fertility is unknown. There were no effects on rat gonadal function, mating or fertility at doses up to 120 mg/kg/day in females and 180 mg/kg/day in males (approx. 6.4 times and 2.6 times the expected human clinical exposure based on AUC following a 1250 mg dose of lapatinib plus capecitabine).

However, when female rats were given oral lapatinib during breeding and the first 6 days of gestation, a significant decrease in live fetuses was seen at 120 mg/kg/day and in fetal body weights at 60 mg/kg/day (approx. 6.4 times and 3.3 times the expected human clinical exposure, respectively based on AUC following a 1250 mg dose of lapatinib plus capecitabine).

OVERDOSE AND TREATMENT

There is no specific antidote for the inhibition of EGFR (ErbB1) and/or HER2/neu (ErbB2) tyrosine phosphorylation. The maximum oral dose of lapatinib (Tykerb®) in clinical trials was 1800 mg once daily.

Taking lapatinib (Tykerb®) more frequently than recommended 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 DOSAGE REGIMEN AND ADMINISTRATION).

Asymptomatic and symptomatic cases of overdose have been reported with lapatinib (Tykerb®). Symptoms observed include known lapatinib (Tykerb®) associated events (see section ADVERSE DRUG REACTIONS) and in some cases sore scalp, sinus tachycardia (with otherwise normal ECG) and/or mucosal inflammation.

Lapatinib (Tykerb®) is not significantly renally excreted and is highly bound to plasma proteins; therefore, hemodialysis is not expected to enhance lapatinib elimination.

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

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

Lapatinib is a novel 4-anilinoquinazoline kinase inhibitor with a unique mechanism of action (MOA): it is a potent, reversible, and selective inhibitor of the intracellular tyrosine kinase domains of both ErbB1 and of HER2/neu (ErbB2) receptors (estimated Kiapp values of 3nM and 13nM, respectively) with a slow off-rate from these receptors (half-life ≥300 minutes). This dissociation rate was found to be slower than other 4-anilinoquinazoline kinase inhibitors studied. Lapatinib inhibits ErbB-driven tumor 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 4 tumor cell lines tested. The clinical significance of these in vitro data is unknown.

The combination of lapatinib and trastuzumab may offer complementary MOAs and possible non-overlapping mechanisms of resistance. The growth inhibitory effects of lapatinib were evaluated in trastuzumab-conditioned cell lines. Lapatinib retained significant activity against HER2-amplified breast cancer cell lines selected for long-term growth in a trastuzumab-containing medium in vitro and was synergistic in combination with trastuzumab in these cell lines. These findings suggest non-cross-resistance between these two HER2/neu (ErbB2) 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 EGFR or HER2 will up regulate these receptors as the tumor becomes resistant to endocrine therapy. Randomized trials in hormone sensitive metastatic breast cancer indicate that a HER2 or EGR tyrosine kinase inhibitor may improve PFS when added to endocrine therapy.

Pharmacodynamics (PD

Cardiac electrophysiology

QT prolongation

Study EGF114271

The effect of lapatinib on the QTc-interval was evaluated in a single-blind, placebo-controlled, single sequence (placebo and active treatment) crossover study in patients with advanced solid tumors (N=58). During the 4-day treatment period, 3 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 3 doses of 2000 mg lapatinib 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 2000 mg lapatinib. 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 a positive relationship between lapatinib plasma concentrations and ΔΔQTcF.

Pharmacokinetics (PK)

Absorption

Absorption of lapatinib following oral administration of lapatinib is incomplete and variable (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 (Cmax) of lapatinib are achieved approximately 4 hours after administration. Daily dosing of 1250 mg produces steady state geometric mean (95% CI) Cmax values of 2.43 (1.57 to 3.77) microg/mL and AUC values of 36.2 (23.4 to 56) microg.hr/mL.

Systemic exposure to lapatinib is increased when administered with food (see sections DOSAGE REGIMEN AND ADMINISTRATION and INTERACTIONS). Lapatinib AUC values were approximately 3- and 4-fold higher (Cmax approximately 2.5 and 3-fold higher) when administered with a low-fat (5% fat [500 calories]) or high-fat (50% fat [1,000 calories]) meal, respectively.

Distribution

Lapatinib is highly bound (>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 (IC50 2.3 microgram/mL), BCRP (IC50 0.014 microgram/mL) and the hepatic uptake transporter OATP 1B1 (IC50 2.3 microgram/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 IC50 values were ≥6.9 microgram/mL).

Biotransformation/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 feces or 10% of the lapatinib concentration in plasma.

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 about 1 day. Lapatinib is predominantly eliminated through metabolism by CYP3A4/5. The primary route of elimination for lapatinib and its metabolites is in feces, with less than 2% of the dose (as lapatinib and metabolites) excreted in urine. Recovery of lapatinib in feces accounts for a median 27% (range 3 to 67%) of an oral dose.

In vitro evaluation of drug interaction potential

Lapatinib inhibits CYP3A (Ki 0.6 to 2.3 microgram/mL) and CYP2C8 (0.3 microgram/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 (*in vitro* IC50 values were ≥6.9 microgram/mL)

Special populations

Pediatric patients (below 18 years)

The pharmacokinetics of Lapatinib (Tykerb®) in pediatric patients have not been established.

Geriatric patients (65 years or above)

Age does not appear to affect lapatinib pharmacokinetics, based on the analysis of individual study results. An examination of combined data, spanning a range of 18 to 82 years suggests no obvious effect.

Gender

Gender does not appear to affect lapatinib pharmacokinetics. An examination of combined data, including >300 females and >450 males, suggests no obvious difference.

Race/ethnicity

The available study data indicates no obvious distinction related to race/ethnicity.

Renal impairment

Lapatinib pharmacokinetics have not been specifically studied in patients with renal impairment or in patients undergoing hemodialysis. 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

Lapatinib pharmacokinetics 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 patients with moderate and severe hepatic impairment, respectively. Administration of lapatinib (Tykerb®) in patients with hepatic impairment requires caution due to increased drug exposure. Dose reduction is recommended for patients with severe pre-existing hepatic impairment. In patients who develop severe hepatotoxicity while on therapy, lapatinib (Tykerb®) should be discontinued permanently (see sections DOSAGE REGIMEN AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

Pharmacogenomics

Polymorphic variations in drug-metabolizing enzymes, transporters, receptors, and other proteins that might affect lapatinib pharmacokinetics have not been explored.

The HLA alleles DQA1*02:01 and DRB1*07:01 were associated with hepatotoxicity in a genetic substudy of a monotherapy trial with lapatinib (Tykerb®) (see section WARNINGS AND PRECAUTIONS).

CLINICAL STUDIES

The combination of lapatinib (Tykerb®) with capecitabine or paclitaxel demonstrated superior efficacy versus capecitabine or paclitaxel monotherapy in study EGF100151.

Data in two randomized studies in the metastatic setting (EGF111438 (CEREBREL) and EGF108919 (COMPLETE) show that lapatinib (Tykerb®) combined with chemotherapy is less effective than trastuzumab combined with chemotherapy.

The combination of lapatinib (Tykerb®) with trastuzumab was evaluated in the randomized clinical study EGF104900 and demonstrated superior efficacy versus lapatinib (Tykerb®) alone in MBC patients who progressed on a prior trastuzumab- containing regimen.

Lapatinib (Tykerb®) was also studied in combination with letrozole and had superior efficacy versus. letrozole alone in HER2+, HR+ advanced or metastatic breast cancer patients.

See below for details.

Lapatinib (Tykerb®) is not indicated in the adjuvant setting.

Combination treatment with lapatinib (Tykerb®) and capecitabine

Study EGF100151

The efficacy and safety of lapatinib (Tykerb®) in combination with capecitabine in breast cancer was evaluated in the randomized phase III study EGF100151. Patients eligible for enrolment had HER2/neu (over-expressing (IHC 3+ or IHC 2+ and FISH positive), locally advanced or metastatic breast cancer, progressing after prior treatment including taxanes, anthracyclines and trastuzumab. LVEF was evaluated in all patients (using echocardiogram [Echo] or multi gated acquisition scan [MUGA]) prior to initiation of treatment with lapatinib (Tykerb®) to ensure baseline LVEF was within the institutionals normal limits. In clinical studies LVEF was monitored at approximately 8 week intervals during treatment with lapatinib to ensure it did not fall below the institutions lower limit of normal. The majority of LVEF decreases (greater than 60% of events) were observed during the first 9 weeks of treatment; however, limited data was available for long term exposure.

Patients were randomized to receive either lapatinib (Tykerb®) 1250 mg once daily (continuously) plus capecitabine (2000 mg/m^2/day on days 1 to 14 every 21 days), or to receive capecitabine alone (2500 mg/m^2/day on days 1 to 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. The results below are based on both the investigator's 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 versus capecitabine monotherapy, as assessed by the independent review panel). See Table 8.

Table-8. Study EGF100151 - Key efficacy data (TTP, ORR)

	Independent assessment		Investigator assessment	
Efficacy outcome	**Lapatinib plus capecitabine (N=198)**	**Capecitabine alone (N=201)**	**Lapatinib plus capecitabine (N=198)**	**Capecitabine alone (N=201)**
TTP				
Progressed or died due to breast cancer	41%	51%	61%	63%
Median TTP (weeks)	27.1	18.6	23.9	18.3
HR, 95% CI (p-value)	0.57 (0.43, 0.77) 0.00013		0.72 (0.56, 0.92) 0.00762	
ORR, 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 (CNS) versus the 13 (6%) progressions on the capecitabine monotherapy arm, as assessed by an independent review panel (see section CLINICAL STUDIES for Lapatinib effect on CNS metastasis).

At the time enrollment was halted (3 April 2006), 399 patients were randomized 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 to capecitabine monotherapy.

An analysis of survival data to 01 October 2008 is summarized in Table 9.

Table-9. Study EGF100151 Key efficacy data (OS)

	Lapatinib (Tykerb®) 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 (p-value)	0.87 (0.71, 1.08) 0.210	

CI = confidence interval

After the study was halted, 36 patients crossed over from capecitabine to lapatinib (Tykerb®) plus 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 20% reduction in risk of death, with a treatment effect hazard ratio of 0.80 (95% [CI]: 0.64, 0.99; p=0.043).

Study EGF111438 (CEREBEL)

A randomized Phase III study (EGF111438) (N=540) compared the effect of lapatinib in combination with capecitabine to trastuzumab in combination with capecitabine on the incidence of the CNS as the site of first relapse in women with HER2 overexpressing metastatic breast cancer. Patients were randomized to either 1250 mg lapatinib once daily (continuously) plus capecitabine (2000 mg/m^2/day on days 1-14 every 21 days), or trastuzumab (loading dose of 8mg/kg followed by 6mg/kg infusions every 3 weeks) plus capecitabine (2500mg/m^2/day, on days 1-14, every 21 days). Randomization was stratified by prior trastuzumab treatment and number of prior treatments for metastatic disease (none versus ≥1st line). The study was stopped 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 primary endpoint results were inconclusive due to a low number of CNS events (8 patients (3.2%) in the lapatinib plus capecitabine arm experienced CNS metastasis as site of first progression, versus 12 patients (4.8%) in the trastuzumab plus capecitabine arm) (see section CLINICAL STUDIES for Lapatinib effect on CNS metastasis). The final results of PFS and OS are shown in Table 10. The final analysis confirmed the superior efficacy of the trastuzumab plus capecitabine arm.

Table-10. Study EGF111438 Key efficacy data (PFS, OS)

Efficacy outcome	Investigator-assessed PFS		Overall Survival	
	Lapatinib + capecitabine	Trastuzumab + capecitabine	Lapatinib + 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 HR [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				
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 randomization 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 lapatinib plus capecitabine versus 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.

Lapatinib effect on CNS metastasis

In terms of objective responses, lapatinib (Tykerb®) monotherapy has demonstrated minimal activity in the treatment of established CNS metastases.

Lapatinib is not recommended for the prevention of CNS metastases.

Combination treatment with lapatinib (Tykerb®) and paclitaxel

Study EGF104535

The efficacy and safety of lapatinib (Tykerb®) in combination with paclitaxel in breast cancer were evaluated in a randomized phase III study EGF104535. Patients had histologically confirmed invasive breast cancer (stage IV)with HER2 overexpression (documented by IHC or FISH) and had not received prior therapy for metastatic disease.

Patients were randomized to paclitaxel (80 mg/m^2 IV on days 1, 8, and 15 of a 28 day schedule) and either 1500 mg/day lapatinib (Tykerb®) or placebo once daily. Patients received a minimum of 6 cycles of lapatinib (Tykerb®) plus paclitaxel. After the 6 cycles were completed, patients continued on lapatinib (Tykerb®) or placebo until disease progression or unacceptable toxicity. The primary endpoint was OS. 444 patients were enrolled in this study. Of the 222 who were on paclitaxel plus placebo, 149 (67%) with disease progression entered the open-label extension phase and received lapatinib (Tykerb®) monotherapy. The median age was 50 years and 7% were older than 65 years. 86% were Asian, 8% Hispanic, and 5% Caucasian. The overall survival data are summarized in Table 11.

Table-11. Study EGF104535 – Key efficacy data OS

Efficacy Outcome	**Lapatinib (Tykerb®) plus paclitaxel (N = 222)**	**Paclitaxel alone (N = 222)**
Died	54%	64%
Median OS (months)[1] (95% CI)	27.8 (23.2, 32.2)	20.5 (17.9, 24.3)
HR[2], 95% CI (two-sided p value)	0.74 (0.58, 0.94) 0.0124	
Cox regression[3] Hazard Ratio 95% CI (two-sided p value)	0.64 (0.49, 0.82) 0.0005	

CI = confidence interval

[1] Kaplan-Meier estimates

[2] Pike estimator of hazard ratio (HR)

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

A summary of other efficacy endpoints are provided in Table 12.

Table-12. Study EGF104535 – Key efficacy data (PFS, HR, RR, DoR)

	Lapatinib (Tykerb®) plus paclitaxel (N = 222)	**Paclitaxel alone (N = 222)**
Median PFS[1], months (95% CI)	9.7 (9.2, 11.1)	6.5 (5.5, 7.3)
HR (95% CI) p value	0.52 (0.42, 0.64) <0.0001	
RR (%) (95% CI)	69 (62.9, 75.4)	50 (42.8, 56.3)
DoR, months (95% CI)	9.3 (7.7, 10.7)	5.8 (5.6, 7.4)

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

[1] Kaplan-Meier estimate.

Study EGF30001

Another randomized, double-blind, controlled phase III study evaluated lapatinib (Tykerb®) and paclitaxel as first-line therapy for metastatic breast cancer in patients with negative or untested ErbB2 status previously untreated in the metastatic setting. Patients (N= 579) were

randomized 1:1 to paclitaxel (175 mg/m^2 IV over 3 hours on day 1, every 3 weeks) and either 1500 mg/day lapatinib (Tykerb®) or placebo once daily. 64% were Caucasian, 18% Hispanic, and 11% Asian. 91 patients (16%) had HER2-positive disease. The primary endpoint was time-to-progression (TTP); secondary endpoints included progression-free survival (PFS), tumor response rate (RR), clinical benefit rate (CBR), overall survival (OS) and safety. No significant differences in TTP or PFS were observed between treatment arms in the unselected ITT population. The median PFS in the HER2-positive subgroup was 34.4 weeks (95% CI: 32.1, 41.6) for lapatinib (Tykerb®) plus paclitaxel combination versus 22.6 weeks (95% CI: 20.1, 32.9) for paclitaxel plus placebo (HR 0.56; 95% CI: 0.34, 0.90; p = 0.007). The OS analyses of the ITT population and HER2 positive subgroup are presented in Table 13.

Table-13. Study EGF30001 – Key efficacy data (OS)

	Lapatinib (Tykerb®) plus paclitaxel	**Paclitaxel alone**
OS (ITT population)	**(N=291)**	**(N=288)**
Died	73%	79%
Median OS (months) (95% CI)	23.8 (19.9, 26.2)	20.2 (17.8, 23.9)
HR, 95% CI (p value)	0.82 (0.7, 1.0) 0.031	
OS HER2+ve Population	**(N=52)**	**(N=39)**
Died	71%	74%
Median OS (months) (95% CI)	24.3 (17.7, 31.3)	19.2 (11.7, 29.7)
HR, 95% CI (p value)	0.77 (0.5, 1.3) 0.281	

CI = confidence interval

EGF108919 (COMPLETE)

The randomized Phase III study (EGF108919) (N=652) compared the efficacy and safety of lapatinib plus a taxane followed by lapatinib alone versus trastuzumab plus a taxane followed by trastuzumab alone as first line therapy for women with HER2 positive metastatic breast cancer. Patients were randomized to either 1250 mg lapatinib once daily plus 80 mg/m^2 paclitaxel: once weekly (days 1, 8 and 15 of a 4-week cycle) or 75 mg/m^2 docetaxel once every 3 weeks (days 1 of a 3 week cycle) for 24 weeks followed by 1500 mg lapatinib once daily, or trastuzumab once weekly (loading dose 4mg/kg followed by 2mg/kg weekly infusions) plus 80 mg/m^2 paclitaxel: once weekly (days 1, 8 and 15 of a 4-week cycle) or trastuzumab every 3 weeks (loading dose 8 mg/kg followed by 6 mg/kg once every 3 weeks) plus 75 mg/m^2 docetaxel once every 3 weeks (days 1 of a 3 week cycle) for 24 weeks followed by 6 mg/kg trastuzumab: once every 3 weeks.

The study was stopped when a pre-planned interim analysis showed that the trastuzumab arm was superior to the lapatinib arm. This was confirmed by the final analysis (see Table 14).

Table-14. Study EGF108919 – Key efficacy data (PFS, OS)

	Lapatinib plus taxane	Trastuzumab plus taxane
PFS (ITT Population)	(N=326)	(N=326)
Median PFS, months **(95% CI)**	8.9 (0.30 - 32.69)	11.3 (0.30 - 38.54)
HR (95% CI) **P-value**	1.367 (1.133, 1.648) 0.0010	
OS (ITT Population)	(N=326)	(N=326)
Died	31%	25%
HR, 95% CI **(p value)**	1.227 (0.946, 1.722) 0.1093	

1 Stratified HR for LTax/L versus TTax/T

Abbreviations: CI=confidence interval.

Combination treatment with lapatinib (Tykerb®) and trastuzumab

Study EGF104900

The efficacy and safety of lapatinib (Tykerb®) in combination with trastuzumab in metastatic breast cancer were evaluated in the randomized trial EGF104900.

Eligible patients were women with stage IV ErbB2 gene amplified (or protein overexpressing) metastatic breast cancer exposed to treatment with anthracyclines and taxanes. In addition, per the protocol, patients were to be reported by the investigators as having progressed on their most recent trastuzumab containing regimen in the metastatic setting. The median number of prior trastuzumab-containing regimens in the metastatic setting was three. Patients were randomized to receive either oral lapatinib (Tykerb®) 1,000 mg once daily plus trastuzumab 4 mg/kg administered as an intravenous (IV) loading dose, followed by 2 mg/kg IV weekly (N = 148), or oral lapatinib (Tykerb®) 1,500 mg once daily (N = 148). Patients with objective disease progression after at least 4 weeks of lapatinib (Tykerb®) monotherapy were eligible to crossover to combination therapy. Of the 148 patients who received monotherapy, 77 (52%) elected to receive combination treatment at the time of disease progression.

The primary objective of this study was to evaluate and compare PFS in patients with metastatic breast cancer treated with lapatinib (Tykerb®) and trastuzumab compared with lapatinib (Tykerb®) monotherapy. Secondary objectives were to evaluate and compare the two treatment arms with respect to OS, overall tumor response rate, clinical benefit response rate and time to response.

The median age was 51 years and 13% were 65 years or older. 94% were Caucasian. Most patients in both treatment arms had visceral disease (215 [73%] overall). Half of the patients in the study population were estrogen receptor negative and progesterone receptor negative (150 [51%] overall). A summary of efficacy endpoints is provided in Table 15 and OS data in Table 16. Subgroup analysis results based on a predefined stratification factor (hormone receptor status) are shown in Table 17.

Table-15. Study EGF104900 Key efficacy data (PFS, HR, RR)

	Lapatinib (Tykerb®) plus trastuzumab (N = 148)	**Lapatinib (Tykerb®) alone (N = 148)**
Median PFS[1], weeks	12.0	8.1
(95% CI)	(8.1, 16.0)	(7.6, 9.0)
Hazard Ratio (95% CI)	0.73 (0.57, 0.93)	
P value	0.008	
Response Rate (%)	10.3	6.9
(95% CI)	(5.9, 16.4)	(3.4, 12.3)

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

[1] Kaplan-Meier estimate.

Table-16. Study EGF104900 – Key efficacy data (OS)

	Lapatinib (Tykerb®) plus trastuzumab (N = 148)	**Lapatinib (Tykerb®) alone (N = 148)**
Died	105	113
Median overall survival (months)[1]	14.0	9.5
(95% CI)	(11.9, 17.2)	(7.6, 12.0)
Hazard ratio, 95% CI	0.74 (0.57, 0.97)	
p-value	0.026	

CI = confidence interval

[1] Kaplan-Meier estimate.

Table-17. Study EGF104900 – Key efficacy data (PFS,OS) in the subgroup with hormone receptor status negative

	Lapatinib plus trastuzumab (N=75)	**Lapatinib alone (N=75)**	**HR (95% CI)**
PFS	15.4 weeks (8.4, 16.9)	8.2 weeks (7.4, 9.3)	0.73 (0.52, 1.03)
OS	17.2 months (13.9, 19.2)	8.9 months (6.7, 11.8)	0.62 (0.42, 0.90)

Combination treatment with lapatinib (Tykerb®) and letrozole

Study EGF30008

Lapatinib (Tykerb®) was studied in combination with 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.

EGF30008 was a randomized, double-blind, placebo-controlled study in patients with hormone-sensitive locally advanced or metastatic breast cancer (MBC), who had not received prior therapy for metastatic disease. 1286 patients were randomized to 2.5 mg letrozole once

daily plus 1500 mg lapatinib (Tykerb®) once daily (N=642) or letrozole plus placebo (N=644). Randomization 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 randomized to treatment, 219 had tumors over-expressing the HER2 receptor which was the pre-specified primary population for the analysis of efficacy.

In the HER2-positive population, investigator-determined progression-free survival (PFS) was significantly greater with letrozole plus lapatinib (Tykerb®) than with letrozole plus placebo (see Table 18).

Table-18. Study EGF30008 – Key efficacy data (PFS)

	HER2–positive population	
	Lapatinib (Tykerb®) 1500 mg/day + Letrozole 2.5 mg/day N=111	**Letrozole alone 2.5 mg/day + placebo N=108**
Median PFS, weeks (95% CI)	35.4 (24.1, 39.4)	13.0 (12.0, 23.7)
Hazard Ratio	0.71 (0.53, 0.96)	
p-value	0.019	

CI= confidence interval

The benefit of lapatinib (Tykerb®) plus 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 this population, combination therapy of lapatinib (Tykerb®) and letrozole improved objective response rate (27.9% and 14.8% respectively) and in Clinical Benefit Rate (47.7% and 28.7% respectively) compared with letrozole treatment alone.

At the time of the final PFS analysis (with median follow-up of 2.64 years), the OS data were not mature and there was no significant difference between treatment groups in the HER2-positive population; this had not changed with additional follow-up (>7.5 years median follow-up time; Table 19).

Table 19. Study EGF30008 – Key efficacy data (Overall Survival in the HER2-positive population)

	1500 mg/day lapatinib + 2.5 mg /day letrozole	2.5 mg/day letrozole + placebo
Overall Survival	N = 111	N = 108
Pre-planned OS analysis (conducted at the time of the final PFS analysis, 03 June 2008)		
Median follow-up (years)	2.64	2.64
Died	50 (45%)	54 (50%)
Hazard Ratio[a] ,95% CI, P-value[b]	0.77 (0.52, 1.14) 0.185	
Final OS analysis (post-hoc analysis, 07 August 2013)		
Median Follow-up (yrs)	7.78	7.55
Died	86 (77%)	78 (72%)
Hazard Ratio 95% CI P-value	0.97 (0.7,1.3) 0.842	

Median values from Kaplan-Meier analysis; HR and p-values from Cox regression models adjusting for important prognostic factors.

a. Estimate of the treatment hazard ratio, where <1 indicates a lower risk with 2.5 mg letrozole + 1500 mg lapatinib versus 2.5 mg letrozole + placebo.

b. p-value from Cox regression model, stratifying for site of disease and prior adjuvant therapy at screening

NON-CLINICAL SAFETY DATA

Safety pharmacology

No neurological, respiratory or cardiovascular effects were identified in a panel of *in vitro* safety pharmacology studies or in *in vivo* animal studies with lapatinib.

Repeat dose toxicity

Lapatinib was evaluated in repeat dose toxicity studies for up to 6 months in rats and up to 9 months in dogs. The principal treatment-related effects were inflammation and atrophy of the skin and adnexal structures, and degeneration and inflammation of the GI tract and accessory digestive organs (including liver), mammary gland and prostate. These effects were seen at ≥60 mg/kg/day in rats and ≥40 mg/kg/day in dogs. The NOAEL in male and female rats was 60 mg/kg/day and 10 mg/kg/day, respectively, with AUC estimates of 24.7 microg.h/mL and 25.1 microg.h/mL, respectively. The NOAEL in male and female dogs was 10 mg/kg/day with AUC estimates of 5.4 microg.h/mL and 8.2 microg.h/mL, respectively. Corresponding systemic exposures at these dose levels were 0.5 and 0.6-fold the human clinical exposure for male and female rats, respectively, and 0.1 and 0.2-fold the human clinical exposure for male and female dogs, respectively.

Carcinogenicity and mutagenicity

In oral carcinogenicity studies with lapatinib, severe skin lesions were seen at the highest doses tested (150 and 300 mg/kg/day in male mice and 300 mg/kg/day in female mice, and 500 mg/kg/day in male rats and 300 mg/kg/day in female rats). Compared to humans given 1250 mg lapatinib (Tykerb®) and 2000 mg/m^2, these doses produced exposures based on AUC up to 1.7-fold higher in mice and male rats, and up to 12-fold higher in female rats. There was

no evidence of carcinogenicity in mice. In rats, an increase in the incidence of benign hemangioma of the mesenteric lymph node occurred in males given 120 mg/kg/day and females given 180 mg/kg/day, but was within the historical control background range. There was also an increase in renal infarcts and papillary necrosis in female rats at ≥60 mg/kg/day and 180 mg/kg/day, respectively (approximate 5.8 and 8.2-fold the clinical exposure in humans given 1250 mg lapatinib and 2000 mg/m^2 capecitabine, respectively). The relevance of these renal findings for humans is uncertain.

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

Reproductive toxicity

For data regarding the impact of lapatinib (Tykerb®) on reproductive function, (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL).

INCOMPATIBILITIES

No known incompatibilities.

AVAILABILITY

HDPE bottle with two-piece child-resistant closure (Box of 70's)

STORAGE

Store at temperatures not exceeding 30°C.

The drug should not be used after the date marked "EXP" on the pack.

Drug must be kept out of the reach and sight of children.

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: **www.fda.gov.ph**
The patient is advised to seek IMMEDIATE medical attention at the first sign of adverse drug reaction.

Manufactured by:
Sandoz S.R.L
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Jud. Mureș, Code 540472, România

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