1 Trade name

TYKERB ™ 250 film-coated tablet 250 mg

2 Description and composition

Pharmaceutical form

Film-coated tablet

Tykerb 250 mg film-coated tablet (yellow film-coated tablets).

Tykerb 250 mg film-coated tablet are oval, biconvex, with one side plain and the other opposite side debossed with GS XJG.

Active substance

Lapatinib ditosylate monohydrate.

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

Excipients

All film-coated tablets
- 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

3 Indications

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-therapy including trastuzumab therapy in the metastatic setting (see section 12 Clinical studies).

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(s) in combination with chemotherapy in the metastatic setting (see section 12 Clinical studies).

TYKERB, in combination with an letrozole for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer, that overexpress HER2 receptor (immunohistochemistry/ICH2+) for whom hormonal therapy is indicated (see section 12 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.

4 Dosage regimen and administration

Dosage regimen and method of administration

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

Prior to the initiation of treatment, left ventricular ejection fraction (LVEF) must be evaluated to ensure that baseline LVEF is within the institutional limits of normal (see section 6 Warnings and 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 (LLN) (see section 4 Dose delay and dose reduction – Cardiac events).

TYKERB should be taken at least 1 hour before, or at least 1 hour after food (see section 7 Interactions – Drug food interactions and 11 Clinical pharmacology – Pharmacokinetics – Absorption).

Missed doses should not be replaced and dosing should resume with the next scheduled daily dose (see section 10 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

TYKERB in combination with capecitabine

The recommended dose of TYKERB is 1250 mg (i.e. 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 12 Clinical studies). Capecitabine should be taken with food or within 30 minutes after food.

TYKERB in combination with trastuzumab

The recommended dose of TYKERB is 1000 mg (i.e. 4 tablets) once daily continuously when taken in combination with trastuzumab.

The recommended dose of trastuzumab is 4 mg/kg administered as an intravenous (IV) loading dose, followed by 2 mg/kg IV weekly (see section 12 Clinical studies).

TYKERB in combination with letrozole

The recommended dose of TYKERB is 1500 mg (i.e. 6 tablets) once daily continuously when taken in combination with letrozole.

When TYKERB is co-administered with letrozole, the recommended dose of letrozole is 2.5 mg once daily. The dose of TYKERB should be once daily (6 tablets administered all at once), deviding the daily dose is not recommended.

Dose delay and dose reduction

Cardiac events (see section 6 Warnings and precautions)

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 institutional LLN. TYKERB may be restarted at a reduced dose (750 mg/day when administered with trastuzumab, 1000 mg/day when administered with capecitabine or 1250 mg/day when administered with letrozole) 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 9 weeks of treatment, however, there is limited data on long term exposure.

Interstitial lung disease/pneumonitis (see section 6 Warnings and precautions and 7 Adverse drug reactions)

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 section 6 Warnings and precautions and 7 Adverse drug reactions)

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). 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. TYKERB should be permanently discontinued in patients with NCI CTCAE grade 4 diarrhea.

Severe cutaneous reactions (see section 6 Warnings and precautions)

TYKERB should be discontinued in patients who experience severe progressive skin rash with blisters or mucosal lesions.

Other toxicities

Discontinuation or interruption of dosing with TYKERB may be considered if a patient develops toxicity greater than or equal to NCI CTCAE grade 2. Dosing can be restarted, when the toxicity improves to grade 1 or lower, at 1000 mg/day when administered with trastuzumab, 1250 mg/day if administered with capecitabine or 1500 mg/day when administered with letrozole. If the toxicity recurs, TYKERB should be restarted at a lower dose (750 mg/day when

administered with trastuzumab, 1000 mg/day when administered with capecitabine or 1250 mg/day when administered with letrozole).

Special populations

Renal impairment

There is no experience of TYKERB in patients with severe renal impairment. However, patients with renal impairment are unlikely to require dose modification of TYKERB given that under than 2% of an administered dose (lapatinib and metabolites) is eliminated renally (see section 11 Clinical pharmacology - Pharmacokinetics - Special populations).

Hepatic impairment

Lapatinib (TYKERB) is metabolized in the liver. Moderate and severe hepatic impairment have been associated with 56% and 85% increases in systemic exposure, respectively. Administration of TYKERB to patients with hepatic impairment requires caution due to increased exposure (see section 6 Warnings and precautions and 11 Clinical pharmacology Pharmacokinetics - Special populations).

Patients with severe hepatic impairment (Child-Pugh Class C) should have their TYKERB dose reduced. A dose reduction from 1250 mg to 750 mg/day or from 1500 mg/day to 1000 mg/day in patients with severe hepatic impairment is predicted to adjust the AUC to the normal range. However, there is no clinical data with this dose adjustment in patients with severe hepatic impairment (see section 6 Warnings and precautions and 11 Clinical pharmacology - Pharmacokinetics - Special populations).

Pediatric patients (below 18 years)

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

Geriatric patients (65 years or above)

There are limited data on the use of TYKERB in patients aged 65 years and older.

Of the total number of metastatic breast cancer patients in clinical studies of TYKERB in combination with capecitabine (N=198) 17% were 65 and over and 1% were 75 and over. No overall differences in safety were observed between these subjects and younger subjects. Of the total number of hormone sensitive metastatic breast cancer patients in the clinical studies of lapatinib in combination with letrozole (N=642) 44% were 65 and over and 12% were 75 and over.

No age-based differences in safety of the combination of lapatinib and letrozole were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between geriatric and younger patients. Greater sensitivity of geriatric patients cannot be rules out.

5 Contraindications

TYKERB is contraindicated in patients with hypersensitivity to any of the ingredients (see section 7 Adverse drug reactions).

6 Warnings and precautions

Cardiac toxicity

TYKERB has been associated with decreases in LVEF (see section 7 Adverse drug reactions). 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 it is within the institutionals normal limits. LVEF should continue to be evaluated during treatment with TYKERB to ensure that it does not decline to an unacceptable level (see section 4 Dosage regimen and administration - Dose delay and dose reduction - Cardiac events and 12 Clinical studies).

In some cases, LVEF decrease may be severe and lead to cardiac failure. Fatal cases have been reported, casuality of deaths is uncertain. In studies across the TYKERB clinical development program cardiac events, including LVEF decreases were reported in approx. 1% of patients. Symptomatic LVEF decreases were observed in approx. 0.3% of patients who received TYKERB. However, when TYKERB was administered in combination with trastuzumab in the metastatic setting, the incidence of cardiac events including LVEF decreases was higher (7%) versus the 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 TYKERB.

A concentration dependent QTc interval increase was observed in a dedicated placebo-controlled crossover study in patients with advanced solid tumors (see section 11 Clinical pharmacology). Caution should be taken if 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 TYKERB administration.

Interstitial lung disease and pneumonitis

TYKERB has been associated with interstitial lung disease and pneumonitis (see section 7 Adverse drug reactions). Patients should be monitored for pulmonary symptoms indicative of interstitial lung disease/pneumonitis (see section 4 Dosage regimen and administration).

Hepatotoxicity

Hepatotoxicity (ALT or AST >3 times the 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 TYKERB is uncertain. 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, TYKERB should be discontinued permanently (see section 7 Adverse drug reactions).

Patients carrying the HLA alleles DQA1*02:01 and DRB1*07:01 have an increased risk of lapatinib (TYKERB)-associated hepatotoxicity. In a large, randomized clinical study of TYKERB monotherapy (EGF114471; n=1,194), the overall risk of severe liver injury (ALT >5

times the ULN, 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 TYKERB is to be administered to patients with severe hepatic impairment, dose reduction is recommended. In patients who develop severe hepatotoxicity on therapy, TYKERB should be discontinued permanently (see section 4 Dosage regimen and administration and 11 Clinical pharmacology - Pharmacokinetics - Special populations).

Diarrhea

Diarrhea, including severe diarrhea, has been reported with TYKERB treatment (see section 7 Adverse drug reactions). Diarrhea may be severe, and deaths have been reported. Diarrhea generally occurs early during TYKERB treatment, with almost half of those patients with diarrhea first experiencing it within 6 days. This usually lasts 4-5 days.

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 persist beyond 24 hours, there is fever, or grade 3 or 4 neutropenia) or interruption or discontinuation of TYKERB (see section 4 Dosage regimen and administration - Dose delay and dose reduction - Diarrhea).

Concomitant treatment with inhibitors or inducers of CYP3A4

Co-administration of CYP3A4 inhibitors or inducers requires caution due to the risk of increased or decreased exposure to TYKERB, respectively (see section 7 Interactions).

Severe cutaneous reactions

Severe cutaneous reactions have been reported with lapatinib. If erythema multiforme or life-threatening reactions such as Stevens-Johnson syndrome, or toxic epidermal necrolysis (e.g. progressive skin rash often with blisters or mucosal lesions) are suspected, discontinue treatment with lapatinib (see section 4 Dosage regimen and administration).

7 Interactions

Lapatinib is predominantly metabolised by CYP3A (see section 11 Clinical pharmacology Pharmacokinetics - Biotransformation/metabolism). 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 TYKERB with known CYP3A4 inhibitors (e.g. erythromycin, telithromycin, ketoconazole, itraconazole, posaconazole, voriconazole, grapefruit juice, ritonavir, saquinavir, cisapride, verapamil, pimozide, nefazodone, cyclosporine) requires caution; clinical response and adverse events should be carefully monitored (see section 6 Warnings and precautions).

If patients must be co-administered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a TYKERB 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 approx. 1 week should be allowed before the 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 TYKERB with known CYP3A4 inducers (e.g. rifampin, rifabutin, phenytoin, carbamazepine or Hypericum perforatum (St. John's wort) requires caution; clinical response and adverse events should be carefully monitored (see section 6 Warnings and precautions).

If patients must be co-administered a strong CYP3A4 inducer, based on pharmacokinetic studies, the TYKERB dose should be titrated gradually from 1250 mg/day up to 4500 mg/day or from 1500 mg/day to 5500 mg/day based on tolerability. This TYKERB dose 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 TYKERB dose should be reduced over approxi. 2 weeks to the indicated dose.

Drugs that affect gastric pH

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

Effect of Tykerb on other drugs

Lapatinib inhibits CYP3A4 *in vitro* at clinically relevant concentrations. Co-administration of TYKERB with oral midazolam resulted in an approx. 45% increase in midazolam AUC. There was no clinically meaningful increase in AUC with IV midazolam. Caution is required when

co-administering TYKERB with orally administered medications with narrow therapeutic windows that are substrates of CYP3A4 (see section 11 Clinical pharmacology - Pharmacokinetics).

Lapatinib inhibits CYP2C8 *in vitro* at clinically relevant concentrations. Caution is required when co-administering TYKERB with medications with narrow therapeutic windows that are substrates of CYP2C8 such as repaglinide (see section 11 Clinical pharmacology - Pharmacokinetics).

Effect of Tykerb on transport proteins

Lapatinib is a substrate for the transport proteins Pgp and BCRP. Inhibitors and inducers of these proteins may therefore alter the exposure and/or distribution of lapatinib (see section 11 Clinical pharmacology - Pharmacokinetics).

Lapatinib inhibits the transport protein Pgp in vitro at clinically relevant concentrations. Co-administration of TYKERB with oral digoxin resulted in a 98% increase in digoxin AUC. Caution is required when co-administering 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 11 Clinical pharmacology - Pharmacokinetics).

Combination therapy

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

Drug-food/drink interactions

The bioavailability of lapatinib is affected by food (see sections 4 Dosage regimen and administration and 11 Clinical pharmacology - Pharmacokinetics).

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 TYKERB (see sections 7 Interactions - Interactions with CYP3A4-inhibitors and 11 Clinical Pharmacology - Biotransformation/Metabolism).

8 Pregnancy, lactation, females and males of reproductive potential

8.1. 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 TYKERB should be used during pregnancy only if the expected benefit for the patients justifies the potential risk to the fetus.

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

Animal data

In embryofetal development studies in rats and rabbits, 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. 6.4 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).

8.2. Lactation

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

8.3. 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 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).

9. Adverse Drug reactions

Summary of the safety profile

Clinical trial data

The safety of TYKERB has been evaluated as monotherapy or in combination with other chemotherapies for various cancers ≥ 20,000 patients including 198 patients in combination with capecitabine, 149 patients in combination with trastuzumab and 654 patients combination with letrozole (see section 12 Clinical studies).

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions (ADRs) from clinical trials are listed by MedDRA system organ class (SOC) in Tables 9-1 to 9-5). 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 TYKERB monotherapy

The following ADRs have been reported to be associated with TYKERB:

Table 9-1 ADRs reported to be associated with 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	
Diarrhoea, which may lead to dehydration[3]	Very common
Nausea	Very common
Vomiting	Very common
Hepatobiliary disorders	
Hepatotoxicity[4]	Uncommon

Hyperbilirubinaemia[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 5 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 Tykerb/Tyverb. Symptomatic LVEF decreases were observed in approx. 0.3% of patients on Tykerb/Tyverb. Observed adverse events included dyspnoea, cardiac failure and palpitations (see sections 4 Dosage and administration - Dose delay and dose reduction - Cardiac events and 6 Warnings and precautions).

[3] Diarrhoea and rash were generally low grade (most diarrhoea events were grade 1 or 2) and did not result in discontinuation of Tykerb/Tyverb. Diarrhoea 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 TYKERB in combination with capecitabine

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

Table 9-2 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 9-3 below were reported to be associated with TYKERB in combination with capecitabine but were seen at a similar frequency in the capecitabine monotherapy arm.

Table 9-3 Additional ADRs occurring in EGF100151 with a similar frequency for the combination versus capecitabine alone

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 TYKERB in combination with trastuzumab

No new additional adverse reactions were reported to be associated with 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 TYKERB clinical program (see section 6 Warnings and precautions - Cardiac toxicity). These data are based on exposure to this combination in 149 patients in the phase III study EGF104900.

ADRs with TYKERB in combination with letronazole

In addition to the ADRs observed with TYKERB monotherapy, the following ADRs were reported to be associated with 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 9-4 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 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 SOC, ADRs are presented in order of decreasing seriousness.

Table 9-5 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)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Phone: +62-21-4244691 Ext.1079
Website: https://e-meso.pom.go.id/ADR

or

Novartis Indonesia
Website: www.novartis.com/report

10 Overdosage

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

Taking 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 4 Dosage regimen and administration).

Asymptomatic and symptomatic cases of overdose have been reported in patients being treated with TYKERB. Symptoms observed include known TYKERB associated events (see section 9 Adverse drug reactions) and in some cases sore scalp, sinus tachycardia (with otherwise normal ECG) and/or mucosal inflammation.

TYKERB is not significantly renally excreted and is highly bound to plasma proteins; therefore, 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.

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

Human epidermal growth factor receptor 2 (HER)2 tyrosine kinase inhibitor, L01EH01.

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 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 TYKERB and trastuzumab may offer complimentary MOA 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 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 ErbB2-directed agents.

Hormone-sensitive breast cancer cells (estrogen receptor [ER] positive and/ or progesterone receptor [PgR]-positive) that co-express HER2 tend to become resistant to established endocrine therapies. Hormone-sensitive breast cancer cells that initially lack overexpression of EGFR or HER2 will up regulate these receptors as the tumor becomes resistant to endocrine therapy. Randomized trials in hormone-sensitive metastatic breast cancer indicate that an HER2 or EGFR tyrosine kinase inhibitor may potentially improve progression free survival (PFS) when added to endocrine therapy.

Pharmacodynamics (PD)

Cardiac electrophysiology

QT prolongation

Study EGF114271

The effect of TYKERB 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 TYKERB 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 TYKERB. 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 TYKERB. The PK/PD analyses confirmed a positive relationship between lapatinib plasma concentrations and ΔΔQTcF.

Pharmacokinetics (PK)

Absorption

Absorption of lapatinib following oral administration of TYKERB is incomplete and variable (approx. 50 to 100% coefficient of variation in AUC). Serum concentrations appear after a median lag time of 0.25 hours (range 0 to 1.5 hours). Peak plasma concentrations (C_{max}) of lapatinib are achieved approx. 4 hours after administration. Daily dosing of 1250 mg produces steady state geometric mean (95% CI) C_{max} values of 2.43 (1.57 to 3.77) microgram/mL and AUC values of 36.2 (23.4 to 56) microgram.hr/mL.

Systemic exposure to lapatinib is increased when administered with food (see section 4 Dosage regimen and administration and 8 Interactions). Lapatinib AUC values were approximately 3- and 4-fold higher (C_{max} approx. 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 p- glycoprotein (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 lapatinib concentration in plasma.

Elimination

The half-life of lapatinib measured after single doses increases with increasing dose. However, daily dosing of TYKERB 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 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 of lapatinib were examined in subjects with moderate (n = 8) or severe (N = 4) hepatic impairment and in 8 healthy control subjects. Systemic exposure (AUC) to lapatinib after a single oral 100mg dose increased approx. 56% and 85% in subjects with moderate and severe hepatic impairment, respectively. Administration of TYKERB in patients with hepatic impairment requires caution due to increased exposure. Dose reduction is recommended for patients with severe pre-existing hepatic impairment. In patients who develop severe hepatotoxicity while on therapy, TYKERB should be discontinued permanently (see section 4 Dosage regimen and administration and 6 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 Tykerb (see section 6 Warnings and precautions - Hepatotoxicity).

12 Clinical studies

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

See below for details.

Tykerb is not indicated in the adjuvant setting.

Combination treatment with TYKERB and capecitabine

Study EGF100151

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 TYKERB 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 1.

Table 12-1 Study EGF100151 – Key efficacy data (TTP, ORR)

	Independent assessment		Investigator assessment	
Efficacy outcome	**Tykerb plus capecitabine (N=198)**	**Capecitabine alone (N=201)**	**Tykerb 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 was 23.7% for patients receiving TYKERB plus capecitabine and 13.9% for patients receiving capecitabine. Median duration of response was 32.1 and 30.6 weeks respectively.

On the combination arm, there were 4 (2%) progressions in the CNS as versus the 13 (6%) progressions on the capecitabine monotherapy arm, as assessed by an independent review panel (see section 12 Clinical studies – TYKERB on CNS metastasis).

At the time enrolment was halted to EGF100151 (03 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 12-2.

Table 12-2 Study EGF100151 – Key efficacy data (OS)

Efficacy outcome	Tykerb plus capecitabine (N=207)	Capecitabine alone (N=201)
OS		
Died	81%	86%
Median OS (weeks)	75.0	64.7
HR, 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 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 HR of 0.80 (95% [CI]: 0.64, 0.99; p=0.043).

Study EGF111438 (CEREBEL)

This randomized phase III study (EGF111438) (N=540) compared the effect of TYKERB 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 TYKERB once daily (continuously) plus capecitabine (2000 mg/m^2/day on days 1-14 every 21 days) or trastuzumab (loading dose of 8 mg/kg followed by 6 mg/kg infusions every 3 weeks) plus capecitabine (2500 mg/m^2/day, on days 1-14, every 21 days). Randomization was stratified by prior tastuzumab treatment and number of prior treatments for metastatic disease (none versus ≥ 1 line). The study was stopped when a pre-planned interim analysis (N=475) showed superior efficacy of the traztuzumab 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 TYKERB plus capecitabine arm experienced CNS metastasis as site of first progression, versus 12 patients (4.8%) in the trastuzumab plus capecitabine arm) (see section 12 Clinical studies – TYKERB effect on CNS metastasis). The

final results of PFS and OS are shown in table 12-3. The final analysis confirmed the superior efficacy of the trastuzumab plus capecitabine arm.

Table 12-3 Study EGF111438 – Key efficacy data (PFS, OS)

Efficacy outcome	Investigator-assessed PFS		OS	
	Tykerb + capecitabine	Trastuzumab + capecitabine	Tykerb + capecitabine	Trastuzumab + capecitabine
All patients				
N	271	269	271	269
Number (%) with event[1]	59%	50%	26%	22%
Kaplan-Meier estimate, months [a]				
Median (95% CI)	6.6 (5.7, 8.1)	8.0 (6.1, 8.9)	22.7 (19.5, -)	27.3 (23.7, -)
Stratified 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)	

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 Tykerb 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.

TYKERB effect on CNS metastasis

Lapatinib has in terms of objective responses demonstrated modest activity in the treatment of established CNS metastases. In the prevention of CNS metastases in the metastatic and early breast cancer settings the observed activity was limited.

Combination treatment with TYKERB and trastuzumab

Study EGF104900

The efficacy and safety of 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. Per protocol, patients were to be reported by 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 3. Patients were randomized to receive either 1000 mg oral TYKERB once daily plus 4 mg/kg trastuzumab administered as IV loading dose followed by 2 mg/kg IV weekly (N = 148) or oral 1500 mg TYKERB once daily (N = 148). Patients with objective disease progression after at least 4 weeks of 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.

Progression-free survival (PFS) was the primary endpoint of the study with response rate and overall survival (OS) as secondary endpoints.

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 hormone receptor negative (150 [50%] overall). A summary of efficacy endpoints is provided in Table 12-4 and OS data is provided in Table 12-5. Subgroup analysis results based on predefined stratification factor (hormone receptor status) are shown in Table 12-6.

Table 12-4 Study EGF104900 Key efficacy data (PFS, HR, RR)

	Tykerb plus trastuzumab (N = 148)	**Tykerb alone (N = 148)**
Median PFS[1], weeks (95% CI)	12.0 (8.1, 16.0)	8.1 (7.6, 9.0)
HR (95% CI) p-value	0.73 (0.57, 0.93) 0.008	
RR (%) (95% CI)	10.3 (5.9, 16.4)	6.9 (3.4, 12.3)

[1] Kaplan-Meier estimate.

Table 12-5 Study EGF104900 – Key efficacy data (OS)

	Tykerb plus trastuzumab (N = 148)	**Tykerb alone (N = 148)**
Died	105	113
Median OS (months)[1] (95% CI)	14.0 (11.9, 17.2)	9.5 (7.6, 12.0)
HR, 95% CI p-value	0.74 (0.57. 0.97) 0.026	

[1] Kaplan-Meier estimates

Table 12-6 Study EGF104900 - Key efficacy data (PFS, OS) in the subgroup with hormone receptor status negative

	Tykerb plus trastuzumab (N=75)	Tykerb 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 TYKERB and letrozole

Study EGF30008

TYKERB was tudied 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, who had not received prior systemic therapy for metastatic disease. 1286 patients were randomized to 2.5 mg letrozole once daily plus 1500 mg 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 (17%) patients had tumor over-expressing the HER2 receptor defined as fluorescence in situ hybridization (FISH) ≥2 or 3+ immunohistochemistry (IHC). There were 952 (74%) HER2-negative patients and a total of 115 (9%) patients whose HER2 status was unconfirmed.

The primary objective was to evaluate and compare progression-free survival (PFS) in the HER2 positive population. Progression-free survival was defined as the interval of time between date of randomisation and the earlier date of first documented sign of disease progression or death due to any cause. The baseline demographic and disease characteristic were balanced between the two treatment arms. The median age was 63 years and 45% were 65 years of age or older. Eighty four percent (84%) of the patients were White. Approximately 50% of the HER2 positive population had prior adjuvant/neo-adjuvant chemotherapy and 56% had prior hormonal therapy. Only 2 patients had prior trastuzumab.

In the HER2-positive population, investigator-determined PFS was significantly greater with letrozole plus TYKERB compared with letrozole plus placebo (see Table 12-7).

Table 12-7 Study EGF30008 – Key efficacy data

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

Hazard Ratio	0.71 (0.53, 0.96)	0.86 (0.76, 0.98)	0.90 (0.77, 1.05)
P-value	0.019	0.026	0.188

CI= confidence interval

The benefit of TYKERB and 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 TYKERB and letrozole improved objective respose rate (27.9% and 14.8% respectively) (p=0.021) and clinical benefit rate (CBR; complete plus partial response plus stable disease for >6 months) (47.7% and 28.7% respectively) (p=0.003) compared with treatment with letrozole plus placebo. Although not yet mature, a trend toward a survival benefit was noted for the TYKERB and letrozole combination, HR= 0.77 (95% CI 0.52-1.14) p=0.185.

In the Intent-to-Treat (ITT) population, investigator-determined PFS was greater between the two treatment arms (see Table 12-7). Although, statistically significant, the difference was not considered clinically relevant.

In the HER2-negative population (n=952), the Kaplan-Meier analyses for PFS did not show a significant difference between the two treatment arms (see Table 12-7). However, the pre-planned Cox regression model taking into account a number of baseline covariates for PFS did show an improvement with the TYKERB and letrozole combination in HER2- negative population. (HR=0.77 (95% CI 0.64-0.94) p=0.010) In addition, age (younger), performance status (0), baseline serum HER2 ECD (<15 ng/mL), number of metastatic sites (<3) and prior adjuvant anti-estrogen stratification (<6 months since discontinuation) were identified as being significant prognostic factors.

Growth factor receptor upregulation occurs with anti-estrogen or endocrine therapy resistance. Therefore, the treatment effect in the pre-defined trial strata of prior endocrine therapy was further analysed (<6 months since discontinuation of endocrine therapy and ≥6 months since discontinuation of endocrine therapy or never having received endocrine therapy). Table 12-8 below describes the PFS in these two subgroups of HER2-negative population. In addition to the PFS benefit of TYKERB and letrozole therapy in the <6 months stratum, a benefit in CBR was also noted when compared with letrozole treatment alone (43.8% and 31.7%, respectively).

Table 12-8 Efficacy Data for Two Subgroups of HER2-Negative Population

	HER2-Negative Population: <6 months[1]		**HER2-Negative Population: ≥6 months[2]**	
	N=200		**N = 752**	
	TYKERB 1500 mg/day + Letrozole 2.5 mg/day	**Letrozole alone 2.5 mg/day**	**TYKERB 1500 mg/day + Letrozole 2.5 mg/day**	**Letrozole alone 2.5 mg/day**
	N = 96	**N =104**	**N = 382**	**N = 370**
Median PFS Kaplan Meier, weeks (95% CI)	36.3 (21.9, 55.3)	13.3 (12.1, 23.7)	64.0 (58.3, 73.1)	65.3 (59.1, 74.3)
Hazard Ratio	0.78 (0.57, 1.07)		0.94 (0.79, 1.13)	
P-value	0.117		0.522	

CI= confidence interval
[1] months since discontinuation of endocrine therapy
[2] months since discontinuation of endocrine therapy/never received

13 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 microgram.h/mL, respectively. The NOAEL in male and female dogs was 10 mg/kg/day with AUC estimates of 5.4 microgram.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 Tykerb and 2000 mg/m^2 capecitabine, 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 (approx. 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 TYKERB (lapatinib) on reproductive function, see section 9 Pregnancy, lactation, females and males of reproductive potential.

14 Pharmaceutical information

14.1 Incompatibilities

No known incompatibilities.

14.2 Shelf Life

The expiry date is indicated on the packaging.

14.3 Special Precautions for Storage

Do not store above 30°C.

14.4 Nature and Contents of Container

TYKERB film-coated tablets are available in high density polyethylene bottles (HDPE) with a child resistant polypropylene closure containing 70 tablets.

14.5 Instructions for Use/Handling

No relevant information.

Not all presentations are available in every country.

HARUS DENGAN RESEP DOKTER

TYKERB film-coated tablets, bottle @ 70 tablets, Reg. No.

Manufactured by:

Novartis Pharmaceuticals S.R.L., Targu Mures, Romania for Novartis Pharma AG, Basel, Switzerland

Imported by:

PT Novartis Indonesia Jakarta, Indonesia

PI based on CDS Update v2.2 – 18-Aug-2021_Novartis SRL

NOVARTIS

TYKERB™ (Lapatinib)

Tablet salut selaput 250 mg

Informasi Produk untuk Pasien

DISETUJUI OLEH BPOM : 24/12/2025 ID : EREG100005VR12500229

Bacalah brosur ini dengan seksama sebelum Anda mengkonsumsi TYKERB

Mohon simpan brosur ini. Anda mungkin akan membutuhkan brosur ini untuk dibaca kembali.

Apabila Anda memiliki pertanyaan lebih lanjut, mohon hubungi dokter atau apoteker Anda.

Obat ini diresepkan untuk Anda. Mohon jangan berikan obat ini kepada orang lain meskipun mereka memiliki gejala penyakit yang serupa dengan Anda.

Jika terjadi efek samping yang berat, atau Anda mengetahui adanya efek samping yang tidak disebutkan dalam leaflet ini, mohon informasikan kepada dokter, apoteker atau tenaga profesional kesehatan Anda.

DAFTAR ISI

1 Apakah TYKERB dan apa kegunaannya

TYKERB termasuk kedalam golongan obat yang disebut dengan *protein kinase inhibitors*. Obat ini digunakan untuk mengobati kanker payudara jenis tertentu. Obat ini dapat memperlambat atau menghentikan pertumbuhan sel kanker.

TYKERB dikombinasikan dengan capecitabine diindikasikan untuk pengobatan kanker payudara stadium lanjut atau yang sudah metastatis, dengan kondisi tumor yang memproduksi HER2/neu (ErbB2) dalam jumlah besar dan telah mengalami perkembangan setelah mendapatkan pengobatan sebelumnya, termasuk pengobatan dengan trastuzumab dalam kondisi metastatis.

TYKERB dikombinasikan dengan trastuzumab diindikasikan untuk pengobatan kanker payudara dengan receptor hormon negatif pada kondisi metastatis, dengan kondisi tumor yang memproduksi HER2/neu (ErbB2) dalam jumlah besar dan telah mengalami perkembangan setelah mendapatkan pengobatan dengan trastuzumab yang dikombinasikan dengan kemoterapi dalam kondisi metastatis.

TYKERB dikombinasikan dengan letrozole diindikasikan untuk pengobatan kanker payudara dengan hormon receptor positif pada kondisi metastatis untuk wanita paska menopause, dengan produksi HER2 receptor (*immunohistochemistry/ICH2+*) dalam jumlah besar.

Belum ada data terkait khasiat TYKERB dikombinasikan dengan trastuzumab dan aromatase inhibitor atau kemoterapi pada pasien dengan kondisi diatas.

2 Apa yang harus diketahui sebelum dan selama mengonsumsi Tykerb

Jangan mengkonsumsi Tykerb

- Jika anda mengalami alergi (hipersensitivitas) terhadap lapatinib atau terhadap kandungan zat lain yang terdapat pada Tykerb.

Jika ada kondisi diatas yang berlaku untuk Anda, **jangan mengkonsumsi Tykerb dan beritahukan kepada dokter Anda.**

Perhatian khusus saat mengkonsumsi Tykerb

Jika ada kondisi di bawah ini yang berlaku untuk Anda, beritahukan kepada dokter, apoteker atau tenaga kesehatan Anda sebelum mengkonsumsi Tykerb:

- Jika Anda memiliki masalah pada jantung
- Jika Anda memiliki masalah pada paru-paru atau masalah pernafasan
- Jika Anda memiliki masalah pada hati
- Jika Anda mengalami diare

Konsultasikan dengan dokter Anda, jika ada kondisi diatas yang berlaku untuk Anda. Anda mungkin membutuhkan pengujian tambahan untuk mengecek fungsi jantung dan hati Anda. Dokter Anda mungkin akan menyesuaikan dosis atau menghentikan pengobatan berdasarkan hasil pengujian ini.

Reaksi kulit yang parah

- Reaksi kulit yang parah dapat terjadi pada penggunaan Tykerb. Gejala yang timbul termasuk ruam kulit, melepuh dan pengelupasan kulit.

Segera informasikan kepada dokter Anda jika Anda mengalami gejala diatas. Karena reaksi kulit yang parah dapat mengancam nyawa, dokter Anda mungkin akan menganjurkan untuk menghentikan pengobatan.

Mengkonsumsi obat lain dengan Tykerb

Mohon beritahukan dokter atau apoteker Anda jika Anda sedang atau baru saja mengkonsumsi obat-obatan lain, termasuk obat-obatan yang bisa didapat tanpa resep dokter.

Beberapa Obat-obatan dapat mempengaruhi cara kerja Tykerb atau sebaliknya. Khususnya jika Anda mengkonsumsi obat-obatan di bawah ini:

- Eritromisin, ketoconazole, itraconazole, posaconazole, voriconazole, rifabutin, rifampicin, telithromisin (yang biasa digunakan untuk pengobatan infeksi)
- Ritonavir, saquinavir (untuk pengobatan infeksi HIV)
- Cisapride (untuk pengobatan masalah pada pencernaan)

- Obat yang menurunkan keasaman lambung (digunakan untuk mengobati sakit maag atau gangguan pencernaan)
- Quanidine, digoxin (untuk pengobatan jantung)
- Verapamil (untuk pengobatan tekanan darah tinggi atau angina)
- Rosuvastatin (untuk pengobatan kolesterol tingi)
- Repaglinide (untuk pengobatan diabetes)
- Phenytoin, carbamazepine (untuk pengobatan kejang)
- Pimozide (untuk pengobatan masalah kesehatan mental)
- Nefazodone (untuk pengobatan depresi)
- St John's Wort (ekstrak herbal yang digunakan untuk mengobati depresi)
- Midazolam (untuk sedasi sebelum operasi (anestesi))
- Siklosporin (untuk menekan sistem kekebalan misalnya setelah transplantasi organ)
- Topotecan, paclitaxel, docetaxel (untuk pengobatan kanker)

Beritahukan kepada dokter Anda, jika Anda sedang mengkonsumsi obat-obatan tersebut diatas.

Penggunaan Tykerb bersama makanan dan minuman

Tykerb dipengaruhi oleh asupan makanan (lihat bagian "Bagaimana Cara mengkonsumsi Tykerb"). Anda tidak boleh meminum *grapefruit juice* pada saat pengobatan dengan Tykerb karena dapat meningkatkan kemungkinan terjadinya efek samping.

Kehamilan dan Menyusui

Gunakan metode kontrasepsi yang dapat diandalkan untuk mencegah terjadinya kehamilan pada saat anda menjalani pengobatan dengan Tykerb.

Jangan mengkonsumsi Tykerb tanpa berkonsultasi terlebih dahulu dengan dokter Anda, jika Anda sedang hamil, mungkin sedang hamil, atau berencana untuk hamil. Dokter Anda akan mempertimbangan manfaat untuk Anda dan resiko untuk bayi Anda jika Anda mengkonsumsi Tykerb selama kehamilan.

Tidak direkomendasikan untuk menyusui selama pengobatan dengan Tykerb. Mintalah nasihat kepada dokter Anda.

3 Bagaimana cara mengkonsumsi Tykerb

Ikuti instruksi yang diberikan oleh dokter Anda secara seksama. Anda harus memastikan dengan dokter atau apoteker Anda jika Anda tidak yakin.

Berapa banyak Tykerb yang dikonsumsi

Tykerb mengandung 250 mg lapatinib.

Dokter Anda akan menentukan dosis Tykerb yang harus Anda konsumsi tergantung kepada tipe kanker payudara yang akan diobati.

Jika Anda diresepkan **Tykerb dikombinasikan dengan capecitabine**, dosis lazim adalah **5 tablet sehari**, sebagai dosis tunggal.

Jika Anda diresepkan **Tykerb dikombinasikan dengan trastuzumab**, dosis lazim adalah **4 tablet sehari**, sebagai dosis tunggal.

Jika Anda diresepkan **Tykerb dikombinasikan dengan letrozole**, dosis lazim adalah **6 tablet sehari**, sebagai dosis tunggal.

Bagaimana cara mengkonsumsi Tykerb

Telan tablet secara utuh dengan air, satu demi satu, pada waktu yang sama setiap hari, setidaknya satu jam sebelum atau satu jam sesudah makan.

Jika Anda sedang dirawat untuk kanker payudara metastatis dengan HER2 berlebih, Anda bisa mengkonsumsi obat lain yang mengandung capecitabin atau trastuzumab saat Anda mengkonsumsi Tykerb. Dokter Anda akan menyarankan dosis capecitabine atau trastuzumab, kapan harus mengkonsumsi dan seberapa sering Anda dapat mengkonsumsi obat tersebut.

Jika Anda sedang dirawat untuk kanker payudara metastatis dengan hormon-sensitif Anda bisa mengkonsumsi obat lain yang mengandung letrozole saat Anda mengkonsumsi Tykerb. Dokter Anda akan menyarankan dosis letrozole, kapan harus mengkonsumsi dan seberapa sering Anda dapat mengkonsumsi obat tersebut.

Dokter Anda dapat merekomendasikan untuk menurunkan dosis atau menghentikan pengobatan, tergantung kepada respon Anda terhadap pengobatan dengan Tykerb.

Dokter Anda juga dapat memeriksa fungsi jantung dan fungsi hati sebelum dan selama Anda diobati dengan Tykerb.

Apabila Anda lupa mengkonsumsi Tykerb

Jangan mengkonsumsi dosis ganda untuk menutupi dosis yang telah Anda lewatkan. Minumlah dosis selanjutnya sesuai jadwal pengobatan Anda.

Apabila Anda mengkonsumsi Tykerb lebih dari yang seharusnya

Apabila Anda mengkonsumsi Tykerb lebih dari yang seharusnya, Anda bisa mengalami efek samping. Segera hubungi dokter Anda atau Rumah Sakit terdekat untuk penanganan segera. Tunjukanlah kemasan tablet tersebut jika memungkinkan.

Jangan menghentikan pengobatan Tykerb tanpa petunjuk dokter

Minumlah Tykerb selama direkomendasikan dokter Anda. Jangan berhenti mengkonsumsi Tykerb kecuali diperintahkan dokter Anda.

4 Efek samping yang mungkin terjadi

Seperti obat-obatan lainnya, pasien yang diobati dengan Tykerb mungkin mengalami efek samping, meskipun tidak semua pasien mendapatkannya.

Efek samping dibawah ini dapat terjadi pada saat penggunaan Tykerb atau dengan kombinasi dengan capecitabine, trastuzumab atau letrozole.

Reaksi alergi yang parah

Efek samping yang langka ini dapat mempengaruhi hingga 1 dari 1000 orang dan berkembang dengan cepat.

Gejala mungkin termasuk:

- Ruam kulit (termasuk gatal dan bentol)
- Mengi yang tidak biasa atau kesulitan bernafas
- Bengkak pada kelopak mata, bibir atau lidah
- Nyeri pada otot atau sendi
- Pingsan

➔ **Segera hubungi dokter Anda** jika Anda mengalami gejala diatas. Hentikan penggunaan Tykerb.

Efek samping yang sangat umum

Efek samping ini dapat mempengaruhi lebih dari 1 dari 10 orang:

- Diare (yang dapat membuat Anda dehidrasi dan memicu terjadinya komplikasi parah yang dapat mengancam jiwa)

  ➔ **Segera hubungi dokter Anda** pada tanda pertama diare (BAB cair), karena diperlukan penanganan sesegera mungkin. Beritahukan juga kepada dokter Anda jika diare memburuk.
- Rendahnya tingkat sel darah putih dan sel darah merah
- Reaksi kulit atau nyeri pada telapak tangan atau telapak kaki (termasuk kesemutan, mati rasa, nyeri, bengkak, atau kemerahan)
- Nyeri otot
- Mati rasa, kesemutan atau kelemahan pada lengan dan kaki
- Kehilangan selera makan
- Gangguan pencernaan atau sakit perut
- Merasa tidak enak badan (mual atau muntah)
- Sembelit

- Kelelahan
- Rambut rontok yang tidak biasa atau penipisan rambut
- Mimisan
- Sakit mulut atau sariawan
- Kesulitan tidur (insomnia)
- Sakit punggung
- Ruam atau kulit kering.

Efek samping yang umum

Efek samping ini dapat mempengaruhi hingga 1 dari 10 orang:

- Pengaruh kerja jantung – seperti detak jantung tidak teratur dan sesak nafas
- Sakit kepala
- Gangguan kuku – seperti infeksi dan pembengkakan pada kutikula (*paronychia*)
- Masalah hati – termasuk gatal-gatal, mata kuning atau kulit kuning (*jaundice*), urin berwarna gelap atau rasa sakit atau tidak nyaman di daerah atas kanan perut.
- Kulit pecah-pecah (*skin fissures*)

Efek samping yang jarang

Efek samping ini dapat mempengaruhi hingga 1 dari 100 orang:

- Pembengkakan paru-paru – ini dapat menyebabkan batuk atau sesak nafas.

Efek samping yang langka

Efek samping ini dapat mempengaruhi hingga 1 dari 1.000 orang:

- Reaksi alergi parah

Efek samping dengan frekuensi yang tidak diketahui (kejadian dari laporan spontan)

- Detak jantung yang tidak teratur (perubahan aktivitas kelistrikan jantung)
- Reaksi kulit yang parah bisa meliputi: ruam, kulit merah, melepuh pada daerah sekitar bibir *(blistering)*, mata atau mulut, pengelupasan kulit, demam atau kombinasinya.

Tykerb dapat menyebabkan diare parah.

Jika Anda mengalami diare ketika menggunakan Tykerb:

- Minum air yang cukup (8 hingga 10 gelas sehari)
- Makan makanan rendah lemak, tinggi protein, dan hindari makanan berlemak atau pedas

- Makan sayuran yang dimasak, hindari sayuran mentah dan buang kulit buah sebelum dimakan
- Hindari susu dan produk turunannya (termasuk es krim)
- Hindari suplemen herbal (beberapa dapat menyebabkan diare).

Hubungi dokter jika diare berlanjut.

Tykerb dapat menyebabkan ruam kulit.

Dokter Anda akan memeriksa kulit Anda sebelum dan selama pengobatan.

Untuk mengatasi kulit sensitif.

- Cuci dengan pembersih bebas sabun
- Gunakan produk kecantikan bebas parfum atau *hypoallergenic*
- Gunakan tabir surya (*Sun Protection Factor* [SPF] 30 atau lebih tinggi).

Jika Anda mengalami efek samping

➔ **Segera beritahukan kepada dokter atau apoteker Anda** jika efek samping yang tertera pada brosur ini menjadi parah atau merepotkan, atau jika Anda mengalami efek samping apapun yang tidak tercantum dalam brosur ini.

Pelaporan efek samping

Apabila ada keluhan efek samping atau kondisi tidak nyaman selama dan setelah penggunaan obat, konsultasikan ke dokter, apoteker, atau perawat. Anda dapat juga melaporkan keluhan efek samping atau kondisi tidak nyaman tersebut secara langsung ke Industri Farmasi melalui kontak berikut:

Novartis Indonesia
Website: www.novartis.com/report

Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut mengenai keamanan obat ini.

5 Cara Penyimpanan Tykerb

- Jauhkan dari jangkauan dan penglihatan anak-anak.
- Jangan gunakan Tykerb setelah tanggal kadaluwarsa yang tercantum pada kemasan
- Simpan pada suhu di bawah 30°C
- Simpan pada kemasan aslinya untuk melindungi dari kelembaban
- Jangan digunakan jika kemasan rusak atau ada tanda-tanda kerusakan.

6 Informasi lebih lanjut

Kandungan Tykerb

- Zat aktif Tykerb adalah lapatinib
- Kandungan lainnya adalah *microcrystalline cellulose, povidone, sodium starch glycolate, magnesium stearate, hypromellose, titanium dioxide, macrogol/PEG400, Polysorbate 80, iron oxide yellow, iron oxide red.*

Bagaimana bentuk Tykerb

Tykerb tablet salut selaput berbentuk oval, bikonveks, salut selaput berwarna kuning dengan satu sisi polos dan sisi lain dicap dengan GS XJG.

Kemasan

TYKERB tablet salut selaput, botol @ 70 tablet, No. Reg.

HARUS DENGAN RESEP DOKTER

Pemegang Ijin Edar

PT. Novartis Indonesia

Pabrik Pembuat

Dibuat oleh Novartis Pharmaceuticals S.R.L., Targu Mures, Romania untuk Novartis Pharma AG, Basel, Swiss.

Diimpor oleh PT Novartis Indonesia, Jakarta, Indonesia.

Apabila Anda memiliki pertanyaan mengenai obat ini, mohon hubungi dokter atau apoteker Anda.

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