TYKERB™

Lapatinib Ditosylate

QUALITATIVE AND QUANTITATIVE COMPOSITION

Lapatinib ditosylate monohydrate 250 mg.

250 mg Tablet

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

The 250 mg tablets contain 405 mg of lapatinib ditosylate monohydrate, equivalent to 250 mg lapatinib free base per tablet.

PHARMACEUTICAL FORM

Film-coated tablets

CLINICAL PARTICULARS

Indications

TYKERB, in combination with capecitabine, is indicated for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress HER2+/neu (ErbB2+) and who have received prior therapy including trastuzumab (*see Clinical Studies*).

Dosage and Administration

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

Prior to the initiation of treatment, left ventricular ejection fraction (LVEF) must be evaluated to ensure that baseline LVEF is within the institutional limits of normal (*see Warning 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 (*see dose delay and dose reduction - cardiac events*).

TYKERB is taken in combination with capecitabine.

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

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

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

Dose delay and dose reduction

Cardiac events (see Warning and Precautions)

TYKERB should be discontinued in patients with symptoms associated with decreased LVEF

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

Interstitial lung disease/pneumonitis (see warning and precautions and Adverse Reactions)
TYKERB should be discontinued in patients who experience pulmonary symptoms indicative of interstitial lung disease/pneumonitis which are NCI CTCAE grade 3 or greater.

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

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

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 less than 2% of an administered dose (lapatinib and metabolites) is eliminated by the kidney (*see Pharmacokinetics - Special Patient Populations*).

Hepatic Impairment
Lapatinib is metabolised in the liver. Moderate and severe hepatic impairment have been associated, respectively, with 56% and 85% increases in systemic exposure, respectively. Administration of TYKERB to patients with hepatic impairment should be undertaken with caution due to increased exposure to the drug. Insufficient safety and efficacy data are available in patients with hepatic impairment to provide a dose adjustment recommendation (*see Warning and Precaution and Pharmacokinetics - Special Patient Populations*).

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

Elderly
There are limited data of 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=164) 15% were 65 and over, and 1% were 75 and over. For single agent TYKERB (N=307) 15% were 65 and over, and 2% were 75 and over. No overall differences in safety of the combination of TYKERB and capecitabine or single agent TYKERB were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Similarly no differences in effectiveness

for the combination of TYKERB and capecitabine on the basis of age were observed.

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

Warnings and Precautions
TYKERB has been associated with reports of decreased in left ventricular ejection fraction [LVEF] (*see Adverse Reaction*). Caution should be taken if TYKERB is to be administered to patients with conditions that could impair left ventricular function. LVEF should be evaluated in all patients prior to initiation of treatment with TYKERB to ensure that the patient has a baseline LVEF that is within the institutions normal limits. LVEF should continue to be evaluated during treatment with TYKERB to ensure that LVEF does not decline to an unacceptable level (*see Dosage and Administration - dose delay and dose reduction - cardiac events and Clinical Studies*).

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

Hepatotoxicity has occurred with lapatinib use and rarely may be severe. Liver function (transaminases, bilirubin and alkaline phosphatase) should be monitored before initiation of treatment and monthly thereafter, or as clinically indicated. Lapatinib dosing should be discontinued if changes in liver function are severe and patients should not be retreated. Hepatotoxicity has also been reported with other tyrosine kinase inhibitors.

Caution is warranted if TYKERB is prescribed to patients with moderate or severe hepatic impairment. (*see Dosage and Administration and Pharmacokinetics - Special Patient Populations*).

If TYKERB is to be administered to patients with severe hepatic impairment, dose reduction should be considered.

Diarrhoea, including severe diarrhoea, has been reported with TYKERB treatment (*see Adverse Reaction*). Proactive management of diarrhoea with anti-diarrhoeal agents is important. Severe cases of diarrhoea may require administration of oral or intravenous electrolytes and fluids, and interruption or discontinuation of TYKERB therapy (*see Dosage and Administration - dose delay and dose reduction - other toxicities*).

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

Coadministration of lapatinib with medications with narrow therapeutic windows that are substrates of CYP3A4 or CYP2C8 should be avoided (*see Interactions*).

Interactions
Lapatinib is predominantly metabolised by CYP3A (*see Pharmacokinetics*). Therefore, inhibitors

or inducers of these enzymes may alter the pharmacokinetics of lapatinib.

Coadministration of lapatinib with known inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, or grapefruit juice) should proceed with caution and clinical response and adverse events should be carefully monitored (*see Warning and Precautions*). If patients must be coadministration a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a dose reduction to 500 mg/day of lapatinib is predicted to adjust the lapatinib AUC to the range observed without inhibitor 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 shuold be allowed before the lapatinib dose is adjusted upward to the indicated dose.

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

Lapatinib inhibits CYP3A4 and CYP2C8 *in vitro* at clinically relevant concentrations. Caution should be exercised and dose reduction of the concomitant substrate drug should be considered when dosing TYKERB concurently with medication with narrow therapeutic windows that are substrates of CYP3A4 or CYP2C8 (*see Pharmacokinetics*).

Lapatinib is a substrate for the transport proteins Pgp and BCRP. Inhibitors and inducers of these protein may alter the exposure and/or distribution of lapatinib (*see Pharmacokinetics*).

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

Concomitant administration of TYKERB with capecitabinedid not meaningfully alter the pharmacokinetics of either agents (or the metabolites of capecitabine).

Pregnancy and Lactation

Fertility
No relevant information

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

treatment with TYKERB.

TYKERB can cause fetal harm when administered to a pregnant women. In a study where pregnant rats were dosed with lapatinib during organogenesis and trough lactation, at a dose of a 120 mg/kg/day (approximately 6.4 times the human clinical exposure based on AUC), 91% of the pups had died by the fourth day after birth, while 34% of the 60 mg/kg/day pups were dead. The highest no-effect dose for this study was 20 mg/kg/day (approximately equal to the human clinical exposure based on AUC).
Lapatinib was studied for effects on embryo-fetal development in pregnant rats and rabbits given oral doses of 30, 60 and 120 mg/kg/day. There were no teratogenic effects; however, minor anomalies (left-sided umbilical artery, cervical rib and precocious ossification) occured in rats at the maternally toxic doses of 120 mg/kg/day (approximately 6.4 times the human clinical exposure based on AUC). In rabbits, lapatinib was associated with maternal toxicity at 60 and 120 mg/kg/day (approximately 0.07 and 0.2 times the human clinical exposure, respectively, based on AUC) and abortions at 120 mg/kg/day. Maternal toxicity was associated with decreased fetal body weights and minor skeletal variations.

Lactation
It is not known whether TYKERB is excreted in human milk. Because many drugs are exreted in human milk and because of the potential for adverse reactions in breast-feeding infants from TYKERB, it is recommended that breast-feeding be discontinued in women who are receiving therapy with TYKERB.

Effects on Ability to Drive and Using Machines
There have been no studies to investigate the effect of TYKERB on driving performace or the ability to operate machinery. A detrimental effect on such activities cannot be predicted from the pharmacology of the TYKERB. The clinical status of the patient and the adverse event profile of TYKERB should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills.

Adverse Reactions
Clinical Trial Data
Safety of TYKERB has been evaluated as monotherapy and in combination with other chemotherapeutic agents for various cancers in more than 3,000 patients including 164 patients who received TYKERB in combination with capecitabine (*see Clinical Sudies*).

The following convention has been utilised for the classification of frequency: Very common (greater than or equal to 1/10), common (greater than or equal to 1/100 and less than 1/10), uncommon (greater than or equal to 1/1000 and less than 1/100), rare (greater than or equal to 1/10,000 and less than 1/1000) and very rare (less than 1/10,000).

The following adverse reactions have been reported to be associated with TYKERB:

Metabolism and nutrition disorders
Very common Anorexia

Cardiac disorders
Common Decreased left ventricular ejection fraction † (*see Dosage and*

Administration - dose delay and dose reduction - cardiac events and Warnings and Precautions).

† Left ventricular ejection fraction (LVEF) decreases have been reported in approximately 1% of patients and were asymptomatic in more than 90% of cases. LVEF decreases resolved or improved in more than 60% of cases on discontinuation of treatment with TYKERB. Symptomatic LVEF decreases were observed in approximately 0.1% of patients who received TYKERB monotherapy. Observed symptoms included dyspnoes, cardiac failure and palpitations. All events resolved promptly on discontinuation of TYKERB.

Respiratory, thoracic and mediastinal disorders
Uncommon Interstitial lung disease/pneumonitis

Gastrointestinal disorders
Very commmon Diarrhoea*, which may lead to dehydration ‡ (*see Dosage and Administration - dose delay and dose reduction - other toxicities and Warnings and Precautions*).
Nausea.
Vomiting.
‡ Most events of Diarrhoea were grade 1 or 2.

Hepatobiliary disorders
Uncommon Hyperbilirubinaemia.

Skin and subcutaneous tissue disorders
Very common Rash* (including dermatitis acneform) (*see Dosage and Administration - dose delay and dose reduction - other toxicities*).

General disorders and administration site conditions
Very common Fatigue

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

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

Gastrointestinal disorders
Very common Dyspepsia.

Skin and subcutaneous tissue disorders
Very common Dry skin.

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

Gastrointestinal disorders

Very common Stomatitis, constipation, abdominal pain.

Skin and subcutaneous tissue disorders
Very common Palmar-plantar erythrodysaesthesia.

General disorders and administrative site conditions
Very common Mucosal inflammation.

Musculoskeletal and connective tissue disorders
Very common Pain in extremity, back pain.

Nervous system disorders
Common Headache

Psychiatric disorders
Very common Insomnia.

Overdose
There is no specific antidote for the inhibition of EGFR (ErbB1) and/or HER2+/NEU (ErbB2+) tyrosine phosphorylation. The maximum oral dose of TYKERB that has been administered in clinical trials is 1800 mg once daily.

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

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

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics
Mechanism of action
Lapatinib is a novel 4-anilinoquinazoline kinase inhibitor with a unique mechanism of action, since it is a potent, reversible, and selective inhibitor of the intracellular tyrosine kinase domains of both EGFR (ErbB1) and/or HER2+/NEU (ErbB2+) receptors (estimated Ki^{app} values of 3nM and 13nM, respectively)with a slow off-rate from these receptors (half-life greater than or equal to 300 minutes). This dissociation rate was found to be slower than other 4-anilinoquinazoline kinase inhibitor studied. Lapatinib inhibits ErbB-driven tumour cell growth *in vitro* and in various animal models.

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

The growth inhibitory effects of lapatinib were evaluated in trastuzumab-conditioned cell lines. Lapatinib retained significant activity against breast cancer cell lines selected for long-term growth in trastuzumab-containing medium *in vitro*. These findings suggest non cross-resistance between these two HER2+/neu (ErbB2+)-directed agents.

Pharmacokinetics

Absorption

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

Divided daily doses of TYKERB resulted in approximately 2-fold higher exposure at steady state (steady state AUC) compared to the same total dose administered once daily.

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

Distribution

Lapatinib is highly bound (greater than 99%) to albumin and alpha-1 acid glycoprotein. *In vitro* studies indicate that lapatinib is a substrate for the transporters Breast Cancer Resistance Protein (BCRP, ABCG2) and p-glycoprotein (Pgp, ABCB1). Lapatinib has also been shown *in vitro* to inhibit these efflux transporters, as well as the hepatic uptake transporter OATP 1B1, at clinically relevant concentrations (IC_{50} values were less than or equal to 2.3 µg/mL). The clinical significance of these effects on the pharmacokinetics of other drugs or the pharmacological activity of other anti-cancer agents is not known.

Metabolism

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

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

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

In healthy volunteers receiving carbamazepine, a CYP3A4 inducer, at 100 mg twice daily for 3 days and 200 mg twice daily for 17 days, systemic exposure to lapatinib was decreased approximately 72%.

Elimination
The half-life of lapatinib measured after single doses increases with increasing dose. However, daily dosing of lapatinib results in achievement of steady state within 6 to 7 days, indicating an effective half-life of 24 hours. Lapatinib is predominantly eliminated through metabolism by CYP3A4/5. The primary route of elimination for lapatinib and its metabolites is in faeces, with less than 2% of the dose (as lapatinib and metabolites) exreted in urine. Recovery of lapatinib in faeces accounts for a median 27% (range 3 to 67%) of an oral dose.

Effects of Age, Gender, or Race : Studies of the effects of age, gender, or race on the pharmacokinetics of lapatinib have not been performed.

Special Patient Populations

Renal Impairment
Lapatinib pharmacokinetics have not been specifically studied in patients with renal impairment or in patients undergoing haemodialysis. There is no experience with TYKERB in patients with severe renal impairment. However, renal impairment is unlikely to affect the pharmacokinetics of lapatinib given that less than 2% of an administered dose (as unchanged lapatinib and metabolites) is eliminated by the kidneys.

Hepatic Impairment
The pharmacokinetics of lapatinib were examined in subjects with moderate (n = 8) or severe (n = 4) hepatic impairment (Child-Pugh scores of7-9, or greater than 9, respectively) and in 8 healthy control subjects. Systemic exposure (AUC) to lapatinib after a single oral 100 mg dose increased approximately 56% and 85% in subjects with moderate and severe hepatic impairment, respectively. Administration of lapatinib in patients with severe hepatic impairment should be undertaken with caution due to increased exposure to the drug. A dose reduction should be considered for patients with severe hepatic impairment. (*see Dosage and Administration and Warnings and Precautions*).

Clinical Studies

The efficacy and safety of TYKERB in combination with capecitabine in breast cancer was evaluated in a randomized, phase III trial. Patients eligible for enrolment had HER2+/neu (ErbB2+) over-expressing, locally advanced or metastatic breast cancer, progressing after prior treatment that included taxanes, anthracyclines and trastuzumab. LVEF was evaluated in all patients (usiang echocardiogram or MUGA) prior to initiation of treatment with TYKERB to ensure baseline LVEF was within the institutions normal limits. In clinical trials, LVEF was monitored at approximately eight week intervals during treatment with lapatinib to ensure it did not decline to below the institutions lower limit of normal. The majority of LVEF decreases

(greater than 60%) were observed during the first nine weeks of treatment, however limited data was available for long term exposure.

Petients were randomized to receive either TYKERB 1250 mg once daily (continously) plus capecitabine (2000 mg/m^2/day on days 1-14 every 21 days), or to receive capecitabine alone (2500 mg/m^2/day on days 1-14 every 21 days). The primary endpoint was time to progression (TTP) and results are based on review by an independent review panel. The study was halted based on the results of a pre-specified interim analysis taht showed an improvement in TTP (51% reduction in the hazard of achieving progression) for patients receiving TYKERB plus capecitabine.

Efficacy Outcome	TYKERB plus capecitabine (N=163)	Capecitabine alone (N=161)
Time to progression		
- Progressed or died due to breast cancer	30%	45%
- Median time to progression (weeks)	36.7	19.1
- Hazard ratio, 95% CI	0.49 (0.34, 0.71)	
- (p value)	0.00008	
Overall Response Rate, 95% CI	22.1% (16.0, 29.2)	14.3% (9.3, 20.7)
Median Duration of Response (weeks)	35.1	30.7

Pre-clinical Safety Data

TYKERB was studied in pregnant rats and rabbits given oral doses of 30, 60, and 120 mg/kd/day. There were no teratogenic effects; however, minor anomalies (left-sided umbilical artery, cervical rib and precocious ossification) occured in rats at the maternally toxic dose of 120 mg/kg/day (8 times the expected human clinical exposure). In rabbits, TYKERB was associated with maternal toxicity at 60 and 120 mg/kg/day (8% and 23% of the expected human clinical exposure, respectively) and abortions at 120 mg/kg/day. Maternal toxicity was associated with decreased fetal body weight, and minor skeletal variations. In the rat pre- and post natal development study, a decrease in pup survival occurred between birth and post natal day 21 at doses of 60 mg/kg/day or higher (5 times the expected human clinical exposure). The highest no-effect dose for this study was 20 mg/kg/day.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies with TYKERB are ongoing. TYKERB was not clastogenic or mutagenic in a battery of assays including the Chinese hamster chromosome aberration assay, the Ames assay, human lymphocyte chromosome aberration assay and an *in vivo* rat bone marraw chromosome aberration assay. There wereno effects on male or female rat gonadal function, mating, or fertility at doses up to 120 mg/ka/day (females) and up to 180 mg/kg/day (males) (6.4 and 2.6 times the expected human clinical exposure, respectively). The effect on human fertility is unknown.

PHARMACEUTICAL PARTICULARS

List of Excipients

All 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

Incompatibilities

No known incompatabilities.

Shelf Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

Do not store above 30^{o}C.

Nature and Contents of Container

TYKERB film-coated tablets are supplied in 7 blisters of 10 tablets.

Instructions for use/Handling

No relevant information.

Not all presentation are available in every country.
TYKERB is a trademark(s) of GlaxoSmithKline group of companies

HARUS DENGAN RESEP DOKTER

Reg. No. xxxxxxxxxxxxxxxxxxxxxxxxx

Manufactured by
Glaxo Operations UK Limited
(trading as Glaxo Wellcome Operations)
Ware, United Kingdom

Imported by
PT. SmithKline Beecham Pharmaceuticals
Jakarta, Indonesia

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