The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug. These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to a renin inhibitor only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should advise the patient to discontinue the use of Tekturna as soon as possible. Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, Tekturna should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Infants with histories of in-utero exposure to a renin inhibitor should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

There is no clinical experience with the use of Tekturna in pregnant women. Reproductive toxicity studies of aliskiren hemifumarate did not reveal any evidence of teratogenicity at oral doses up to 600 mg aliskiren/kg/day (20 times the maximum recommended human dose (MRHD) of 300 mg/day on a mg/m^2 basis) in pregnant rats or up to 100 mg aliskiren/kg/day (seven times the MRHD on a mg/m^2 basis) in pregnant rabbits. Fetal birth weight was adversely affected in rabbits at 50 mg/kg/day (3.2 times the MRHD on a mg/m^2 basis). Aliskiren was present in placenta, amniotic fluid and fetuses of pregnant rabbits.

Head and Neck Angioedema
Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with aliskiren. This may occur at any time during treatment. ACE inhibitors have been associated with a higher rate of angioedema in Black than in non-Black patients, but whether angioedema rates are higher in Blacks with aliskiren is not known. Tekturna should be promptly discontinued and appropriate therapy and monitoring provided until complete and sustained resolution of signs and symptoms has occurred. Experience with ACE inhibitors indicates that even in those instances where only swelling of the tongue is seen initially, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient to prevent respiratory involvement. Very rarely, fatalities have been reported in patients with angioedema associated with laryngeal edema or tongue edema with ACE inhibitors. Patients with involvement of the tongue, glottis or larynx are more likely to experience airway obstruction, especially those with a history of airway surgery. Where there is involvement of the tongue, glottis or larynx, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and

measures necessary to ensure a patent airway should be promptly provided (see ADVERSE REACTIONS).

Hypotension
An excessive fall in blood pressure was rarely seen (0.1%) in patients with uncomplicated hypertension treated with Tekturna alone. Hypotension was also infrequent during combination therapy with other antihypertensive agents (<1%). In patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients (e.g., those receiving high doses of diuretics), symptomatic hypotension could occur after initiation of treatment with Tekturna. This condition should be corrected prior to administration of Tekturna, or the treatment should start under close medical supervision.

If an excessive fall in blood pressure occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline (see DOSAGE AND ADMINISTRATION). A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

PRECAUTIONS

General

Impaired Renal Function
Patients with greater than moderate renal dysfunction (creatinine 1.7 mg/dL for women and 2.0 mg/dL for men and/or estimated GFR <30mL/min), a history of dialysis, nephrotic syndrome, or renovascular hypertension were excluded from clinical trials of Tekturna® (aliskiren) in hypertension. Caution should be exercised in these patients because of the paucity of safety information with Tekturna in these patients and the potential for other drugs acting on the renin-angiotensin system to increase serum creatinine and blood urea nitrogen.

Hyperkalemia
Increases in serum potassium > 5.5 meq/L were infrequent with Tekturna alone (0.9% compared to 0.6% with placebo). However, when used in combination with an ACE inhibitor in a diabetic population, increases in serum potassium were more frequent (5.5%). Routine monitoring of electrolytes and renal function is indicated in this population.

Information for Patients

Pregnancy
Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Angioedema
Angioedema, including laryngeal edema, may occur at any time during treatment with Tekturna. Patients should be so advised and told to report immediately any signs or symptoms suggesting

angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Drug Interactions
Patients should report any medications they take with aliskiren.

Furosemide
When aliskiren was given with furosemide, the blood concentrations of furosemide were reduced significantly. Patients receiving furosemide could find its effect diminished after starting aliskiren.

Carcinogenesis/Mutagenesis/Impairment of Fertility
Carcinogenic potential was assessed in a 2-year rat study and a 6-month transgenic (rasH2) mouse study with aliskiren hemifumarate at oral doses of up to 1500 mg aliskiren/kg/day. Although there were no statistically significant increases in tumor incidence associated with exposure to aliskiren, mucosal epithelial hyperplasia (with or without erosion/ulceration) was observed in the lower gastrointestinal tract at doses of 750 or more mg/kg/day in both species, with a colonic adenoma identified in one rat and a cecal adenocarcinoma identified in another, rare tumors in the strain of rat studied. On a systemic exposure ($AUC_{0\text{-}24hr}$) basis, 1500 mg/kg/day in the rat is about 4 times, and is in the mouse about 1.5 times, the maximum recommended human dose (300 mg aliskiren/day). Mucosal hyperplasia in the cecum or colon of rats was also observed at oral doses of 250 mg/kg/day (the lowest tested dose) as well as at higher doses in 4- and 13-week studies.

Aliskiren hemifumarate was devoid of genotoxic potential in the Ames reverse mutation assay with *S. typhimurium* and *E. coli*, the in vitro Chinese hamster ovary cell chromosomal aberration assay, the in vitro Chinese hamster V79 cell gene mutation test and the in vivo mouse bone marrow micronucleus assay.

Fertility of male and female rats was unaffected at doses of up to 250 mg aliskiren/kg/day (8 times the maximum recommended human dose of 300 mg Tekturna/60 kg on a mg/m^2 basis.

Pregnancy
Pregnancy Categories C (first trimester) and D (second and third trimesters) (see WARNINGS, Fetal/Neonatal Morbidity and Mortality).

Nursing Mothers
It is not known whether aliskiren is excreted in human milk. Aliskiren was secreted in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness of aliskiren in pediatric patients have not been established.

Geriatric Use
Of the total number of patients receiving aliskiren in clinical studies, 1,275 (19 %) were 65 years or older and 231 (3.4%) were 75 years or older. Blood pressure responses and adverse effects were generally similar to those in younger patients

ADVERSE REACTIONS

Tekturna® (aliskiren) has been evaluated for safety in more than 6,460 patients, including over 1,740 treated for longer than 6 months, and more than 1,250 for longer than 1 year. In placebo-controlled clinical trials, discontinuation of therapy due to a clinical adverse event, including uncontrolled hypertension occurred in 2.2% of patients treated with Tekturna, vs 3.5% of patients given placebo.

Two cases of angioedema with respiratory symptoms were reported with aliskiren use in the clinical studies. Two other cases of periorbital edema without respiratory symptoms were reported as possible angioedema and resulted in discontinuation. The rate of these angioedema cases in the completed studies was 0.06 %.

In addition, 26 other cases of edema involving the face, hands, or whole body were reported with aliskiren use, including 4 leading to discontinuation. In the placebo controlled studies, however, the incidence of edema involving the face, hands or whole body was 0.4% with aliskiren compared with 0.5% with placebo. In a long term active control study with aliskiren and HCTZ arms, the incidence of edema involving the face, hand or whole body was 0.4% in both treatment arms.

Aliskiren produces dose-related gastrointestinal (GI) adverse effects. Diarrhea was reported by 2.3% of patients at 300 mg, compared to 1.2% in placebo patients. In women and the elderly (age $\geq$ 65) increases in diarrhea rates were evident starting at a dose of 150 mg daily, with rates for these subgroups at 150 mg comparable to those seen at 300 mg for men or younger patients (all rates about 2.0%-2.3%). Other GI symptoms included abdominal pain, dyspepsia, and gastroesophageal reflux, although increased rates for abdominal pain and dyspepsia were distinguished from placebo only at 600 mg daily. Diarrhea and other GI symptoms were typically mild and rarely led to discontinuation. Aliskiren was associated with a slight increase in cough in the placebo-controlled studies (1.1% for any aliskiren use vs. 0.6% for placebo). In active-controlled trials with ACE inhibitor (ramipril, lisinopril) arms, the rates of cough for the aliskiren arms were about one-third to one-half the rates in the ACE inhibitor arms.

Other adverse effects with increased rates for aliskiren compared to placebo included rash (1% vs. 0.3%), elevated uric acid (0.4% vs. 0.1%), gout (0.2% vs. 0.1%), and renal stones (0.2% vs. 0%). Single episodes of tonic-clonic seizures with loss of consciousness were reported in two patients treated with aliskiren in the clinical trials. One of these patients did have predisposing causes for seizures and had a negative electroencephalogram (EEG) and cerebral imaging following the seizures (for the other patient EEG and imaging results were not reported.) Aliskiren was discontinued and there was no re-challenge.

The following adverse events occurred in placebo-controlled clinical trials at an incidence of more than 1% of patients treated with aliskiren, but also occurred at about the same or greater incidence in patients receiving placebo: headache, nasopharyngitis, dizziness, fatigue, upper respiratory tract infection, back pain and cough.

Clinical Laboratory Findings

In controlled clinical trials, clinically relevant changes in standard laboratory parameters were rarely associated with the administration of Tekturna. In multiple-dose studies in hypertensive patients Tekturna had no clinically important effects on total cholesterol, HDL, fasting triglycerides, fasting glucose, or uric acid.

Blood Urea Nitrogen, Creatinine
Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 7% of patients with essential hypertension treated with Tekturna alone vs. 6% on placebo.

Hemoglobin and Hematocrit
Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.08 g/dL and 0.16 volume percent, respectively, for all aliskiren monotherapy) were observed. The decreases were dose-related and were 0.24 g/dL and 0.79 volume percent for 600 mg daily. This effect is also seen with other agents acting on the renin angiotensin system, such as angiotensin inhibitors and angiotensin receptor blockers, and may be mediated by reduction of angiotensin II which stimulates erythropoietin production via the AT1 receptor. These decreases led to slight increases in rates of anemia with aliskiren compared to placebo were observed (0.1% for any aliskiren use, 0.3% for aliskiren 600 mg daily, vs. 0% for placebo). No patients discontinued therapy due to anemia.

Serum Potassium
Increases in serum potassium >5.5 meq/L were infrequent in patients with essential hypertension treated with Tekturna alone (0.9% compared to 0.6% with placebo). However, when used in combination with an angiotensin-converting enzyme inhibitor (ACEI) in a diabetic population increases in serum potassium were more frequent (5.5%) and routine monitoring of electrolytes and renal function is indicated in this population.

Serum Uric Acid
Aliskiren monotherapy produced small median increases in serum uric acid levels (about 6 μmol/L) while HCTZ produced larger increases (about 30 μmol/L). The combination of aliskiren with HCTZ appears to be additive (about a 40 μmol/L increase). The increases in uric acid appear to lead to slight increases in uric acid-related AEs: elevated uric acid (0.4% vs. 0.1%), gout (0.2% vs. 0.1%), and renal stones (0.2% vs. 0%).

Creatine Kinase
Increases in creatine kinase of >300% were recorded in about 1% of aliskiren monotherapy patients vs. 0.5% of placebo patients. Five cases of creatine kinase rises, three leading to discontinuation and one diagnosed as subclinical rhabdomyolysis and another as myositis, were reported as adverse events with aliskiren use in the clinical trials. No cases were associated with renal dysfunction.

OVERDOSAGE
Limited data are available related to overdosage in humans. The most likely manifestation of overdosage would be hypotension. If symptomatic hypotension should occur, supportive treatment should be initiated.

DOSAGE AND ADMINISTRATION
The usual recommended starting dose of Tekturna® (aliskiren) is 150 mg once daily. In patients whose blood pressure is not adequately controlled, the daily dose may be increased to 300 mg. Doses above 300 mg did not give an increased blood pressure response but increased the rate of diarrhea. The antihypertensive effect of a given dose is substantially attained (85%-90%) by 2 weeks.

Tekturna may be administered with other antihypertensive agents. Most exposure to date is with diuretics and an angiotensin receptor blocker (valsartan) and the drugs together have a greater effect at

their maximum recommended doses than either drug alone. It is not known whether additive effects are present when aliskiren is used with angiotensin-converting enzyme inhibitors or beta blockers.

No initial dosage adjustment is required in elderly patients, for patients with mild-to-severe renal impairment, or for patients with mild-to-severe hepatic insufficiency. Care should be exercised when dosing Tekturna in patients with severe renal impairment, as clinical experience with such patients is limited.

Patients should establish a routine pattern for taking Tekturna with regard to meals. High fat meals decrease absorption substantially (see Absorption and Distribution).

HOW SUPPLIED

Tekturna® (aliskiren) is supplied as a light-pink, biconvex unscored round tablet containing 150 mg of aliskiren, and as a light-red biconvex ovaloid tablet containing 300 mg of aliskiren. Tablets are imprinted with NVR on one side and IL, IU, on the other side of the 150, and 300 mg tablets, respectively.

All strengths are packaged in bottles and unit-dose blister packages (10 strips of 10 tablets) as described below in Table 4.

Table 4: Tekturna Tablets Supply

Tablet	Color	Imprint	Imprint	NDC 0078-XXXX-XX		
		Side 1	Side 2	Bottle of 30	Bottle of 90	Blister Packages of 100
150 mg	Light-pink	NVR	IL	0485-15	0485-34	0485-35
300 mg	Light-red	NVR	IU	0486-15	0486-34	0486-35

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Protect from moisture.

Dispense in tight container (USP).

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T2007-05

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

PATIENT INFORMATION

T2007-06

TEKTURNA® (PRONOUNCED TEK-TURN-A)
(aliskiren)
Tablets

Dosing Strengths:
150 mg tablets
300 mg tablets

Available by Prescription Only

Please read all of the available information before you start taking Tekturna. This leaflet does not take the place of talking with your doctor about your condition and treatment. If you have any questions about Tekturna, ask your doctor or pharmacist, visit www.Tekturna.com, or call 1-888-Tekturna (1-888-835-8876).

IMPORTANT WARNING: If you get pregnant, stop taking Tekturna and call your doctor right away. Tekturna may harm an unborn baby, causing injury and even death. If you plan to become pregnant, talk to your doctor about other treatment options before taking Tekturna.

What Is High Blood Pressure (Hypertension)?
Blood pressure is the force that pushes the blood through your blood vessels to all the organs of your body. You have high blood pressure when the force of your blood moving through your blood vessels is too great. Renin (pronounced REE-nin) is a chemical in the body that starts a process that makes blood vessels narrow, leading to high blood pressure.

High blood pressure makes the heart work harder to pump blood throughout the body and causes damage to the blood vessels. If high blood pressure is not treated, it can lead to stroke, heart attack, heart failure, kidney failure, and vision problems.

What Is Tekturna?
Tekturna is a type of prescription medicine called a direct renin inhibitor that works in the body to help lower blood pressure (hypertension).

How Does Tekturna Work?
Tekturna reduces the effect of renin and the harmful process that narrows blood vessels. Tekturna helps blood vessels relax and widen so blood pressure is lowered.

Who Should Not Take Tekturna?

- **If you get pregnant, stop taking Tekturna and call your doctor right away. If you plan to become pregnant, talk to your doctor about other treatment options for your high blood pressure.**
- **Do not take Tekturna if you are allergic to any of its ingredients.**

Aliskiren is the active ingredient in Tekturna. The inactive ingredients (the ingredients that bind the tablet together) are colloidal silicon dioxide, crospovidone, hypromellose, iron oxide colorants, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, and titanium dioxide. These inactive ingredients are considered safe and are commonly used in many medications. Talk to your doctor if you have questions.

Tekturna has not been studied in children under 18 years of age.

What Should I Tell My Doctor Before Taking Tekturna?

Tell your doctor about all your medical conditions, including whether you:

- are pregnant or planning to become pregnant.
- are breast-feeding. It is not known if Tekturna passes into your breast milk. You should choose either to take Tekturna or breast-feed, but not both.
- have kidney problems.
- are allergic to any of the ingredients in Tekturna.

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. Especially tell your doctor if you are taking:

- other medicines for high blood pressure or a heart problem.
- water pills (also called "diuretics").
- medicines for treating fungus or fungal infections.

Your doctor or pharmacist will know what medicines are safe to take together.

How Should I Take Tekturna?

- Take Tekturna once a day, at the same time each day. As with any blood pressure medication, it is important to take Tekturna on a regular daily basis exactly as prescribed by your doctor.
- Tekturna can be taken by itself or safely in combination with other medicines to lower high blood pressure. It can also be safely taken in combination with medications for other conditions such as high cholesterol or diabetes. Your doctor may change your dose if needed.
- Tekturna can be taken with or without food.

If you miss a dose, take it as soon as you remember. If it is close to your next dose, do not take the missed dose. Just take the next dose at your regular time. If you take too much Tekturna, call your doctor or Poison Control Center, or go to the nearest hospital emergency room.

What Are Possible Side Effects Of Tekturna?

Tekturna may cause the following serious side effect:

- **Low blood pressure (hypotension).** Your blood pressure may get too low if you also take water pills, are on a low-salt diet, get dialysis treatments, have heart problems, or get sick with vomiting or diarrhea. Lie down if you feel faint or dizzy. Call your doctor right away.

Side effects were usually mild and brief. Few patients decided to stop taking Tekturna because of side effects. In clinical studies, the most common side effect experienced by more patients taking Tekturna than patients taking a sugar pill (placebo) was diarrhea. Other less common reactions to Tekturna include cough, and rash.

If you develop an allergic reaction involving swelling of the face, lips, throat and/or tongue which may cause difficulty in breathing and swallowing, stop taking Tekturna and contact your doctor immediately.

For a complete list of side effects, ask your doctor or pharmacist. Tell your doctor if you get any side effect that bothers you or will not go away.

How Do I Store Tekturna?

- Store Tekturna tablets at room temperature between 59° to 86°F.
- Keep Tekturna in the original prescription bottle in a dry place. Do not remove the desiccant (drying agent) from the bottle.
- Keep Tekturna and all medicines out of the reach of children.

General Information About Tekturna

Do not give Tekturna to other people, even if they have the same condition or symptoms you have. It may harm them.

This leaflet summarizes the most important information about Tekturna.

For more information about Tekturna, ask your doctor or pharmacist, visit www.Tekturna.com, or call 1-888-Tekturna (1-888-835-8876).

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NOVARTIS
Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TYKERB safely and effectively. See full prescribing information for TYKERB.

TYKERB® (lapatinib) tablets
Initial U.S. Approval: 2007

----------INDICATIONS AND USAGE----------

TYKERB, a kinase inhibitor, is indicated in combination with capecitabine, for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab. (1)

----------DOSAGE AND ADMINISTRATION----------

The recommended dosage of TYKERB is 1,250 mg (5 tablets) given orally once daily on Days 1-21 continuously in combination with capecitabine 2,000 mg/m^2/day (administered orally in 2 doses approximately 12 hours apart) on Days 1-14 in a repeating 21 day cycle. (2.1)

- TYKERB should be taken at least one hour before or one hour after a meal. However, capecitabine should be taken with food or within 30 minutes after food. (2.1)
- TYKERB should be taken once daily. Do not divide daily doses of TYKERB. (2.1, 12.3)
- Modify dose for cardiac and other toxicities, severe hepatic impairment, and CYP3A4 drug interactions. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

250 mg tablets (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Decreases in left ventricular ejection fraction have been reported. Confirm normal LVEF before starting TYKERB and continue evaluations during treatment. (5.1)
- Dose reduction in patients with severe hepatic impairment should be considered. (2.2, 5.2, 8.7)
- Diarrhea, including severe diarrhea, has been reported during treatment. Manage with anti-diarrheal agents, and replace fluids and electrolytes if severe. (5.3)
- Lapatinib prolongs the QT interval in some patients. Consider ECG and electrolyte monitoring. (5.4)
- Fetal harm can occur when administered to a pregnant woman. Women should be advised not to become pregnant when taking TYKERB. (5.5)

---------- ADVERSE REACTIONS ----------

The most common (>20%) adverse reactions during treatment with TYKERB plus capecitabine were diarrhea, palmar-plantar erythrodysesthesia, nausea, rash, vomiting, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- TYKERB is likely to increase exposure to concomitantly administered drugs which are metabolized by CYP3A4 or CYP2C8. (7.1)
- Avoid strong CYP3A4 inhibitors. If unavoidable, consider dose reduction of TYKERB in patients coadministered a strong CYP3A4 inhibitor. (2.2, 7.2)
- Avoid strong CYP3A4 inducers. If unavoidable, consider gradual dose increase of TYKERB in patients coadministered a strong CYP3A4 inducer. (2.2, 7.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: March 2007

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TYKERB is indicated in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dose of TYKERB is 1,250 mg (5 tablets) given orally once daily on Days 1-21 continuously in combination with capecitabine 2,000 mg/m^2/day (administered orally in 2 doses approximately 12 hours apart) on Days 1-14 in a repeating 21 day cycle. TYKERB should be taken at least one hour before or one hour after a meal. The dose of TYKERB should be once daily; dividing the daily dose is not recommended *[see Clinical Pharmacology (12.3)]*. Capecitabine should be taken with food or within 30 minutes after food. If a day's dose is missed, the patient should not double the dose the next day. Treatment should be continued until disease progression or unacceptable toxicity occurs.

2.2 Dose Modification Guidelines

Cardiac Events: TYKERB should be discontinued in patients with a decreased left ventricular ejection fraction (LVEF) that is grade 2 or greater by NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) and in patients with an LVEF that drops below the institution's lower limit of normal *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*. TYKERB may be restarted at a reduced dose (1,000 mg/day) after a minimum of 2 weeks if the LVEF recovers to normal and the patient is asymptomatic.

Hepatic Impairment: Patients with severe hepatic impairment (Child-Pugh Class C) should have their TYKERB dose reduced. A dose reduction to 750 mg/day in patients with severe hepatic impairment is predicted to adjust the area under the curve (AUC) to the normal range and should be considered. However, there is no clinical data with this dose adjustment in patients with severe hepatic impairment.

Concomitant Strong CYP3A4 Inhibitors: The concomitant use of strong CYP3A4 inhibitors should be avoided (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole). Grapefruit may also increase plasma concentrations of lapatinib and should be avoided. If patients must be coadministered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a dose reduction to 500 mg/day of lapatinib is predicted to adjust the lapatinib AUC to the range observed without inhibitors and should be considered. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors. If the strong inhibitor is

discontinued, a washout period of approximately 1 week should be allowed before the lapatinib dose is adjusted upward to the indicated dose. *[See Drug Interactions (7.2).]*

Concomitant Strong CYP3A4 Inducers: The concomitant use of strong CYP3A4 inducers should be avoided (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John's Wort). If patients must be coadministered 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 to the indicated dose. *[See Drug Interactions (7.2).]*

Other Toxicities: Discontinuation or interruption of dosing with TYKERB may be considered when patients develop greater than or equal to grade 2 NCI CTC toxicity and can be restarted at 1,250 mg/day when the toxicity improves to grade 1 or less. If the toxicity recurs, then TYKERB should be restarted at a lower dose (1,000 mg/day).

See manufacturer's prescribing information for capecitabine dosage adjustment guidelines in the event of toxicity.

3 DOSAGE FORMS AND STRENGTHS

250 mg tablets — oval, biconvex, and orange, film-coated with GS XJG debossed on one side.

4 CONTRAINDICATIONS

None.

See manufacturer's prescribing information for capecitabine contraindications.

5 WARNINGS AND PRECAUTIONS

5.1 Decreased Left Ventricular Ejection Fraction

TYKERB has been reported to decrease LVEF *[see Adverse Reactions (6.1)]*. In the randomized clinical trial, the majority (>60%) of LVEF decreases occurred within the first 9 weeks of treatment; however, data on long-term exposure are limited. 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 institution's normal limits. LVEF should continue to be evaluated during treatment with TYKERB to ensure that LVEF does not decline below the institution's normal limits *[see Dosage and Administration (2.2)]*.

5.2 Patients with Severe Hepatic Impairment

If TYKERB is to be administered to patients with severe hepatic impairment, dose reduction should be considered *[see Dosage and Administration (2.2) and Use in Specific Populations (8.7)]*.

5.3 Diarrhea

Diarrhea, including severe diarrhea, has been reported during treatment with TYKERB *[see Adverse Reactions (6.1)]*. Proactive management of diarrhea with anti-diarrheal agents is important. Severe cases of diarrhea may require administration of oral or intravenous electrolytes and fluids, and interruption or discontinuation of therapy with TYKERB.

5.4 QT prolongation

QT prolongation measured by automated machine-read evaluation of ECG was observed in an uncontrolled, open-label dose escalation study of lapatinib in advanced cancer patients *[see Clinical Pharmacology (12.4)]*. Lapatinib should be administered with caution to patients who have or may develop prolongation of QTc. These conditions include patients with hypokalemia or hypomagnesemia, with congenital long QT syndrome, patients taking anti-arrhythmic medicines or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy. Hypokalemia or hypomagnesemia should be corrected prior to lapatinib administration. The prescriber should consider baseline and on-treatment electrocardiograms with QT measurement.

5.5 Pregnancy

Pregnancy Category D

TYKERB can cause fetal harm when administered to a pregnant woman. In a study where pregnant rats were dosed with lapatinib during organogenesis and through lactation, at a dose of 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) occurred in rats at the maternally toxic dose 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.

There are no adequate and well-controlled studies with TYKERB in pregnant women. Women should be advised not to become pregnant when taking TYKERB. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The safety of TYKERB has been evaluated in more than 3,500 patients in clinical trials. The efficacy and safety of TYKERB in combination with capecitabine in breast cancer was

112 evaluated in 198 patients in a randomized, Phase 3 trial. *[See Clinical Studies (14).]* Adverse
113 reactions which occurred in at least 10% of patients in either treatment arm and were higher in
114 the combination arm are shown in Table 1.
115 Because clinical trials are conducted under widely varying conditions, adverse reaction
116 rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical
117 trials of another drug and may not reflect the rates observed in practice.
118 The most common adverse reactions (>20%) during therapy with TYKERB plus
119 capecitabine were gastrointestinal (diarrhea, nausea, and vomiting), dermatologic (palmar-
120 plantar erythrodysesthesia and rash), and fatigue. Diarrhea was the most common adverse
121 reaction resulting in discontinuation of study medication.
122 The most common grade 3 and 4 adverse reactions (NCI CTC v3) were diarrhea and
123 palmar-plantar erythrodysesthesia. Selected laboratory abnormalities are shown in Table 2.
124