Latinib

Lapatinib Ditosylate Monohydrate INN

DRUG INTERNATIONAL LTD.

COMPOSITION

Each tablet contains Lapatinib 250mg as Lapatinib Ditosylate Monohydrate INN.

CLINICAL PHARMACOLOGY

Mechanism of Action

Lapatinib is a 4-anilinoquinazoline kinase inhibitor of the intracellular tyrosine kinase domains of both Epidermal Growth Factor Receptor (EGFR [ErbB1]) and of Human Epidermal Receptor Type 2 (HER2 [ErbB2]) receptors (estimated Kiapp values of 3nM and 13nM, respectively) with a dissociation half-life of greater than or equal to 300 minutes. Lapatinib inhibits ErbB-driven tumor cell growth in vitro and in various animal models. 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 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 in vitro findings suggest non-cross-resistance between these two agents. Hormone receptor-positive breast cancer cells (with ER [Estrogen Receptor] and/or PgR [Progesterone Receptor]) that coexpress the HER2 tend to be resistant to established endocrine therapies. Similarly, hormone receptor-positive breast cancer cells that initially lack EGFR or HER2 upregulate these receptor proteins as the tumor becomes resistant to endocrine therapy.

Pharmacokinetics

Absorption: Absorption following oral administration of Lapatinib is incomplete and variable. Serum concentrations appear after a median lag time of 0.25 hours (range 0 to 1.5 hours). Peak plasma concentrations (Cmax) of Lapatinib are achieved approximately 4 hours after administration. Daily dosing of Lapatinib results in achievement of steady state within 6 to 7 days, indicating an effective half-life of 24 hours. At the dose of 1,250 mg daily, steady-state geometric mean [95% confidence interval (CI)] values of Cmax were 2.43 mcg/mL (1.57 to 3.77 mcg/mL) and AUC were 36.2 mcg.h/mL (23.4 to 56 mcg.h/mL). Divided daily doses of Lapatinib 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. Lapatinib AUC values were approximately 3- and 4-fold higher (Cmax approximately 2.5- and 3-fold higher) when administered with a lowfat (5% fat-500 calories) or with a high-fat (50% fat-1,000 calories) meal, respectively.

Distribution: Lapatinib is highly bound (greater than 99%) to 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 (P-gp, ABCB1). Lapatinib has also been shown to inhibit P-gp, BCRP, and the hepatic uptake transporter OATP 1B1, in vitro at clinically relevant concentrations.

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 accounts for more than 14% of the dose recovered in the feces or 10% of Lapatinib concentration in plasma.

Elimination: At clinical doses, the terminal phase half-life following a single dose was 14.2 hours; accumulation with repeated dosing indicates an effective half-life of 24 hours. Elimination of Lapatinib is predominantly through metabolism by CYP3A4/5 with negligible (less than 2%) renal excretion. Recovery of parent Lapatinib in feces accounts for a median of 27% (range 3% to 67%) of an oral dose.

INDICATIONS

Lapatinib is indicated in combination with:

- Capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress human epidermal growth factor receptor 2 (HER2) and who have received prior therapy including an Anthracycline, a Taxane, and Trastuzumab.

Limitations of Use: Patients should have disease progression on Trastuzumab prior to initiation of treatment with Lapatinib in combination with Capecitabine.

- Letrozole for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated.

Lapatinib in combination with an aromatase inhibitor has not been compared to a Trastuzumab-containing chemotherapy regimen for the treatment of metastatic breast cancer.

DOSAGE AND ADMINISTRATION

Recommended Dosing:

HER2-Positive Metastatic Breast Cancer: The recommended dose of Lapatinib is 1,250 mg given orally once daily on Days 1-21 continuously in combination with Capecitabine 2,000 mg/m2/day (administered orally in 2 doses approximately 12 hours apart) on Days 1-14 in a repeating 21-day cycle. Lapatinib should be taken at least one hour before or one hour after a meal. The dose of Lapatinib should be once daily (5 tablets administered all at once); dividing the daily dose is not recommended.

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.

Hormone Receptor-Positive, HER2-Positive Metastatic Breast Cancer: The recommended dose of Lapatinib is 1,500 mg given orally once daily continuously in combination with Letrozole. When coadministered with Lapatinib, the recommended dose of Letrozole is 2.5 mg once daily. Lapatinib should be taken at least one hour before or one hour after a meal. The dose of Lapatinib should be once daily (6 tablets administered all at once); dividing the daily dose is not recommended.

Dose Modification Guidelines:

Cardiac Events: Lapatinib should be discontinued in patients with a decreased left ventricular ejection fraction (LVEF) that is Grade 2 or greater by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v3.0), and in patients with an LVEF that drops below the institution's lower limit of normal (LLN) and Adverse Reactions (6.1)]. Lapatinib in combination with Capecitabine may be restarted at a reduced dose (1,000 mg/day) and in combination with Letrozole may be restarted at a reduced dose of 1,250 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 dose of Lapatinib reduced. A dose reduction from 1,250 mg/day to 750 mg/day (HER2-positive metastatic breast cancer indication) or from 1,500 mg/day to 1,000 mg/day (hormone receptor-positive, HER2-positive breast cancer indication) 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 are no clinical data with this dose adjustment in patients with severe hepatic impairment.

Diarrhea: Lapatinib should be interrupted in patients with diarrhea which is NCI CTCAE Grade 3 or Grade 1 or 2 with complicating features (moderate to severe abdominal cramping, nausea or vomiting greater than or equal to NCI CTCAE Grade 2, decreased performance status, fever, sepsis, neutropenia, frank bleeding, or dehydration). Lapatinib may be reintroduced at a lower dose (reduced from 1,250 mg/day to 1,000 mg/day or from 1,500 mg/day to 1,250 mg/day) when diarrhea resolves to Grade 1 or less. TYKERB should be permanently discontinued in patients with diarrhea which is NCI CTCAE Grade 4.

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.

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 (HER2-positive metastatic breast cancer indication) or from 1,500 mg/day up to 5,500 mg/day (hormone receptor-positive, HER2-positive breast cancer indication) 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.

Other Toxicities: Discontinuation or interruption of dosing with Lapatinib may be considered when patients develop greater than or equal to Grade 2 NCI CTCAE toxicity, and can be restarted at the standard dose of 1,250 or 1,500 mg/day when the toxicity improves to Grade 1 or less. If the toxicity recurs, then Lapatinib in combination with Capecitabine should be restarted at a lower dose (1,000 mg/day) and in combination with Letrozole should be restarted at a lower dose of 1,250 mg/day. Or as directed by the registered physician.

ADVERSE EFFECTS

The most common adverse reactions during treatment with Lapatinib plus Capecitabine were diarrhea, palmar-plantar erythrodysesthesia, nausea, rash, vomiting, and fatigue. The most common adverse reactions during treatment with Lapatinib plus Letrozole were diarrhea, rash, nausea, and fatigue.

CONTRAINDICATIONS

Lapatinib is contraindicated in patients with known severe hypersensitivity (e.g., anaphylaxis) to this product or any of its components.

DRUG INTERACTIONS

Effects of Lapatinib on Drug-Metabolizing Enzymes and Drug Transport Systems: Lapatinib inhibits CYP3A4, CYP2C8, and P-glycoprotein (P-gp, ABCB1) in vitro at clinically relevant concentrations and is a weak inhibitor of CYP3A4 in vivo. Caution should be exercised and dose reduction of the concomitant substrate drug should be considered when dosing Lapatinib concurrently with medications with narrow therapeutic windows that are substrates of CYP3A4, CYP2C8, or P-gp. Lapatinib did not significantly inhibit the following enzymes in human liver microsomes: CYP1A2, CYP2C9, CYP2C19, and CYP2D6 or UGT enzymes in vitro, however, the clinical significance is unknown.

Midazolam: Following coadministration of Lapatinib and Midazolam (CYP3A4 substrate), 24-hour systemic exposure (AUC) of orally administered Midazolam increased 45%, while 24-hour AUC of intravenously administered Midazolam increased 22%.

Paclitaxel: In cancer patients receiving Lapatinib and Paclitaxel (CYP2C8 and P-gp substrate), 24-hour systemic exposure (AUC) of Paclitaxel was increased 23%. This increase in Paclitaxel exposure may have been underestimated from the in vivo evaluation due to study design limitations.

Digoxin: Following coadministration of Lapatinib and Digoxin (P-gp substrate), systemic AUC of an oral Digoxin dose increased approximately 2.8-fold. Serum Digoxin concentrations should be monitored prior to initiation of Lapatinib and throughout coadministration. If Digoxin serum concentration is greater than 1.2 ng/mL, the Digoxin dose should be reduced by half.

Drugs That Inhibit or Induce Cytochrome P450 3A4 Enzymes: Lapatinib undergoes extensive metabolism by CYP3A4, and concomitant administration of strong inhibitors or inducers of CYP3A4 alter Lapatinib concentrations significantly. Dose adjustment of Lapatinib should be considered for patients who must receive concomitant strong inhibitors or concomitant strong inducers of CYP3A4 enzymes.

Ketoconazole: In healthy subjects receiving Ketoconazole, a CYP3A4 inhibitor, at 200 mg twice daily for 7 days, systemic exposure (AUC) to Lapatinib was increased to approximately 3.6-fold of control and half-life increased to 1.7-fold of control.

Carbamazepine: In healthy subjects receiving the CYP3A4 inducer, Carbamazepine, at 100 mg twice daily for 3 days and 200 mg twice daily for 17 days, systemic exposure (AUC) to Lapatinib was decreased approximately 72%.

Drugs That Inhibit Drug Transport Systems: Lapatinib is a substrate of the efflux transporter P-glycoprotein (P-gp, ABCB1). If Lapatinib is administered with drugs that inhibit P-gp, increased concentrations of Lapatinib are likely, and caution should be exercised.

Acid-Reducing Agents: The aqueous solubility of Lapatinib is pH dependent, with higher pH resulting in lower solubility. However, Esomeprazole, a proton pump inhibitor, administered at a dose of 40 mg once daily for 7 days, did not result in a clinically meaningful reduction in Lapatinib steady-state exposure.

PRECAUTIONS

Decreased Left Ventricular Ejection Fraction: Lapatinib has been reported to decrease LVEF. In clinical trials, the majority (greater than 57%) of LVEF decreases occurred within the first 12 weeks of treatment; however, data on longterm exposure are limited. Caution should be taken if Lapatinib is to be administered to patients with conditions that could impair left ventricular function. LVEF should be evaluated in all patients prior to initiation of treatment with Lapatinib 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 Lapatinib to ensure that LVEF does not decline below the institution's normal limits.

Hepatotoxicity: Hepatotoxicity [alanine aminotransferase, (ALT) or aspartate aminotransferase, (AST) greater than 3 times the upper limit of normal (ULN) and total bilirubin greater than 2 times the ULN] has been observed in clinical trials (less than 1% of patients) and postmarketing experience. The hepatotoxicity may be severe and deaths have been reported. Causality of the deaths is uncertain. The hepatotoxicity may occur days to several 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, therapy with Lapatinib should be discontinued and patients should not be retreated with Lapatinib.

Patients With Severe Hepatic Impairment: If Lapatinib is to be administered to patients with severe preexisting hepatic impairment, dose reduction should be considered. In patients who develop severe hepatotoxicity while on therapy, Lapatinib should be discontinued and patients should not be retreated with Lapatinib.

Diarrhea: Diarrhea has been reported during treatment with Lapatinib. The diarrhea may be severe, and deaths have been reported. Diarrhea generally occurs early during treatment with Lapatinib, with almost half of those patients with diarrhea first experiencing it within 6 days. This usually lasts 4 to 5 days. Lapatinib -induced diarrhea is usually low-grade, with severe diarrhea of NCI CTCAE Grades 3 and 4 occurring in less than 10% and less than 1% of patients, respectively. Early identification and intervention is critical for the optimal management of diarrhea. Patients should be instructed to report any change in bowel patterns immediately. Prompt treatment of diarrhea with antidiarrheal agents (such as Loperamide) after the first unformed stool is recommended. Severe cases of diarrhea may require administration of oral or intravenous electrolytes and fluids, use of antibiotics such as Fluoroquinolones (especially if diarrhea is persistent beyond 24 hours, there is fever, or Grade 3 or 4 neutropenia), and interruption or discontinuation of therapy with Lapatinib.

Interstitial Lung Disease/Pneumonitis: Lapatinib has been associated with interstitial lung disease and pneumonitis in monotherapy or in combination with other chemotherapies. Patients should be monitored for pulmonary symptoms indicative of interstitial lung disease or pneumonitis. Lapatinib should be discontinued in patients who experience pulmonary symptoms indicative of interstitial lung disease/pneumonitis which are greater than or equal to Grade 3 (NCI CTCAE v3.0).

QT Prolongation: A concentration-dependent QT prolongation has been associated with Lapatinib. Monitor patients who have or may develop prolongation of QTc during treatment with Lapatinib. These conditions include patients with hypokalemia or hypomagnesemia, with congenital long QT syndrome, patients taking antiarrhythmic medicines or other medicinal products with known risk for QT prolongation/ Torsades de Pointes (TdP), and cumulative high-dose anthracycline therapy. Correct hypokalemia or hypomagnesemia prior to Lapatinib administration.

Severe Cutaneous Reactions: Severe cutaneous reactions have been reported with Lapatinib. If life-threatening reactions such as erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis (e.g., progressive skin rash often with blisters or mucosal lesions) are suspected, discontinue treatment with Lapatinib.

Pediatric Use: The safety and effectiveness of Lapatinib in pediatric patients have not been established.

Use in Pregnancy: Based on findings in animal studies and its mechanism of action, Lapatinib can cause fetal harm when administered to a pregnant woman. There are no available human data to inform of the drug associated risks. Advise pregnant women and females of reproductive potential of the potential risk to the fetus.

Use in Lactation: There are no data on the presence of Lapatinib in human milk, or its effects on the breastfed child, or milk production. Because of the potential for serious adverse reactions in a breastfed child from Lapatinib, advise lactating women not to breastfeed during treatment with Lapatinib and for 1 week after the last dose.

OVERDOSE

There is no known antidote for overdoses of Lapatinib. The maximum oral doses of Lapatinib that have been administered in clinical trials are 1,800 mg once daily. More frequent ingestion of Lapatinib could result in serum concentrations exceeding those observed in clinical trials and could result in increased toxicity. Therefore, missed doses should not be replaced and dosing should resume with the next scheduled daily dose. Asymptomatic and symptomatic cases of overdose have been reported. The doses ranged from 2,500 to 9,000 mg daily and where reported, the duration varied between 1 and 17 days. Symptoms observed include Lapatinib -associated events and in some cases sore scalp, sinus tachycardia (with otherwise normal ECG), and/or mucosal inflammation. Because Lapatinib is not significantly renally excreted and is highly bound to plasma proteins, hemodialysis would not be expected to be an effective method to enhance the elimination of Lapatinib. Treatment of overdose with Lapatinib should consist of general supportive measures.

PHARMACEUTICAL INFORMATION

Storage: Store below 30°C in a dry place. Keep out of the reach of children.

Packing: Each container contains 30 tablets in a box.