

Lapacent™ 250

Lapatinib 250 mg

Presentation

Lapacent™ 250: Each tablet contains Lapatinib ditosylate monohydrate INN equivalent to Lapatinib 250 mg

Description

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 \geq 300 minutes. Lapatinib inhibits ErbB-driven tumor cell growth in vitro and in various animal models.

Hormone receptor-positive breast cancer cells (with ER [Estrogen Receptor] and/or PgR [Progesterone Receptor]) that co express the HER2 tend to be resistant to established endocrine therapies. Similarly, hormone receptor-positive breast cancer cells that initially lack EGFR or HER2, up regulate these receptor proteins as the tumor becomes resistant to endocrine therapy.

Indications and Uses

Lapatinib, 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. Limitation 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 Administrations

The recommended dosage of Lapatinib for advanced or metastatic breast cancer is 1,250 mg (5 tablets) 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.

The recommended dose of Lapatinib for hormone receptor-positive, HER2positive metastatic breast cancer is 1,500 mg (6 tablets) given orally once daily continuously in combination with Letrozole. When Lapatinib is co administered with Letrozole, 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. However, Capecitabine should be taken with food or within 30 minutes after food.
- Lapatinib should be taken once daily. Do not divide daily doses of Lapatinib
- Modify dose for cardiac and other toxicities, severe hepatic impairment, diarrhea, and CYP3A4 drug interactions

Side-effects

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

Contraindications

Known severe hypersensitivity (e.g., anaphylaxis) to this product or any of its components

Precautions

- Decreases in left ventricular ejection fraction (LVEF) have been reported. Normal LVEF should be confirmed before starting Lapatinib and continue evaluations during treatment
- Lapatinib has been associated with hepatotoxicity. Liver function tests should be monitored before initiation of treatment, every 4 to 6 weeks during treatment, and as clinically indicated. If patients experience severe changes in liver function tests Lapatinib should be discontinued and should not be restarted
- Dose reduction in patients with severe hepatic impairment should be considered
- Diarrhea, including severe diarrhea, has been reported during treatment. Should be managed with anti-diarrheal agents, and fluids and electrolytes should be replaced if severe
- Lapatinib has been associated with interstitial lung disease and pneumonitis. Lapatinib should be discontinued if patients experience severe pulmonary symptoms

- Lapatinib may prolong the QT interval in some patients. ECG and electrolyte monitoring should be considered.
- Severe cutaneous reactions have been reported. Lapatinib should be discontinued if life-threatening reactions are suspected
- Fetal harm can occur when administered to a pregnant woman. Women should be advised not to become pregnant when taking Lapatinib

Pregnancy and Lactation

Pregnancy Category D

Based on animal data, Lapatinib can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies with Lapatinib in pregnant women. Women should be advised not to become pregnant when taking Lapatinib. 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.

It is not known whether Lapatinib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Lapatinib, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

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

Geriatric Use

No overall differences in safety or effectiveness were observed between elderly subjects and younger subjects, and 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.

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.

Midazolam: Following co administration 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%.

Digoxin: Following co administration 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 co administration. If Digoxin serum concentration is >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.

Commercial Pack

Lapacent™ 250: Each box contains 3 blister strips of 12 tablets.

Lapacent™ 250: Each bottle contains 30 tablets.