LEPTA 250mg Tablet

(L a p a t i n i b)

لیپٹا ۲۵۰ ملی گرام ٹیبلٹ

(لیپٹینیب)

COMPOSITION

Lepta Tablet 250mg

Each film coated tablet contains:

Lapatinib (as ditosylate monohydrate).....250mg

(Innovator's Specifications)

DESCRIPTION

Lapatinib is an anti-cancer drug for the treatment of breast cancer and other solid tumors. It is present as the monohydrate of the ditosylate salt. It is used in patients with advanced metastatic breast cancer in conjunction with the chemotherapy drug Capecitabine.

MECHANISM OF ACTION

Lapatinib is human epidermal growth factor receptor type 2 (HER2/ERBB2) and epidermal growth factor receptor (HER1/EGFR/ERBB1) tyrosine kinases inhibitor. It binds to the intracellular phosphorylation domain to prevent receptor auto-phosphorylation upon ligand binding.

INDICATIONS

LEPTA 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 LEPTA 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.

LEPTA 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

HER2-Positive Metastatic Breast Cancer

The recommended dose of LEPTA 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. LEPTA should be taken at least one hour before or one hour after a meal. The dose of LEPTA 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 LEPTA is 1,500 mg given orally once daily continuously in combination with letrozole. When co-administered with LEPTA, the recommended dose of letrozole is 2.5 mg once daily. LEPTA should be taken at least one hour before or one hour after a meal. The dose of LEPTA should be once daily (6 tablets administered all at once); dividing the daily dose is not recommended.

Cardiac Events

LEPTA 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). LEPTA 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 LEPTA 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

LEPTA 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). LEPTA 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. LEPTA 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 co-administered, 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 LEPTA 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 co-administered a strong CYP3A4 inducer, based on pharmacokinetic studies, the dose of LEPTA 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 LEPTA 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 LEPTA dose should be reduced to the indicated dose.

Other Toxicities

Discontinuation or interruption of dosing with LEPTA 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 LEPTA 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.

PHARMACOKINETICS

Absorption

Absorption following oral administration of LEPTA 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 LEPTA 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 LEPTA 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.

Effects of Age, Gender, or Race

WARNINGS AND PRECAUTIONS

Decreased Left Ventricular Ejection Fraction

LEPTA 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 long-term exposure are limited. Caution should be taken if LEPTA 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 LEPTA 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 LEPTA 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 post-marketing 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 LEPTA should be discontinued and patients should not be retreated with LEPTA.

Patients with Severe Hepatic Impairment

If LEPTA 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, LEPTA should be discontinued and patients should not be retreated with LEPTA.

Diarrhea

Diarrhea has been reported during treatment with LEPTA. The diarrhea may be severe, and deaths have been reported. Diarrhea generally occurs early during treatment with LEPTA, with almost half of those patients with diarrhea first experiencing it within 6 days. This usually lasts 4 to 5 days. LEPTA-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 LEPTA.

Interstitial Lung Disease/Pneumonitis

LEPTA 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. LEPTA 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 LEPTA. Monitor patients who have or may develop prolongation of QTc during treatment with LEPTA. 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 LEPTA administration.

Severe Cutaneous Reactions

Severe cutaneous reactions have been reported with LEPTA. 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 LEPTA.

Embryo-Fetal Toxicity

Based on its mechanism of action and findings in animal studies, LEPTA can cause fetal harm when administered to a pregnant woman. In animal reproductive studies, administration of lapatinib to pregnant rats during the period of organogenesis and through lactation led to death of offspring within the first 4 days after birth at maternal exposures that were ≥ 3.3 times the human clinical exposure based on AUC following 1250 mg dose of lapatinib plus capecitabine. When administered to pregnant animals during the period of organogenesis, lapatinib caused fetal anomalies (rats) or abortions (rabbits) at maternally toxic doses

(with maternal exposures approximately 6.4 and 0.2 times, respectively, the human clinical exposure based on AUC following 1250 mg dose of lapatinib plus capecitabine).
Advise pregnant women and females of reproductive potential of the potential risk to the fetus. Verify the pregnancy status of females of reproductive potential prior to initiation of LEPTA. Advise females of reproductive potential to use effective contraception during treatment with LEPTA and for 1 week after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with LEPTA and for 1 week after the last dose.

Patient Counseling Information

Advise the patient to read the FDA-approved patient labeling (PATIENT INFORMATION).
Inform patients of the following:

Decreased Left Ventricular Ejection Fraction (LVEF)

LEPTA has been reported to decrease left ventricular ejection fraction which may result in shortness of breath, palpitations, and/or fatigue [see WARNINGS AND PRECAUTIONS]. Advise patients to inform their healthcare provider if they develop these symptoms while taking LEPTA.

Hepatotoxicity and Hepatic Impairment

Periodic laboratory testing will be performed while taking LEPTA. Advise patients to report signs and symptoms of liver dysfunction to their healthcare provider right away.

Diarrhea

LEPTA often causes diarrhea which may be severe in some cases. Instruct patients on how to manage and/or prevent diarrhea and to inform their healthcare provider immediately if there is any change in bowel patterns or severe diarrhea occurs during treatment with LEPTA.

Interstitial Lung Disease/Pneumonitis

Advise patients to report pulmonary signs or symptoms indicative of ILD or pneumonitis.

Severe Cutaneous Reactions

Advise patients to report severe cutaneous reactions to their healthcare provider if they develop these symptoms while taking LEPTA.

Drug and Food Interactions

LEPTA may interact with many drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products.
LEPTA may interact with grapefruit. Advise patients not to take LEPTA with grapefruit products.

Dosing Administration

LEPTA should be taken at least one hour before or one hour after a meal, in contrast to capecitabine which should be taken with food or within 30 minutes after food. The dose of LEPTA should be taken once daily. Dividing the daily dose is not recommended.

Embryo-Fetal Toxicity

Inform female patients of the risk to a fetus and potential loss of the pregnancy. Advise females to inform their healthcare provider if they are pregnant or become pregnant.
Advise females of reproductive potential to use effective contraception during treatment with LEPTA and for 1 week after the last dose.
Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week following the last dose.

Lactation

Advise patients not to breastfeed during treatment and for 1 week after the last dose of LEPTA

SIDE EFFECTS

Lepta (lapatinib) is a cancer medication used together with another medicine called capecitabine to treat a certain type of advanced breast cancer that has spread to other parts of the body, and is usually given after other cancer medications have been tried without successful treatment of symptoms. Common side effects of Lepta include:
LEPTA may cause serious side effects, including:

- Heart problems, including decreased pumping of blood from the heart and an abnormal heartbeat. Signs and symptoms of an abnormal heartbeat include feeling like your heart is pounding or racing, dizziness, tiredness, feeling lightheaded and shortness of breath.
- Liver problems. Liver problems can be severe and deaths have happened. Signs and symptoms of liver problems include itching, yellowing of your skin or the white part of your eyes, dark urine, and pain or discomfort in the right upper stomach area.
- Diarrhea. Diarrhea is common with LEPTA and may sometimes be severe. Severe diarrhea can cause loss of body fluid (dehydration) and some deaths have happened. Call your healthcare provider right away if you have a change in bowel pattern or if you have severe diarrhea. Follow your healthcare provider's instructions for what to do to help prevent or treat diarrhea.
- Lung problems. Symptoms of a lung problem with LEPTA include a cough that will not go away or shortness of breath.
- Severe skin reactions. LEPTA may cause severe skin reactions. Tell your healthcare provider right away if you develop a skin rash, red skin, blistering of the lips, eyes, or mouth, peeling of the skin, fever, or any combination of these. As severe skin reactions can be life-threatening, your healthcare provider may tell you to stop taking LEPTA.

Common side effects of LEPTA in combination with capecitabine or letrozole include diarrhea, red, painful hands and feet, nausea, rash, vomiting, inflamed mouth, digestive tract and airways, mouth sores, headache, unusual hair loss or thinning, shortness of breath, dry skin, itching, tiredness, painful arms, legs and back, loss of appetite, indigestion, nose bleeds, nail disorders such as nail bed changes, nail pain, infection and swelling of the cuticles, and difficulty sleeping.
Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of LEPTA. For more information, ask your healthcare provider or pharmacist.
Lepta is not recommended for use during pregnancy. It may harm a fetus. Consult your doctor to discuss using at least 2 forms of birth control (e.g., condoms, birth control pills) while taking this medication. If you become pregnant or think you may be pregnant, tell your doctor. It is unknown if this drug passes into breast milk. Because of the possible risk to the infant, breastfeeding while using this drug is not recommended.

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 LEPTA 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 co-administration of LEPTA 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 LEPTA 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 co-administration of LEPTA 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 LEPTA and throughout co-administration. 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 (see Ketoconazole and Carbamazepine sections, below). Dose adjustment of LEPTA 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 LEPTA is administered with drugs that inhibit P-gp, increased concentrations of lapatinib are likely, and caution should be exercised. 7.4 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.

OVERDOSE

There is no known antidote for overdoses of LEPTA. The maximum oral doses of lapatinib that have been administered in clinical trials are 1,800 mg once daily. More frequent ingestion of LEPTA 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 LEPTA-associated events and in some cases sore scalp, sinus tachycardia (with otherwise normal ECG), and/or mucosal inflammation.
Because LEPTA 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 LEPTA should consist of general supportive measures.

CONTRAINDICATIONS

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

STORAGE & INSTRUCTIONS

Store between 20-25°C.
Protect from heat, sunlight and moisture.
Keep away from the reach of children.
To be sold on the prescription of a registered oncologist or on demand from cancer hospitals and institutions only.

HOW SUPPLIED

Lepta Tablet 250mg
70 tablets.

خوراک وطریقہ استعمال:

سرطان کے ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

دوا کو ۲۰-۲۵ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔

دوا کو دھوپ، گرمی اور نمی سے محفوظ رکھیں۔

بچوں کی پہنچ سے دور رکھیں۔

صرف مستند انکولوجسٹ یا کینسر ہسپتال کے نسخہ پر فروخت کریں۔

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PHARMASOL
PRIVATE LIMITED
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Lahore, Pakistan.