Lapatinib Tablets I.P. 250 mg

Herduo®

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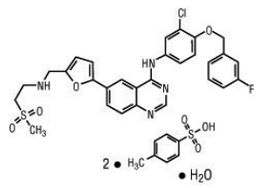
WARNING: HEPATOTOXICITY

See full prescribing information for complete boxed warning

Hepatotoxicity has been observed. The hepatotoxicity may be severe and deaths have been reported. Causality of the deaths is uncertain.

DESCRIPTION

Lapatinib is a small molecule and a member of the 4-anilinoquinazoline class of kinase inhibitors. It is present as the monohydrate of the ditosylate salt, with chemical name N-(3-chloro-4-{[(3-fluorophenyl)methyl]oxy}phenyl)-6-[5-({[2(methylsulfonyl)ethyl]amino} methyl)-2-furanyl]-4-quinazolinamine bis(4-methylbenzenesulfonate) monohydrate. It has the molecular formula $C_{29}H_{26}ClFN_4O_4S$ $(C_7H_8O_3S)_2$ H_2O and a molecular weight of 943.5. Lapatinib ditosylate monohydrate has the following chemical structure:



Lapatinib is a yellow solid, and its solubility in water is 0.007 mg/mL and in 0.1N HCl is 0.001 mg/mL at 25°C.

Each 250 mg tablet of HERDUO contains 405 mg of lapatinib ditosylate monohydrate, equivalent to 398 mg of lapatinib ditosylate or 250 mg lapatinib free base.

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 K_i^{app} values of 3nM and 13nM, respectively) with a dissociation half-life of ≥ 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-crossresistance 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 hour). Peak plasma concentrations (C_{max}) 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) values of C_{max} were 2.43 mcg/mL (1.57 to 3.77 mcg/mL) and AUC were 36.2 mcg.hr/mL (23.4 to 56 mcg.hr/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 (C_{max} approximately 2.5- and 3-fold higher) when administered with a low fat (5% fat-500 calories) or with a high fat (50% fat-1,000 calories) meal, respectively.

Distribution: Lapatinib is highly bound (>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 in-vitro to inhibit these efflux transporters, as well as the hepatic uptake transporter OATP 1B1, 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 (<2%) renal excretion. Recovery of parent lapatinib in feces accounts for a median of 27% (range 3 to 67%) of an oral dose.

DRUG INTERACTIONS

Effects of Lapatinib on Drug Metabolizing Enzymes and Drug Transport Systems

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 lapatinib concurrently with medications with narrow therapeutic windows that are substrates of CYP3A4 or CYP2C8. 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.

Lapatinib inhibits human P-glycoprotein. If lapatinib is administered with drugs that are substrates of P-gp, increased concentrations of the substrate drug are likely, and caution should be exercised.

Paclitaxel: In cancer patients receiving lapatinib and the CYP2C8 substrate paclitaxel, 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.

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 1100 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.

INDICATIONS AND USAGE

HERDUO is indicated in combination with:

- Capecitabine is indicated for the treatment of patients with advanced or metastatic breast cancer whose tumor overexpress HER2+/neu and who have received prior therapy including trastuzumab.
- Letrozole is indicated for the treatment of postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated.
- Trastuzumab is indicated for the treatment of patients with hormone receptor - negative metastatic breast cancer whose tumors overexpress HER2/neu (ErbB2) and who have progressed on prior trastuzumab therapy in combination with chemotherapy in the metastatic setting.

DOSAGE AND ADMINISTRATION

Recommended Dosing

HER2 Positive Metastatic Breast Cancer: The recommended dose of HERDUO 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. HERDUO should be taken at least one hour before or one hour after a meal. The dose of HERDUO 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 HERDUO is 1,500 mg given orally once daily continuously in combination with letrozole. When coadministered with HERDUO, the recommended dose of letrozole is 2.5 mg once daily. HERDUO should be taken at least one hour before or one hour after a meal. The dose of HERDUO 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) and in patients with an LVEF that drops below the institution's lower limit of normal. 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.

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 Grade 2 NCI CTCAE toxicity and can be restarted at 1,250 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.

DOSAGE FORMS AND STRENGTHS

250 mg tablets

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Decreased Left Ventricular Ejection Fraction

Lapatinib has been reported to decrease LVEF. In clinical trials, the majority (>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 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 (ALT or AST >3 times the upper limit of normal and total bilirubin >2 times the upper limit of normal) has been observed. 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 pre-existing 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, including severe diarrhea, has been reported during treatment with lapatinib. 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 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 Grade 3 (NCI CTCAE).

QT Prolongation

QT prolongation was observed in an uncontrolled, open-label dose escalation study of lapatinib in advanced cancer patients. 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.

Use in Pregnancy

Lapatinib can cause fetal harm when administered to a pregnant woman. Based on findings in animals, lapatinib is expected to result in adverse reproductive effects. Lapatinib administered to rats during organogenesis and through lactation led to death of offspring within the first 4 days after birth.

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.

ADVERSE REACTIONS

The most common adverse reactions (>20%) during therapy with lapatinib plus capecitabine were gastrointestinal (diarrhea, nausea, and vomiting), dermatologic (palmar-plantar erythrodysesthesia and rash), and fatigue. Diarrhea was the most common adverse reaction.

The most common Grade 3 and 4 adverse reactions (NCI CTCAE v3) were diarrhea and palmar-plantar erythrodysesthesia.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
allergy/immunology	anaphylaxis (<1%)
blood/bone marrow/ febrile neutropenia	no information found
cardiovascular (arrhythmia)	***QT/QTc prolongation***
cardiovascular (general)	***LVEF reduction*** (1-3%)
constitutional symptoms	***fatigue*** (10-20%, severe <3%)
dermatology/skin	dry skin (3%)
	hair disorder (3%)
	nail disorders, including paronychia (<1%)
	pruritus/urticaria (3-18%)
	rash (18-43%, severe 1-4%)
	skin disorder, undefined (1%)
gastrointestinal	emetogenic potential: low
	anorexia (16%, severe <1%)
	diarrhea (36-59%, severe 3-10%)
	nausea (10-20%, severe 1-2%)
	vomiting (13%, severe 2%)
hepatobiliary/pancreas	hepatoxicity (<1%)
infection	skin infection (<1%)
metabolic/laboratory	ALT or AST > 3 times ULN (<1%)
	total bilirubin > 1.5 times ULN (<1%)
pain	back pain (11%, severe 3%)
pulmonary	dyspnea (14%, severe <5%)
	interstitial lung disease (<1%); discontinue if symptoms grade 3 or greater
	pneumonitis (<1%); discontinue if symptoms grade 3 or greater

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category D

Based on findings in animals, lapatinib can cause fetal harm when administered to a pregnant woman. Lapatinib administered to rats during organogenesis and through lactation led to death of offspring within the first 4 days after birth. When administered to pregnant animals during the period of organogenesis, lapatinib caused fetal anomalies (rats) or abortions (rabbits) at maternally toxic doses. 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.

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 following 1,250 mg dose of lapatinib plus capecitabine), 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 following 1,250 mg dose of lapatinib plus capecitabine). 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 following 1,250 mg dose of lapatinib plus capecitabine) and abortions at 120 mg/kg/day. Maternal toxicity was associated with decreased fetal body weights and minor skeletal variations.

Nursing Mothers

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

Of the total number of metastatic breast cancer patients in clinical studies of lapatinib in combination with capecitabine (N = 198), 17% were 65 years of age and older, and 1% were 75 years of age and older. Of the total number of hormone receptor positive, HER2 positive metastatic breast cancer patients in clinical studies of lapatinib in combination with letrozole (N = 642), 44% were 65 years of age and older, and 12% were 75 years of age and older. 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.

Renal Impairment

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

Hepatic Impairment

The pharmacokinetics of lapatinib were examined in subjects with pre-existing moderate or severe hepatic impairment (Child-Pugh Class B/C, respectively) and in healthy control subjects. Systemic exposure (AUC) to lapatinib after a single oral 100-mg dose increased approximately 14% and 63% in subjects with moderate and severe pre-existing 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 pre-existing hepatic impairment. In patients who develop severe hepatotoxicity while on therapy, lapatinib should be discontinued and patients should not be retreated with lapatinib.

OVERDOSAGE

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.

There has been a report of one patient who took 3,000 mg of lapatinib for 10 days. This patient had Grade 3 diarrhea and vomiting on Day 10. The event resolved following IV hydration and interruption of treatment with lapatinib and letrozole.

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.

HOW SUPPLIED

The 250 mg tablets of HERDUO are available in bottle of 30 tablets & bottle of 150 tablets. One bottle and package insert housed in a carton.

STORAGE

Store below 30°C and protected from light

References

1. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022059s007lbl.pdf
2. http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Lapatinib_monograph_1Oct2015.pdf

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