Doses are also adjusted in hepatic impairment (see Administration in Hepatic Impairment, below).

Use of strong inhibitors of CYP3A4 should be avoided with ixabepilone. If no alternative is available, a dose reduction of ixabepilone to 20 mg/m^2 should be considered. Once the inhibitor is stopped, a washout period of about 1 week should be allowed before the dose of ixabepilone is increased back to the original dose.

◊ References.

1. Gianni L. Ixabepilone and the narrow path to developing new cytotoxic drugs. *J Clin Oncol* 2007; **25:** 3389–91.
2. Fornier MN. Ixabepilone, first in a new class of antineoplastic agents: the natural epothilones and their analogues. *Clin Breast Cancer* 2007; **7:** 757–63.
3. Thomas ES, *et al.* Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. *J Clin Oncol* 2007; **25:** 5210–17.

Administration in hepatic impairment. Therapy with ixabepilone and capecitabine *combination therapy* is contra-indicated in patients with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 2.5 times the upper limit of normal (ULN), or in those with bilirubin greater than the ULN. Patients with values equal to or below these figures may be given the standard dose of ixabepilone.

In *monotherapy*, the following doses of ixabepilone may be given:

- mild; AST and ALT equal to or less than 2.5 times the ULN, and bilirubin equal to or less than the ULN: 40 mg/m^2 *or* AST or ALT equal to or less than 10 times the ULN and bilirubin equal to or less than 1.5 times the ULN: 32 mg/m^2
- moderate; AST and ALT equal to or less than 10 times the ULN and bilirubin greater than 1.5 times the ULN, but equal to or less than 3 times the ULN: patients should be started at 20 mg/m^2, and the dosage in subsequent cycles escalated up to, but not exceeding, 30 mg/m^2 if tolerated
- severe; AST or ALT greater than 10 times the ULN or bilirubin greater than 3 times the ULN: not recommended

Data are limited for patients with a baseline AST or ALT greater than 5 times the ULN.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Ixempra.

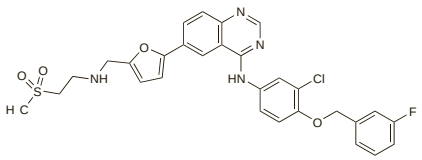
Lapatinib Tosilate *(rINNM)*

GW-572016F; Lapatinib Ditosylate *(USAN)*; Lapatinib, Tosilate de; Lapatinibi Tosilas; Tosilato de lapatinib. *N*-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methylsulfonyl)ethyl]amino}methyl)furan-2-yl]quinazolin-4-amine bis(4-methylbenzenesulfonate) monohydrate.

Лапатиниба Тозилат

$C_{29}H_{26}ClFN_4O_4S,2C_7H_8O_3S,H_2O$ = 943.5.

CAS — 231277-92-2 (lapatinib); 388082-78-8 (lapatinib tosilate).



(lapatinib)

Adverse Effects, Treatment, and Precautions

The most common adverse effects of lapatinib tosilate are gastrointestinal disturbances, dermatological reactions such as palmar-plantar erythrodysesthesia and rash, and fatigue. Diarrhoea may be severe and dose-limiting. Decreases in left ventricular ejection fraction (LVEF) have been reported with lapatinib, usually within the first 9 weeks of treatment. LVEF should be evaluated in all patients before therapy is started, and periodically evaluated during treatment. Prolongation of the QT interval has also been reported, and lapatinib should be given with caution to those patients with relevant risk factors such as hypokalaemia or hypomagnesaemia, congenital QT prolongation, use of antiarrhythmics, or cumulative high-dose anthracycline therapy. Other reported adverse effects include stomatitis, mucosal inflammation, pain in extremities, back pain, dyspnoea, and insomnia. Lapatinib should be given with caution in severe hepatic impairment; doses may need to be reduced.

Interactions

Lapatinib tosilate undergoes extensive metabolism by cytochrome P450 isoenzyme CYP3A4. Inhibitors of CYP3A4, such as ketoconazole, can increase exposure to lapatinib. Conversely, CYP3A4 inducers, such as carbamazepine, can reduce exposure to lapatinib. Use of lapatinib with strong inhibitors or inducers of CYP3A4 should be avoided; if they are to be given together, dose adjustments may be required (see Uses and Administration, below). Grapefruit juice may also increase plasma concentrations of lapatinib and should be avoided. *In vitro* studies indicate that lapatinib itself inhibits CYP3A4 and CYP2C8; it should be used cautiously with substrates of these isoenzymes that have a narrow therapeutic index.

Lapatinib is a substrate of P-glycoprotein and P-glycoprotein inhibitors can increase plasma concentrations of lapatinib. Lapatinib itself also inhibits human P-glycoprotein and may in turn increase plasma concentrations of drugs that are substrates of P-glycoprotein.

Pharmacokinetics

Absorption after an oral dose of lapatinib tosilate is variable and incomplete. Peak plasma concentrations occur after about 4 hours. Systemic exposure to lapatinib is increased when it is given with food. It is highly protein bound. Lapatinib undergoes extensive metabolism, mainly by cytochrome P450 isoenzymes CYP3A4 and CYP3A5; CYP2C19 and CYP2C8 account for some minor metabolism. The terminal half-life after a single dose has been reported to be about 14 hours; accumulation with repeated dosing indicates an effective half-life of 24 hours. About 27% and 14% of an oral dose is recovered in the faeces, as parent lapatinib and metabolites, respectively; renal excretion is negligible.

Uses and Administration

Lapatinib tosilate is a dual tyrosine kinase inhibitor directed against two members of the human epidermal growth factor receptor family, namely epidermal growth factor receptor (EGFR; ErbB1) and human epidermal receptor type 2 (HER2; ErbB2). Lapatinib is used with capecitabine (p.691) for the treatment of patients with advanced or metastatic breast cancer (p.661) whose tumours overexpress HER2, and who have had previous therapy including an anthracycline, a taxane, and trastuzumab.

Doses of lapatinib tosilate are expressed in terms of the base; lapatinib tosilate 405 mg is equivalent to about 250 mg of lapatinib.

The recommended dose of lapatinib is 1.25 g given orally once daily on days 1 to 21 of a 21-day cycle. Capecitabine is given at a dose of 2 g/m^2 daily (given orally in 2 doses about 12 hours apart) on days 1 to 14 of the cycle. Treatment may be continued until disease progression or unacceptable toxicity occurs. If a daily dose is missed, the next day's dose should not be doubled. Lapatinib is given at least one hour before or one hour after food.

Dosage should be reduced in patients with severe hepatic impairment (see Administration in Hepatic Impairment, below). Treatment with lapatinib should be stopped in patients who develop a decreased left ventricular ejection fraction (LVEF); however, patients may be restarted at a reduced dose of lapatinib 1 g daily after a minimum of 2 weeks if the LVEF recovers to normal and if the patient is asymptomatic. Lapatinib may need to be stopped or treatment interrupted if other severe toxicities develop. Patients can be restarted at the recommended dose when the toxicity improves. However, if toxicity recurs, lapatinib should be restarted at the lower dose of 1 g daily.

If use with potent inhibitors or inducers of cytochrome P450 isoenzyme CYP3A4 cannot be avoided, dose adjustments of lapatinib are considered necessary, based on pharmacokinetic studies. Lapatinib should be given at a dose of 500 mg daily when given with a potent CYP3A4 inhibitor; if the inhibitor is stopped, a washout period of about 1 week should be allowed before the lapatinib dose is increased to the usual recommended dose. When given with a potent inducer of this isoenzyme, the dose of lapatinib should be titrated gradually from 1.25 g daily up to 4.5 g daily, based on tolerability; if the inducer is stopped, the dose of lapatinib should be reduced to the usual recommended dose.

Lapatinib is also under investigation for the treatment of head and neck squamous cell carcinoma.

◊ References.

1. Nelson MH, Dolder CR. Lapatinib: a novel dual tyrosine kinase inhibitor with activity in solid tumors. *Ann Pharmacother* 2006; **40:** 261–9.
2. Moy B, Goss PE. Lapatinib: current status and future directions in breast cancer. *Oncologist* 2006; **11:** 1047–57.
3. Geyer CE, *et al.* Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 2006; **355:** 2733–43.
4. Montemurro F, *et al.* Lapatinib: a dual inhibitor of EGFR and HER2 tyrosine kinase activity. *Expert Opin Biol Ther* 2007; **7:** 257–68.
5. Ito Y, *et al.* Does lapatinib, a small-molecule tyrosine kinase inhibitor, constitute a breakthrough in the treatment of breast cancer? *Breast Cancer* 2007; **14:** 156–62.
6. Dhillon S, Wagstaff AJ. Lapatinib. *Drugs* 2007; **67:** 2101–8.

Administration in hepatic impairment. Systemic exposure to lapatinib after a single 100-mg oral dose increased by about 14% and 63% in subjects with moderate (Child-Pugh Class B) and severe (Child-Pugh Class C) hepatic impairment, when compared with healthy control subjects. Caution is advised when lapatinib is given to patients with severe hepatic impairment. Oral doses should be reduced to 750 mg daily. However, licensed product information warns that there are no clinical data with this dose adjustment in patients with severe hepatic impairment.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Tykerb; ***Fr.:*** Tyverb; ***Switz.:*** Tyverb; ***UK:*** Tyverb; ***USA:*** Tykerb.

Lenalidomide *(BAN, USAN, rINN)*

CC-5013; CDC-501; Lénalidomide; Lenalidomidum. 3-(4-Amino-1-oxo-1,3-dihydro-2*H*-isoindol-2-yl)piperidine-2,6-dione.

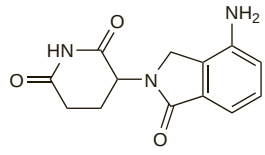
Леналидомид

$C_{13}H_{13}N_3O_3$ = 259.3.

CAS — 191732-72-6.

ATC — L04AX04.

ATC Vet — QL04AX04.



Adverse Effects, Treatment, and Precautions

Lenalidomide is associated with significant neutropenia and thrombocytopenia. Anaemia is also common. Patients may require dose reduction or therapy may need to be delayed or stopped. Full blood counts should be monitored weekly for the first 8 weeks of therapy, and monthly thereafter. There is also an increased risk of deep-vein thrombosis and pulmonary embolism with lenalidomide. Other adverse effects include gastrointestinal disturbances, pruritus, rash, and fatigue. Dyspnoea, muscle cramps, hypotension, tremor, hypoaesthesia, and infections such as pneumonia are common. Peripheral neuropathy has been reported, as have cases of hypothyroidism; thyroid function should be monitored. Cardiac disorders and hepatotoxicity have also been reported. Caution is advised in patients with renal impairment as lenalidomide is excreted via the kidneys.