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.

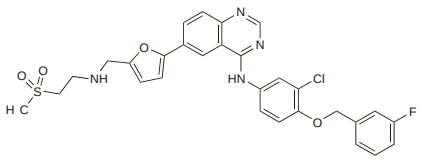
Lapatinib Tosilate *(rINNM)*

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.

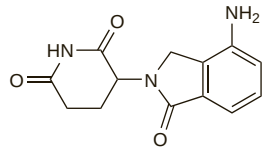
Леналидомид

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

Because of potential teratogenicity lenalidomide use is restricted in women of child-bearing potential, see also under Thalidomide, p.2397.

Interactions

Lenalidomide may increase peak plasma concentrations of digoxin. Epoetins or other drugs that increase the risk of thrombosis should be used with caution in patients taking lenalidomide.

Pharmacokinetics

Lenalidomide is rapidly absorbed with maximum plasma concentrations occurring between about 0.6 and 1.5 hours after an oral dose. Giving lenalidomide with food may reduce plasma concentrations but not the extent of absorption. Binding to plasma proteins is about 30%. About two-thirds of a dose is eliminated unchanged through the kidneys. The elimination half-life is about 3 hours after a 5 mg-dose; half-life increases with dose. Clearance decreases proportionally with renal function.

Uses and Administration

Lenalidomide is an analogue of thalidomide (p.2397) that has immunomodulatory and antiangiogenic properties. It is given orally for the treatment of patients with transfusion-dependent anaemia due to myelodysplastic syndromes (p.654) associated with certain abnormalities of chromosome 5 (deletion 5q abnormalities). The recommended initial dose is 10 mg daily. Lenalidomide is also used orally with dexamethasone for the treatment of patients with multiple myeloma (p.658) who have received at least one prior therapy. The recommended starting dose of lenalidomide is 25 mg daily, given for 21 days of a 28-day cycle. The recommended oral dose of dexamethasone is 40 mg daily on days 1 to 4, days 9 to 12, and days 17 to 20 of each 28-day cycle, for the first 4 cycles, and then 40 mg daily on days 1 to 4 of each 28-day cycle thereafter.

Lenalidomide is associated with significant neutropenia and thrombocytopenia, and dosage is adjusted according to haematological toxicity.

◊ References.

1. List A, *et al.* Efficacy of lenalidomide in myelodysplastic syndromes. *N Engl J Med* 2005; **352:** 549–57.
2. Anderson KC. Lenalidomide and thalidomide: mechanisms of action—similarities and differences. *Semin Hematol* 2005; **42** (suppl 4): S3–S8.
3. Hideshima T, *et al.* Current therapeutic uses of lenalidomide in multiple myeloma. *Expert Opin Invest Drugs* 2006; **15:** 171–9.
4. List A, *et al.* Myelodysplastic Syndrome-003 Study Investigators. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *N Engl J Med* 2006; **355:** 1456–65.
5. Shah SR, Tran TM. Lenalidomide in myelodysplastic syndrome and multiple myeloma. *Drugs* 2007; **67:** 1869–81.
6. Rao KV. Lenalidomide in the treatment of multiple myeloma. *Am J Health-Syst Pharm* 2007; **64:** 1799–1807.
7. Lacy MQ, *et al.* Long-term results of response to therapy, time to progression, and survival with lenalidomide plus dexamethasone in newly diagnosed myeloma. *Mayo Clin Proc* 2007; **82:** 1179–84.
8. Dimopoulos M, *et al.* Multiple Myeloma (010) Study Investigators. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med* 2007; **357:** 2123–32.
9. Weber DM, *et al.* Multiple Myeloma (009) Study Investigators. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med* 2007; **357:** 2133–42.
10. Chanan-Khan AA, Cheson BD. Lenalidomide for the treatment of B-cell malignancies. *J Clin Oncol* 2008; **26:** 1544–52.

Administration in renal impairment. Lenalidomide is eliminated mainly via the kidneys as unchanged drug. Clearance decreases as renal function decreases, prolonging the elimination half-life and increasing exposure to the drug. A study recommended that dose adjustments be made for patients with creatinine clearance (CC) less than 50 mL/minute; a 40% reduction to 60% of the starting dose was recommended for these patients. For those with CC less than 30 mL/minute, the reduced dose should be given at extended dosing intervals. About 30% of circulating lenalidomide was removed by a 4-hour session of haemodialysis.[1]

UK licensed product information makes the following recommendations at the start of oral therapy for patients with multiple myeloma and renal impairment:

- mild renal impairment (CC greater than or equal to 50 mL/minute): 25 mg once daily (full dose)
- moderate renal impairment (CC from 30 mL/minute to less than 50 mL/minute): 10 mg once daily. This dose may be increased to 15 mg once daily after 2 cycles if the patient is not responding to treatment, but is tolerating lenalidomide
- severe renal impairment (CC less than 30 mL/minute, not requiring dialysis): 15 mg every other day
- end-stage renal disease (CC less than 30 mL/minute, requiring dialysis): 15 mg, three times weekly, after dialysis

1. Chen N, *et al.* Pharmacokinetics of lenalidomide in subjects with various degrees of renal impairment and in subjects on hemodialysis. *J Clin Pharmacol* 2007; **47:** 1466–75.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Revlimid; ***Fr.:*** Revlimid; ***Port.:*** Revlimid; ***UK:*** Revlimid; ***USA:*** Revlimid.

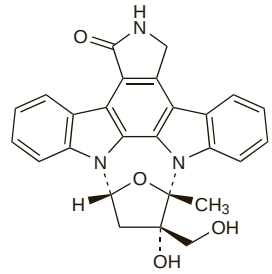
Lestaurtinib *(USAN, rINN)*

A-154475.0; CEP-701; KT-5555; Lestaurtinibum; SP-924. (9*S*,10*S*,12*R*)-10-Hydroxy-10-(hydroxymethyl)-9-methyl-2,3,9,10,11,12-hexahydro-1*H*-9,12-epoxydiindolo[1,2,3-*fg*:3′,2′,1′-*kl*]pyrrolo[3,4-*i*][1,6]benzodiazocin-1-one.

Лестауртиниб

$C_{26}H_{21}N_3O_4$ = 439.5.

CAS — 111358-88-4.



Profile

Lestaurtinib is a tyrosine kinase inhibitor that is under investigation for the treatment of acute myeloid leukaemia.

Letrozole *(BAN, USAN, rINN)* ⊗

CGS-20267; Letrotsoli; Letrozol; Létrozole; Letrozolum. 4,4′-(1*H*-1,2,4-Triazol-1-ylmethylene)dibenzonitrile.

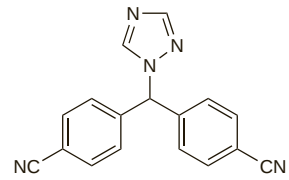
Летрозол

$C_{17}H_{11}N_5$ = 285.3.

CAS — 112809-51-5.

ATC — L02BG04.

ATC Vet — QL02BG04.



Pharmacopoeias. In *Eur.* (see p.vii) and *US*.

Ph. Eur. 6.2 (Letrozole). A white or yellowish, crystalline powder. Practically insoluble in water; sparingly soluble in methyl alcohol; freely soluble in dichloromethane.

USP 31 (Letrozole). A white to yellowish, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; freely soluble in dichloromethane. Store in airtight containers.

Adverse Effects and Precautions

As for Anastrozole, p.681.

Effects on the musculoskeletal system. Postmenopausal women with primary breast cancer were reported to have significant decreases in bone mineral density at the hip and lumbar spine after 24 months of letrozole therapy.[1]

1. Perez EA, *et al.* Effect of letrozole versus placebo on bone mineral density in women with primary breast cancer completing 5 or more years of adjuvant tamoxifen: a companion study to NCIC CTG MA.17. *J Clin Oncol* 2006; **24:** 3629–35.

Effects on the skin. Toxic epidermal necrolysis, attributed to letrozole, has been reported in a patient with breast cancer who was also receiving dexamethasone and omeprazole.[1] She had been switched from tamoxifen to letrozole a few weeks before the reaction occurred.

1. Chia WK, *et al.* Toxic epidermal necrolysis in patient with breast cancer receiving letrozole. *Lancet Oncol* 2006; **7:** 184–5.

Interactions

Tamoxifen. In a study[1] of postmenopausal women with breast cancer, the addition of tamoxifen reduced letrozole plasma concentrations by a mean of about 38%, but the effect of letrozole on hormone concentrations was unchanged. The mechanism and possible clinical effect of this interaction are unknown.

1. Dowsett M, *et al.* Impact of tamoxifen on the pharmacokinetics and endocrine effects of the aromatase inhibitor letrozole in postmenopausal women with breast cancer. *Clin Cancer Res* 1999; **5:** 2338–43.

Pharmacokinetics

Letrozole is rapidly and completely absorbed from the gastrointestinal tract. About 60% of letrozole in the circulation is bound to plasma protein, mainly albumin. Most of an oral dose is slowly metabolised to an inactive carbinol metabolite, which is then excreted as the glucuronide in the urine. Letrozole has a terminal elimination half-life of about 2 days.

Uses and Administration

Letrozole is a selective nonsteroidal inhibitor of the aromatase (oestrogen synthetase) system, similar to anastrozole (p.681). It is used in the treatment of advanced or locally advanced breast cancer (p.661) in postmenopausal women. It may be given as neoadjuvant (pre-operative) therapy to those with localised hormone-receptor positive disease, to allow subsequent breast-conserving surgery. Letrozole is also used for the adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer; treatment is generally given for 5 years or until tumour relapse occurs, although optimal duration of therapy is unknown. In postmenopausal women given 5 years of adjuvant tamoxifen for early breast cancer, letrozole may be used as extended adjuvant therapy; treatment should continue for 4 years or until tumour relapse occurs, although optimal duration of therapy is unknown. The usual dose is 2.5 mg daily by mouth.

◊ References.

1. Mouridsen H, *et al.* Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. *J Clin Oncol* 2001; **19:** 2596–2606.
2. Buzdar A, *et al.* Phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. *J Clin Oncol* 2001; **19:** 3357–66.
3. Ellis MJ, *et al.* Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. *J Clin Oncol* 2001; **19:** 3808–16.
4. Goss PE, *et al.* A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med* 2003; **349:** 1793–1802.
5. Simpson D, *et al.* Letrozole: a review of its use in postmenopausal women with breast cancer. *Drugs* 2004; **64:** 1213–30.
6. Goss PE, *et al.* Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst* 2005; **97:** 1262–71.
7. The Breast International Group (BIG) 1-98 Collaborative Group. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med* 2005; **353:** 2747–57.
8. Scott LJ, Keam SJ. Letrozole: in postmenopausal hormone-responsive early-stage breast cancer. *Drugs* 2006; **66:** 353–62.
9. Gelmon K. Prescribing extended adjuvant letrozole. *Breast* 2007; **16:** 446–55.
10. Goss PE, *et al.* Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer who complete 5 years of tamoxifen. *J Clin Oncol* 2008; **26:** 1948–55.
11. Muss HB, *et al.* Efficacy, toxicity, and quality of life in older women with early-stage breast cancer treated with letrozole or placebo after 5 years of tamoxifen: NCIC CTG intergroup trial MA.17. *J Clin Oncol* 2008; **26:** 1956–64.

Administration in hepatic impairment. Licensed product information in the UK and USA states that no dosage adjustment of letrozole is required for patients with mild to moderate hepatic impairment (Child-Pugh category A and B). While letrozole is contra-indicated in the UK in severe hepatic impairment (Child-Pugh category C), in the USA, it is recommended that the dose of letrozole be reduced by 50% in those patients with cirrhosis and severe hepatic impairment; the recommended dose for these patients is 2.5 mg given every other day.

Infertility. Letrozole has been investigated[1-4] as an adjunct to assisted reproduction technologies in the management of infertility (p.2080). However, concerns about this unlicensed use have been raised by the Canadian manufacturer (*Novartis, Canad.*) because of the potential for maternal and fetal toxicity, and fetal malformations:[5] licensed product information contra-indicates the use of letrozole in premenopausal women, and there have