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.

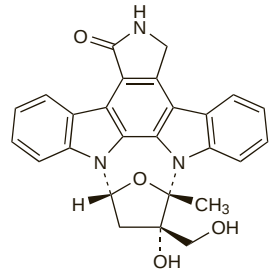
Lestaurtinib *(USAN, rINN)*

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.

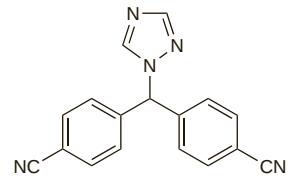
Летрозол

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

been reports of congenital anomalies in the infants of women treated with letrozole for infertility.

1. Healey S, *et al.* Effects of letrozole on superovulation with gonadotropins in women undergoing intrauterine insemination. *Fertil Steril* 2003; **80:** 1325–9.
2. Al-Fozan H, *et al.* A randomized trial of letrozole versus clomiphene citrate in women undergoing superovulation. *Fertil Steril* 2004; **82:** 1561–3.
3. Garcia-Velasco JA, *et al.* The aromatase inhibitor letrozole increases the concentration of intraovarian androgens and improves in vitro fertilization outcome in low responder patients: a pilot study. *Fertil Steril* 2005; **84:** 82–7.
4. Al-Fadhli R, *et al.* A randomized trial of superovulation with two different doses of letrozole. *Fertil Steril* 2006; **85:** 161–4.
5. Novartis, Canada. Health Canada endorsed important safety information: contraindication of Femara (letrozole) in premenopausal women (issued 17th November, 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/femara_hpc-cps-eng.pdf (accessed 31/07/08)

Preparations

USP 31: Letrozole Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Cendalon; Fecinole; Femara; Kebirzol; ***Austral.:*** Femara; ***Austria:*** Femara; ***Belg.:*** Femara; ***Braz.:*** Femara; ***Canad.:*** Femara; ***Chile:*** Femara; ***Cz.:*** Femara; ***Denm.:*** Femar; ***Fin.:*** Femar; ***Fr.:*** Femara; ***Ger.:*** Femara; ***Gr.:*** Femara; ***Hong Kong:*** Femara; ***Hung.:*** Femara; ***India:*** Femara; Fempro; Oncolet; Trozet; ***Indon.:*** Femara; ***Irl.:*** Femara; ***Israel:*** Femara; ***Ital.:*** Femara; ***Jpn:*** Femara; ***Malaysia:*** Femara; ***Mex.:*** Femara; ***Neth.:*** Femara; ***Norw.:*** Femar; ***NZ:*** Femara; ***Philipp.:*** Femara; ***Pol.:*** Aromek; Femara; Lametta; ***Port.:*** Femara; ***Rus.:*** Femara (Фемара); ***S.Afr.:*** Femara; ***Singapore:*** Femara; ***Spain:*** Femara; Insegar; ***Swed.:*** Femar; ***Switz.:*** Femara; ***Thai.:*** Femara; ***Turk.:*** Femara; ***UK:*** Femara; ***USA:*** Femara; ***Venez.:*** Femara.

Lobaplatin *(rINN)*

D-19466; Lobaplatine; Lobaplatino; Lobaplatinum. *cis*-[*trans*-1,2-Cyclobutanebis(methylamine)][(*S*)-lactato-*O*^{1},*O*^{1}]platinum.

Лобаплатин

$C_9H_{18}N_2O_3Pt$ = 397.3.

CAS — 135558-11-1.

Profile

Lobaplatin is an analogue of cisplatin (p.698) that has been investigated for its antineoplastic properties. Thrombocytopenia is reported to be dose-limiting. It may be active against some cancer cells resistant to cisplatin or carboplatin.

◊ References.

1. Welink J, *et al.* Pharmacokinetics and pharmacodynamics of lobaplatin (D-19466) in patients with advanced solid tumors, including patients with impaired renal or liver function. *Clin Cancer Res* 1999; **5:** 2349–58.
2. McKeage MJ. Lobaplatin: a new antitumour platinum drug. *Expert Opin Invest Drugs* 2001; **10:** 119–28.
3. Anonymous. Lobaplatin: D 19466. *Drugs R D* 2003; **4:** 369–72.

Lomustine *(BAN, USAN, rINN)*

CCNU; Lomustiini; Lomustin; Lomustina; Lomustinas; Lomustinum; Lomustyna; Lomusztin; NSC-79037; RB-1509; WR-139017. 1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea.

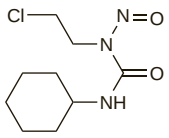
Ломустин

$C_9H_{16}ClN_3O_2$ = 233.7.

CAS — 13010-47-4.

ATC — L01AD02.

ATC Vet — QL01AD02.



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

Ph. Eur. 6.2 (Lomustine). A yellow, crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in acetone and in dichloromethane. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Carmustine, p.694. Neurological reactions such as confusion and lethargy have been reported.

Handling and disposal. A method for the destruction of lomustine *waste* by reaction with hydrobromic acid in glacial acetic acid has been described.[1] The residue produced by the degradation of lomustine by this method showed no mutagenicity. This method is not suitable for the degradation of carmustine or semustine.

1. Castegnaro M, *et al.*, eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents. *IARC Scientific Publications 73.* Lyon: WHO/International Agency for Research on Cancer, 1985.

Overdosage. A patient who inadvertently received 200 mg of lomustine for 7 days instead of a single 200-mg dose developed pancytopenia and subsequent multiorgan dysfunction including liver dysfunction, abdominal pain, pulmonary toxicity with tachypnoea and hypoxaemia, and CNS toxicity leading to confusion and disorientation.[1] Although the white cell count recovered other signs of toxicity did not and the patient developed fever and hypotension and died 59 days after the initial dose of lomustine. In another case of accidental overdose, a 30-year old female received a cumulative dose of 28 mg/kg over 7 days.[2] Severe myelosuppression developed soon after the overdose and lasted for 50 days. The patient was treated with granulocyte colony-stimulating factor and antibacterial cover, norethisterone (to prevent menstruation), and acetylcysteine (to protect against organ toxicity). Gastrointestinal necrosis occurred, and liver enzymes remained elevated even after recovery from the overdose, but the patient survived and her tumour regressed without further chemotherapy.

1. Trent KC, *et al.* Multiorgan failure associated with lomustine overdose. *Ann Pharmacother* 1995; **29:** 384–6.
2. Abele M, *et al.* CCNU overdose during PCV chemotherapy for anaplastic astrocytoma. *J Neurol* 1998; **245:** 236–8.

Interactions

For a general outline of antineoplastic drug interactions, see p.642.

Cimetidine. For a report of a possible interaction between lomustine and cimetidine, see under Carmustine, p.695.

Theophylline. Leucopenia and thrombocytopenia in a 45-year-old woman were believed to have been secondary to an interaction between theophylline and lomustine.[1]

1. Zeltzer PM, Feig SA. Theophylline-induced lomustine toxicity. *Lancet* 1979; **ii:** 960–1.

Pharmacokinetics

Lomustine is absorbed from the gastrointestinal tract and is rapidly metabolised, with peak plasma concentrations of metabolites occurring within 4 hours of an oral dose. Metabolites have a prolonged plasma half-life reported to range from 16 to 48 hours. Active metabolites readily cross the blood-brain barrier and appear in the CSF in concentrations higher than those in plasma. About half a dose is excreted as metabolites in the urine within 24 hours and about 75% is excreted within 4 days.

Uses and Administration

Lomustine is a nitrosourea with actions and uses similar to those of carmustine (p.695). It has been used in the treatment of brain tumours (p.660) and resistant or relapsed Hodgkin's disease and other lymphomas (p.655), and also lung cancer (p.668), malignant melanoma (p.673), and various solid tumours.

When given as a single agent, lomustine is licensed for oral use in adults and children as a single dose of 120 to 130 mg/m^2; division of the dose over 3 consecutive days may reduce gastrointestinal effects. A dose of 100 mg/m^2 should be given to patients with compromised bone-marrow function. Doses are also generally reduced when lomustine is given as part of a combination regimen. Providing blood counts have returned to acceptable levels, doses may be repeated every 6 to 8 weeks, and should be adjusted according to the haematological response (see also Bone-marrow Depression, p.639).

Preparations

BP 2008: Lomustine Capsules.

Proprietary Preparations (details are given in Part 3)

Arg.: CeeNU; ***Austral.:*** CeeNU; ***Braz.:*** Citostal; ***Canad.:*** CeeNU; ***Chile:*** CeeNU; ***Cz.:*** CeeNU; ***Ger.:*** Cecenu; ***Hong Kong:*** CeeNU; ***Israel:*** CeeNU†; ***Malaysia:*** CeeNU†; ***Mex.:*** CeeNU; ***Neth.:*** Belustine; ***NZ:*** CeeNU; ***Philipp.:*** CeeNU; ***S.Afr.:*** CeeNU; ***Singapore:*** CeeNU†; ***Switz.:*** Prava; ***UK:*** CCNU; ***USA:*** CeeNU.

Lonidamine *(BAN, rINN)*

AF-1890; Diclondazolic Acid; Lonidamina; Lonidaminum; TH-070. 1-(2,4-Dichlorobenzyl)indazole-3-carboxylic acid.

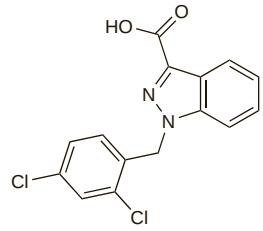
Лонидамин

$C_{15}H_{10}Cl_2N_2O_2$ = 321.2.

CAS — 50264-69-2.

ATC — L01XX07.

ATC Vet — QL01XX07.



Profile

Lonidamine is an antineoplastic that is thought to act by inhibiting mitochondrial function in tumour cells. It has been given orally in the treatment of various solid neoplasms, including those of the lung, breast, prostate, and brain.

Preparations

Proprietary Preparations (details are given in Part 3)

Ital.: Doridamina†.

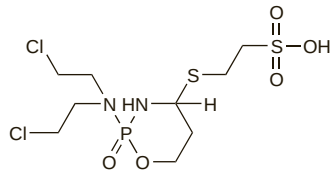
Mafosfamide *(rINN)*

Mafosfamid; Mafosfamida; Mafosfamidi; Mafosfamidum. (±)-2-({2-[Bis(2-chloroethyl)amino]tetrahydro-2*H*-1,3,2-oxazaphosphorin-4-yl}thio)ethanesulphonic acid *P-cis* oxide.

Мафосфамид

$C_9H_{19}Cl_2N_2O_5PS_2$ = 401.3.

CAS — 88859-04-5.



Profile

Mafosfamide is a derivative of cyclophosphamide (p.702) that has been used to treat bone marrow for transplantation. It is also under investigation in the treatment of neoplastic meningitis.

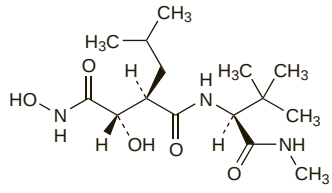
Marimastat *(BAN, USAN, rINN)*

BB-2516; Marimastatum. (2*S*,3*R*)-3-{(*S*)-[2,2-Dimethyl-1-(methylcarbamoyl)propyl]carbamoyl}-2-hydroxy-5-methylhexanohydroxamic acid.

Маримастат

$C_{15}H_{29}N_3O_5$ = 331.4.

CAS — 154039-60-8.



Profile

Marimastat is an oral inhibitor of matrix metalloproteinases, enzymes which are thought to play a role in the metastasis of cancer cells. It has been investigated in various malignant disorders.