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.

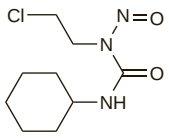
Ломустин

$C_9H_{16}ClN_3O_2$ = 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.

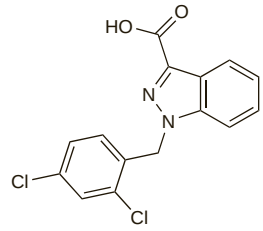
Лонидамин

$C_{15}H_{10}Cl_2N_2O_2$ = 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†.

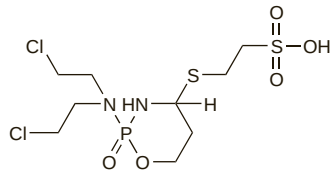
Mafosfamide *(rINN)*

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.

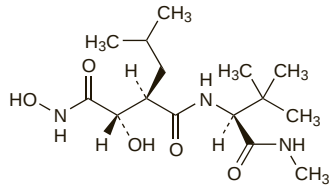
Marimastat *(BAN, USAN, rINN)*

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.