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.

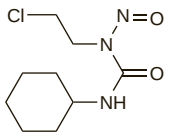
Ломустин

$C_9H_{16}ClN_3O_2$ = 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.

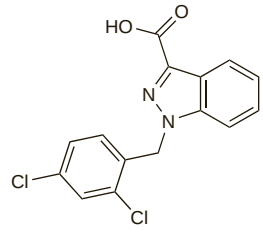
Лонидамин

$C_{15}H_{10}Cl_2N_2O_2$ = 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†.

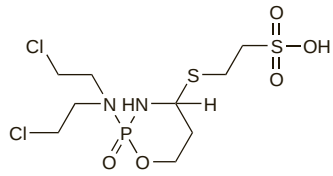
Mafosfamide *(rINN)*

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.

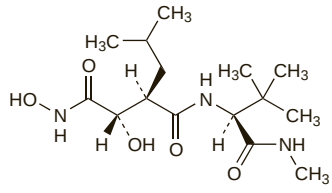
Marimastat *(BAN, USAN, rINN)*

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.

Masoprocol *(USAN, rINN)*

CHX-10; CHX-100; Masoprocolum; Mesonordihydroguaiaretic Acid; *meso*-NDGA. *meso*-4,4′-(2,3-Dimethyltetramethylene)-dipyrocatechol.

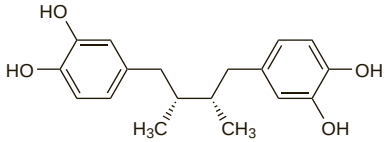
Мазопрокол

$C_{18}H_{22}O_4$ = 302.4.

CAS — 27686-84-6.

ATC — L01XX10.

ATC Vet — QL01XX10.



Profile

Masoprocol is a 5-lipoxygenase inhibitor isolated from the chaparral or creosote bush, *Larrea tridentata* (p.2280). It is reported to have antineoplastic activity. It has been used in the topical treatment of actinic (solar) keratoses. Local irritation and contact dermatitis have occurred.

Melanoma Vaccines

ATC — L03AX12.

Profile

A number of therapeutic vaccines designed to stimulate an antibody response are being developed for the treatment of melanoma (p.673).

One available preparation contains melanoma lysate (*Melacine*; *Schering, Canada*). It is used intramuscularly in a regimen with cyclophosphamide for the treatment of metastatic disease. Patients who show a clinical response may continue the melanoma vaccine as maintenance therapy. Adverse effects include injection site reactions such as granuloma formation, gastrointestinal disturbances, flu-like syndrome, and hypersensitivity reactions.

Other potential melanoma vaccines may be based on whole cells, GM2 ganglioside, heat shock proteins, or autologous tumour cells conjugated to an immunogenic hapten.

◊ Reviews.

1. Kim CJ, *et al.* Immunotherapy for melanoma. *Cancer Control* 2002; **9:** 22–30.
2. Minev BR. Melanoma vaccines. *Semin Oncol* 2002; **29:** 479–93.
3. Parmiani G, *et al.* Immunotherapy of melanoma. *Semin Cancer Biol* 2003; **13:** 391–400.
4. Sondak VK, Sosman JA. Results of clinical trials with an allogenic melanoma tumor cell lysate vaccine: Melacine. *Semin Cancer Biol* 2003; **13:** 409–15.
5. Castelli C, *et al.* Heat shock proteins: biological functions and clinical application as personalized vaccines for human cancer. *Cancer Immunol Immunother* 2004; **53:** 227–33.
6. Komenaka I, *et al.* Immunotherapy for melanoma. *Clin Dermatol* 2004; **22:** 251–65.
7. Oki Y, Younes A. Heat shock protein-based cancer vaccines. *Expert Rev Vaccines* 2004; **3:** 403–11.
8. Elliott B, Dalgleish A. Melanoma vaccines. *Hosp Med* 2004; **65:** 668–73.
9. Bystryn JC, Reynolds SR. Melanoma vaccines: what we know so far. *Oncology (Williston Park)* 2005; **19:** 97–108.
10. Saleh F, *et al.* Melanoma immunotherapy: past, present, and future. *Curr Pharm Des* 2005; **11:** 3461–73.
11. Lens M. The role of vaccine therapy in the treatment of melanoma. *Expert Opin Biol Ther* 2008; **8:** 315–23.
12. Rosenthal R, *et al.* Active specific immunotherapy phase III trials for malignant melanoma: systematic analysis and critical appraisal. *J Am Coll Surg* 2008; **207:** 95–105.

Preparations

Proprietary Preparations (details are given in Part 3)

Canad.: Melacine†.

Melphalan *(BAN, USAN, rINN)*

CB-3025; Melfalaani; Melfalán; Melfalan; Melphalanum; NSC-8806 (melphalan hydrochloride); PAM; Phenylalanine Mustard; Phenylalanine Nitrogen Mustard; L-Sarcolysine; WR-19813. 4-Bis(2-chloroethyl)amino-L-phenylalanine.

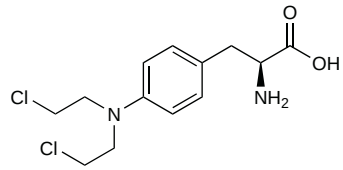
Мелфалан

$C_{13}H_{18}Cl_2N_2O_2$ = 305.2.

CAS — 148-82-3 (melphalan); 3223-07-2 (melphalan hydrochloride).

ATC — L01AA03.

ATC Vet — QL01AA03.



NOTE. Merphalan (CB-3007; NSC-14210; sarcolysine) is the racemic form of melphalan; Medphalan (CB-3026; NSC-35051) is the D-isomer of melphalan.

Pharmacopoeias. In *Br.*, *Jpn*, and *US*.

BP 2008 (Melphalan). A white or almost white powder. Practically insoluble in water, in chloroform, and in ether; slightly soluble in methyl alcohol; dissolves in dilute mineral acids. Protect from light.

USP 31 (Melphalan). An off-white to buff powder with a faint odour. Practically insoluble in water, in chloroform, and in ether; slightly soluble in alcohol and in methyl alcohol; soluble in dilute mineral acids. Store in airtight, glass containers. Protect from light.

Stability. A study of the stability of melphalan 40 and 400 micrograms/mL in infusion fluids reported that the time for a 10% loss of drug at 20° in sodium chloride 0.9% injection was 4.5 hours, compared with 2.9 hours in lactated Ringer's injection, which has a considerably lower chloride ion content, and only 1.5 hours in glucose 5% injection.[1] At 25° the corresponding figures were 2.4, 1.5, and 0.6 hours, and at 37° they were 0.6, 0.4, and 0.3 hours. It was concluded that melphalan is sufficiently stable at 20° in sodium chloride injection to permit infusion, but that increased temperature and decreased chloride ion concentration were associated with faster degradation rates.[1] Another study recommended that solutions of melphalan be handled at temperatures above 5° for the minimum time but found that a solution containing 20 micrograms/mL in sodium chloride 0.9% could be stored for at least 6 months at –20° without significant deterioration.[2] A more recent study, while recommending storage at 4° between preparation and use of the infusion, considered that giving it at a room temperature of 20° or below, and use of hypertonic (3%) saline as a diluent, would be sufficient to allow prolonged infusion.[3] The practicalities of such a procedure were not addressed.

1. Tabibi SE, Cradock JC. Stability of melphalan in infusion fluids. *Am J Hosp Pharm* 1984; **41:** 1380–2.
2. Bosanquet AG. Stability of melphalan solutions during preparation and storage. *J Pharm Sci* 1985; **74:** 348–51.
3. Pinguet F, *et al.* Effect of sodium chloride concentration and temperature on melphalan stability during storage and use. *Am J Hosp Pharm* 1994; **51:** 2701–4.

Adverse Effects and Treatment

For general discussions see Antineoplastics, p.635 and p.639.

The onset of neutropenia and thrombocytopenia is variable; the nadir of bone-marrow depression usually occurs at 2 to 3 weeks after starting treatment with melphalan, with recovery after 4 to 5 weeks.

Skin rashes and hypersensitivity reactions, including anaphylaxis, may occur. Cardiac arrest has been reported in association with such effects. Gastrointestinal disturbances may sometimes occur, particularly at high doses where diarrhoea, vomiting, and stomatitis may become dose-limiting. Haemolytic anaemia, vasculitis, pulmonary fibrosis, and hepatic disorders including hepatitis and jaundice have been reported. Suppression of ovarian function is common in premenopausal women; temporary or permanent sterility may occur in male patients. Extravasation of melphalan injection can cause skin ulceration and necrosis. As with other alkylating agents, melphalan also has carcinogenic, mutagenic, and teratogenic potential.

Mucositis. Amifostine has been shown to reduce the frequency and severity of melphalan-induced oral mucositis.[1]

1. Spencer A, *et al.* Prospective randomised trial of amifostine cytoprotection in myeloma patients undergoing high-dose melphalan conditioned autologous stem cell transplantation. *Bone Marrow Transplant* 2005; **35:** 971–7.

Overdosage. A 12-month old child given melphalan 140 mg intravenously (a tenfold overdose) developed pronounced lymphopenia within 24 hours but had no other significant adverse effects until the seventh day, when neutropenia, thrombocytopenia, oral ulceration, and diarrhoea developed.[1] Bone marrow recovered within 40 days. Treatment was by vigorous hyperalimentation and close surveillance during this period and the patient subsequently remained well 9 months afterwards, without complications. Cases of intravenous melphalan overdose have also been reported in adults,[2] resulting in bone-marrow depression, haemorrhagic diarrhoea, and electrolyte disturbances. Bone-marrow depression has also been reported after cumulative oral doses of 360 mg over 3 weeks,[3] and 560 mg over 2 weeks.[4] Filgrastim was used in one of these cases to stimulate bone-marrow recovery.[4]

1. Coates TD. Survival from melphalan overdose. *Lancet* 1984; **ii:** 1048.
2. Jost LM. Überdosierung von Melphalan (Alkeran): Symptome und Behandlung: eine Übersicht. *Onkologie* 1990; **13:** 96–101.
3. Grimes DJ, *et al.* Complete remission of paraproteinaemia and neuropathy following iatrogenic oral melphalan overdose. *Br J Haematol* 1993; **83:** 675–7.
4. Jirillo A, *et al.* Accidental overdose of melphalan per os in a 69-year-old woman treated for advanced endometrial carcinoma. *Tumori* 1998; **84:** 611.

Precautions

For general discussions see Antineoplastics, p.641.

Care is required in patients with impaired renal function.

Handling and disposal. *Urine and faeces* produced for up to 48 hours and 7 days respectively after a dose of melphalan by mouth should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Interactions

Use of nalidixic acid with high-dose intravenous melphalan in children has resulted in fatal haemorrhagic enterocolitis.

Ciclosporin. For reference to enhanced toxicity when melphalan was given with ciclosporin, see under Ciclosporin, p.1826.

Food. The bioavailability of oral melphalan is significantly reduced, by up to 45%, by food. Some recommend that melphalan should not be taken with food, and that if dosage is switched from after to before food patients should be monitored for increased toxicity.[1]

1. Nathan C, Betmouni R. Melphalan: avoid with food. *Pharm J* 1996; **257:** 264.

Interferons. The fever induced by interferon alfa resulted in a reduction in the area under the plasma concentration-time curve for melphalan in a study of 10 patients, although the peak plasma concentration and time to peak concentration were not affected.[1] The effect was thought to represent increased chemical reactivity of melphalan at the elevated temperature.

1. Ehrsson H, *et al.* Oral melphalan pharmacokinetics: influence of interferon-induced fever. *Clin Pharmacol Ther* 1990; **47:** 86–90.

Pharmacokinetics

Absorption of melphalan from the gastrointestinal tract is variable; the mean bioavailability is reported to be 56% but it may range from 25 to 89%. Absorption is reduced by the presence of food (see above). On absorption it is rapidly distributed throughout body water with a volume of distribution of about 0.5 litres/kg, and has been reported to be inactivated mainly by spontaneous hydrolysis. About 60 to 90% is bound to plasma proteins, mainly albumin. The terminal plasma half-life of melphalan has been reported to be of the order of 30 to 150 minutes. Melphalan is excreted in the urine, about 10% as unchanged drug.

◊ References.

1. Nath CE, *et al.* Melphalan pharmacokinetics in children with malignant disease: influence of body weight, renal function, carboplatin therapy and total body irradiation. *Br J Clin Pharmacol* 2005; **59:** 314–24.
2. Nath CE, *et al.* Population pharmacokinetics of melphalan in paediatric blood or marrow transplant recipients. *Br J Clin Pharmacol* 2007; **64:** 151–64.
3. Padussis JC, *et al.* Pharmacokinetics and drug resistance of melphalan in regional chemotherapy: ILP versus ILI. *Int J Hyperthermia* 2008; **24:** 239–49.

Uses and Administration

Melphalan is an antineoplastic that acts as a bifunctional alkylating agent. It is used mainly in the treatment of multiple myeloma. Melphalan has also been given to patients with carcinoma of the breast and ovary, neuroblastoma, Hodgkin's disease, and in polycythaemia vera, and has been given by intra-arterial regional perfusion for malignant melanoma and soft-tissue sarcomas. See also the cross-references given below. Melphalan is also used in the treatment of amyloidosis, see below.

Melphalan is usually given orally as a single daily dose or in divided doses; it is also given intravenously as the hydrochloride. Doses are calculated in terms of the base; 1.12 mg of melphalan hydrochloride is equiva-