ate; Metex; Metoject†; ***Fin.***: Ebetrex; Emthexat†; Metoject; Trexan; ***Fr.***: Imeth; Ledertrexate; Metoject; Novatrex; ***Ger.***: Bendatrexat†; Lantarel; Metex; MTX; Neotrexat†; ***Gr.***: Emthexate; Methobion; Methoblastin; Metoject; ***Hung.***: Metoject; Trexan; ***India***: Alltrex; Biotrexate; Caditrex; Dermatrex; Dermotrex; Folitrax; Hi-Trex; Imutrex; Merex; Methocel; Methocip; Methorex; Metorex; Metrex; Mexate; Neotrexate; Oncotrex; Onotrex; ***Indon.***: Emthexate; ***Irl.***: Metoject; ***Israel***: Abitrexate; Metoject; ***Ital.***: Reumaflex; Sactiva; Securact; ***Jpn***: Metolate; ***Malaysia***: Emthexate; ***Mex.***: Atrexel; Ifamet†; Ledertrexate; Medsatrexate; Otaxem; Texate; Trixilem; ***Neth.***: Ebetrexat†; Emthexate; Metoject; ***Norw.***: Ebetrex; Metex; Metoject†; ***NZ***: Emthexate; Methoblastin; ***Philipp.***: Alltrex; Emthexate; Hextrate†; Methobax†; Pterin; Zexate; ***Pol.***: Metex; Metoject; Trexan; ***Port.***: Fauldexato; Ledertrexato; Metex; Metoject; ***Rus.***: Metoject (Методжект); Zexat (Зексат); ***S.Afr.***: Abitrexate; Emthexate†; Methacor; Methacor; ***Singapore***: Abitrexate; Ebetrexat; Emthexate; MTX; ***Spain***: Bertanel; Emthexate†; Metoject; ***Swed.***: Ebetrex; Metoject; Metotab; ***Switz.***: Metoject; ***Thai.***: Abitrexate; Alltrex; Emthexate; Metrex; Neometho; Onkomet; Trixilem; Zexate†; ***Turk.***: Emthexate; Metoart; Metoject; MTX; Trexan; ***UK***: Ebetrex†; Matrex; Maxtrex; Metoject; ***USA***: Otrexup; Rheumatrex; Trexall; ***Venez.***: Zexate.

Pharmacopoeial Preparations

BP 2014: Methotrexate Injection; Methotrexate Tablets;
USP 36: Methotrexate for Injection; Methotrexate Injection; Methotrexate Tablets.

2-Methoxyoestradiol

2-ME2; 2-Methoxyestradiol; NSC-659853; 2-Метоксиэстрадиол.
(17β)-2-Methoxyestra-1,3,5(10)-triene-3,17-diol.
$C_{19}H_{26}O_3$=302.4
CAS — 362-07-2.
UNII — 6I2QW73SR5.

NOTE. The names Panzem and PulmoLAR have been used as trade marks for 2-methoxyoestradiol.

Profile

2-Methoxyoestradiol is a metabolite of oestradiol (p. 2271.1). It does not have direct oestrogenic activity, but works through multiple cellular pathways to produce antineoplastic effects, including inhibition of angiogenesis and induction of apoptosis. 2-Methoxyoestradiol is under investigation in the treatment of various diseases, including glioblastoma, multiple myeloma, carcinoid tumours, as well as ovarian, prostate, breast, and renal cell cancers. It is also under investigation for pulmonary arterial hypertension and rheumatoid arthritis.

Midostaurin *(USAN, rINN)*

Benzoylstaurosporine; CGP-41251; Midostaurina; Midostaurine; Midostaurinum; PKC-412; Мидостаурин.
N-[(9*S*,10*R*,11*R*,13*R*)-2,3,10,11,12,13-Hexahydro-10-methoxy-9-methyl-1-oxo-9,13-epoxy-1*H*,9*H*-diindolo[1,2,3-*gh*:3′,2′,1′-*lm*]pyrrolo[3,4-*j*][1,7]benzodiazonin-11-yl]-*N*-methylbenzamide.
$C_{35}H_{30}N_4O_4$=570.6
CAS — 120685-11-2.
UNII — ID912S5VON.

Profile

Midostaurin is a multikinase inhibitor effective against tyrosine kinase and protein kinase C, and those of receptors for growth factors including vascular endothelial growth factor and platelet-derived growth factor. It is under investigation for the treatment of acute myeloid leukaemia, myelodysplastic syndrome, and systemic mastocytosis.

Mifamurtide *(BAN, rINN)*

Mifamurtida; Mifamurtidum; MTP-PE; Muramyl Tripeptide Phosphatidyl Ethanolamine; Muramyl Tripeptide Phosphatidyl Monoethanolamine; Мифамуртид.
2-[(*N*-[(2*R*)-[(2-Acetamido-2,3-dideoxy-D-glucopyranos-3-yl)oxy]propanoyl]-L-alanyl-D-isoglutaminyl-L-alanyl)amino]ethyl (2*R*)-2,3-bis(hexadecanoyloxy)propyl hydrogen phosphate.
$C_{59}H_{109}N_6O_{19}P$=1237.5
CAS — 83461-56-7.
ATC — L03AX15.
ATC Vet — QL03AX15.
UNII — 1LM890Q4FY.

NOTE. The name Mifamurtide has been used for both the base and the sodium salt. The name Junovan has been used as a trade mark for mifamurtide.

Mifamurtide Sodium *(rINNM)*

CGP-19835A; L-MTP-PE (liposomal mifamurtide sodium); Mifamurtida sódica; Mifamurtide (USAN); Mifamurtide Sodique; Mifamurtidum Natricum; Мифамуртид Натрий.
2-[(*N*-[(2*R*)-2-[(3*R*,4*R*,5*S*,6*R*)-3-(Acetylamino)-2,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-4-yloxy]propanoyl]-L-alanyl-D-isoglutaminyl-L-alanyl)amino]ethyl (2*R*)-2,3-bis(hexanoyloxy)propyl sodium phosphate hydrate.
$C_{59}H_{108}N_6NaO_{19}P.xH_2O$=1259.5 (anhydrous)
CAS — 838853-48-8.

NOTE. The name Mifamurtide has been used for both the base and the sodium salt.

Uses and Administration

Mifamurtide is an immunomodulator that activates monocytes and macrophages to increase their capacity to destroy cancer cells. A liposomal formulation of mifamurtide is used with other chemotherapy to treat non-metastatic, resected osteosarcoma in patients from 2 to 30 years of age. The reconstituted suspension is filtered then diluted in 50 mL sodium chloride 0.9% and given by intravenous infusion over 1 hour. Mifamurtide 2 mg/m^2 is given twice weekly (at least 3 days apart) for 12 weeks, followed by once weekly for an additional 24 weeks. A total of 48 infusions is given in 36 weeks.

References.

1. Meyers PA. Muramyl tripeptide (mifamurtide) for the treatment of osteosarcoma. *Expert Rev Anticancer Ther* 2009; **9:** 1035–49.
2. Frampton JE. Mifamurtide: a review of its use in the treatment of osteosarcoma. *Paediatr Drugs* 2010; **12:** 141–53.
3. Chou AJ, *et al.* Addition of muramyl tripeptide to chemotherapy for patients with newly diagnosed metastatic osteosarcoma: a report from the Children's Oncology Group. *Cancer* 2009; **115:** 5339–48.

Administration in children. Mifamurtide is given in a liposomal formulation to children aged from 2 years with osteosarcoma; see above for dosage details.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p. 726.1, p. 730.2, and p. 732.2.

Common adverse effects with mifamurtide include blood disorders such as anaemia, thrombocytopenia, granulocytopenia, transient neutropenia, and leucopenia; CNS disorders such as headache, dizziness, paraesthesia, hypoaesthesia, somnolence or insomnia, tremor, fatigue, confusion, depression, and anxiety; musculoskeletal disorders such as pain, spasm, arthralgia, and myalgia; and skin disorders such as rash, pruritus, dry skin, alopecia, and hyperhidrosis. Gastrointestinal disturbances such as nausea, vomiting, diarrhoea or constipation, abdominal pain, and anorexia are very common.

Other adverse effects that occur commonly during treatment include infusion-site reactions, phlebitis, flushing, dehydration, hypokalaemia, vertigo, tinnitus, hearing loss, blurred vision, hepatic pain, dysmenorrhoea, haematuria, dysuria, pollakiuria, fever, chills, and oedema.

Common respiratory disorders include dyspnoea or tachypnoea, cough, haemoptysis, epistaxis, sinus or nasal congestion, pleural effusion, or pharyngolaryngeal pain. Respiratory distress has been reported occasionally in patients with pre-existing asthma; mifamurtide therapy should be stopped if a severe respiratory reaction occurs. Prophylactic bronchodilators may be considered in those with a history of reversible airways obstruction.

Cardiac disorders such as tachycardia and hypertension or hypotension are common. Subacute thrombosis has been reported very rarely. Patients with a history of venous thrombosis, vasculitis, or unstable cardiovascular disease should be closely monitored, and treatment delayed or stopped if symptoms are persistent or worsening. Clotting parameters should be monitored after the first dose and again after several doses.

Mifamurtide has occasionally been associated with an inflammatory response, including pericarditis and pleuritis, and it should be used with caution in those with a history of auto-immune disorders, inflammatory disease, or other collagen vascular diseases. Patients should be monitored for signs of uncontrolled inflammatory reactions such as arthritis or synovitis. Allergic reactions also have occurred occasionally with mifamurtide; symptoms include rash, dyspnoea, and severe hypertension.

Caution is required in patients with hepatic or renal impairment due to a lack of data; hepatic and renal function should be monitored until treatment is complete.

Interactions

For a general outline of antineoplastic drug interactions, see p. 733.3.

Mifamurtide modulates the immune system and its use is not recommended with calcineurin inhibitors or with regular use of corticosteroids. The use of mifamurtide with high-dose NSAIDs is also not recommended as *in vitro* studies have shown that high-dose NSAIDs can block the macrophage-activating action of mifamurtide.

Licensed product information suggests liposomal mifamurtide should not be administered at the same time as other lipophilic formulations.

Pharmacokinetics

Mifamurtide is rapidly cleared from the plasma after intravenous injection and is distributed into the liver, spleen, nasopharynx, thyroid, and to a lesser extent, into the lungs. The cells of the reticuloendothelial system clear mifamurtide liposomes by phagocytosis. The mean half-life is biphasic, that for the initial phase being about 15 minutes while the terminal half-life is about 18 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Mepact; ***Cz.***: Mepact; ***Denm.***: Mepact; ***Ger.***: Mepact; ***Gr.***: Mepact; ***Irl.***: Mepact; ***Israel***: Mepact; ***Ital.***: Mepact; ***Neth.***: Mepact; ***Norw.***: Mepact; ***Pol.***: Mepact; ***Port.***: Mepact; ***Spain***: Mepact; ***Swed.***: Mepact; ***Switz.***: Mepact; ***UK***: Mepact.

Milatuzumab *(USAN, rINN)*

Immu-115; Milatuzumabum; Милатузумаб.
Immunoglobulin G1, anti-(human class II antigen invariant chain) (human-mouse monoclonal hLL1 heavy chain), disulfide with human-mouse monoclonal hLL1 κ-chain, dimer.
CAS — 899796-83-9.
UNII — 2OP4E0GC6V.

Profile

Milatuzumab is a humanised monoclonal antibody directed against the CD74 antigen. It is under investigation for the treatment of multiple myeloma, chronic lymphocytic leukaemia, and non-Hodgkin's lymphoma. Milatuzumab conjugated to doxorubicin (p. 782.3) is also being studied for multiple myeloma treatment.

References.

1. Berkova Z, *et al.* Milatuzumab—a promising new immunotherapeutic agent. *Expert Opin Invest Drugs* 2010; **19:** 141–9.

Miltefosine *(BAN, rINN)*

D-18506; HDPC; Hexadecilfosfocolina; Hexadecylphosphocholine; Miltefosiini; Miltefosin; Miltefosina; Miltéfosine; Miltefosinum; Мильтефозин.
[2-(Trimethylammonio)ethyl][hexadecyloxyphosphonate].
$C_{21}H_{46}NO_4P$=407.6
CAS — 58066-85-6.
ATC — L01XX09.
ATC Vet — QL01XX09.
UNII — 53EY29W7EC.

Profile

Miltefosine is a phospholipid derivative that is structurally related to the phospholipid components of the cell membrane and is thought to exert its antineoplastic actions by disruption of cell-membrane function. A 6% solution is applied once or twice daily as a topical antineoplastic agent for skin metastases of breast cancer. Topical miltefosine is also being investigated for the treatment of cutaneous T-cell lymphoma and *Acanthamoeba* keratitis (p. 919.3); topical and oral formulations have been tried for disseminated amoebic infections (p. 920.1). Systemic miltefosine is being investigated for urticaria. Oral miltefosine is used for the treatment of visceral and cutaneous leishmaniasis in a dose of 1.5 to 2.5 mg/kg daily (maximum daily dose 150 mg) for 28 days.

Acanthamoeba infections. References[1,2] to the potential value of miltefosine against *Acanthamoeba* infections (p. 920.1).

1. Aichelburg AC, *et al.* Successful treatment of disseminated Acanthamoeba sp. infection with miltefosine. *Emerg Infect Dis* 2008; **14:** 1743–6.
2. Walochnik J, *et al.* Anti-acanthamoeba efficacy and toxicity of miltefosine in an organotypic skin equivalent. *J Antimicrob Chemother* 2009; **64:** 539–45.

Leishmaniasis. Miltefosine, given orally in doses of 50 to 150 mg daily, or about 2.5 mg/kg daily, for 28 days, appears to be of benefit[1-7] in the treatment of visceral leishmaniasis (p. 923.1), and has been licensed for this purpose in India and Germany. Benefit has also been reported in patients given similar doses for New World cutaneous leishmaniasis,[8] (p. 922.1) and it has also been licensed in some South American countries, but success may depend on the infecting *Leishmania* species.[9] A small