Formestane *(BAN, rINN)* ⊗

CGP-32349; Formestaani; Formestan; Formestano; Formestanum; 4-Hydroxyandrostenedione; 4-OHA; 4-OHAD. 4-Hydroxyandrost-4-ene-3,17-dione.

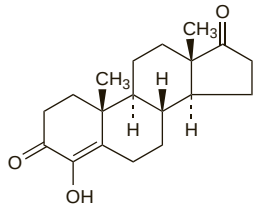
Форместан

$C_{19}H_{26}O_3$ = 302.4.

CAS — 566-48-3.

ATC — L02BG02.

ATC Vet — QL02BG02.



Adverse Effects, Treatment, and Precautions

The most frequent adverse effects of formestane are local irritation and pain at the site of injection. Patients may experience hot flushes due to oestrogen deprivation. Other occasional or rare adverse effects include rashes and pruritus, alopecia or hypertrichosis, drowsiness, dizziness, emotional lability, oedema of the leg, thrombophlebitis, vaginal spotting or bleeding, gastrointestinal disturbances, pelvic or muscle cramps, arthralgia, exacerbation of bone pain, and a vasovagal reaction. Hypersensitivity reactions to the drug or the formulation have occurred.

Care should be taken to avoid intravascular injection. Injection into or near the sciatic nerve may result in pain and nerve trauma. Caution is required if patients drive or operate machinery.

Effects on carbohydrate metabolism. Recurrent hypoglycaemic episodes developed in a diabetic patient previously well maintained on gliclazide after addition of formestane to treatment for metastatic breast cancer.[1] Episodic hypoglycaemia continued after dosage reduction, and eventually withdrawal, of gliclazide, suggesting that the effect was not simply an interaction with the sulfonylurea.

1. Brankin E, *et al.* Hypoglycaemia associated with formestane treatment. *BMJ* 1997; **314:** 869.

Pharmacokinetics

Intramuscular formestane is reported to form a depot that slowly releases active drug into the systemic circulation; maximum plasma concentrations occur about 30 to 48 hours after a single dose and then decline fairly rapidly over 2 to 4 days before declining more slowly, with an apparent elimination half-life of 5 to 6 days. The systemic uptake has been estimated at 20 to 25% of the dose in 14 days. Formestane is about 85% bound to plasma protein in the circulation. It is metabolised by conjugation to the inactive glucuronide: less than 1% of the dose is excreted in urine unchanged.

Uses and Administration

Formestane is an inhibitor of the aromatase (oestrogen synthetase) system which is responsible for the production of oestrogens from androgens. It has been used for its anti-oestrogenic properties in the endocrine treatment of advanced breast cancer in postmenopausal women (p.661).

It is given by intramuscular injection, as an aqueous suspension, in doses of 250 mg every 2 weeks. Injections should be given into each buttock alternately.

◊ Reviews.

1. Wiseman LR, McTavish D. Formestane: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the management of breast cancer and prostatic cancer. *Drugs* 1993; **45:** 66–84.
2. Anonymous. Formestane for advanced breast cancer in postmenopausal women. *Drug Ther Bull* 1993; **31:** 85–7.
3. Carlini P, *et al.* Formestane, a steroidal aromatase inhibitor after failure of non-steroidal aromatase inhibitors (anastrozole and letrozole): is a clinical benefit still achievable? *Ann Oncol* 2001; **12:** 1539–43.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Lentaron†; ***Austria:*** Lentaron; ***Braz.:*** Lentaron†; ***Chile:*** Lentaron†; ***Cz.:*** Lentaron†; ***Denm.:*** Lentaron†; ***Ger.:*** Lentaron†; ***Gr.:*** Lentaron†; ***Hong Kong:*** Lentaron†; ***Ital.:*** Lentaron†; ***Malaysia:*** Lentaron†; ***S.Afr.:*** Lentare†; ***Spain:*** Lentaron†; ***Turk.:*** Lentaron.

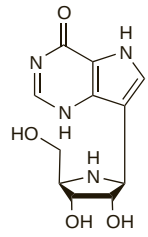
Forodesine Hydrochloride *(USAN, rINNM)*

BCX-1777 (forodesine or forodesine hydrochloride); Forodésine, Chlorhydrate de; Forodesini Hydrochloridum; Hidrocloruro de forodesina. (–)-7-[(2*S*,3*S*,4*R*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)pyrrolidin-2-yl]-1,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one hydrochloride.

Фородезина Гидрохлорид

$C_{11}H_{14}N_4O_4$,HCl = 302.7.

CAS — 209799-67-7 (forodesine); 284490-13-7 (forodesine hydrochloride).



(forodesine)

Profile

Forodesine is an inhibitor of purine nucleoside phosphorylase. It is under investigation in the treatment of T-cell lymphomas, chronic lymphocytic leukaemia, and acute lymphoblastic leukaemia.

Fotemustine *(BAN, rINN)*

Fotemustin; Fotemustina; Fotémustine; Fotemustinum; S-10036. (±)-Diethyl {1-[3-(2-chloroethyl)-3-nitrosoureido]ethyl}phosphonate.

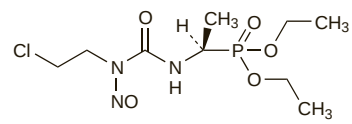
Фотемустин

$C_9H_{19}ClN_3O_5P$ = 315.7.

CAS — 92118-27-9.

ATC — L01AD05.

ATC Vet — QL01AD05.



Profile

Fotemustine is a nitrosourea derivative and alkylating agent with actions similar to those of carmustine (p.694). It is used in the treatment of disseminated malignant melanoma, particularly where cerebral metastases are present (p.673) and has been tried in primary malignancies of the brain (p.660). When used as a single agent it is licensed for intravenous or intra-arterial infusion in usual doses of 100 mg/m^2 weekly for 3 weeks to induce remission, followed after 4 to 5 weeks, if blood counts permit, by maintenance dosage with 100 mg/m^2 every 3 weeks. Intravenous infusions are given over 1 hour and intra-arterial infusions over 4 hours. Liver function should be monitored regularly during induction treatment. Regular blood counts should be taken and dosage should be reduced or withheld if white cell or platelet counts are below acceptable levels (see also Bone-marrow Depression, p.639). Bone-marrow suppression may be delayed, with the nadir of the white cell counts 5 or 6 weeks after dosing. Solutions for infusion must be freshly prepared and protected from light.

◊ References.

1. Rougier P, *et al.* Fotemustine in patients with advanced gastric cancer, a phase II trial from the EORTC-GITCCG. *Eur J Cancer* 1996; **32A:** 1432–3.
2. Marzolini C, *et al.* Pharmacokinetics of temozolomide in association with fotemustine in malignant melanoma and malignant glioma patients: comparison of oral, intravenous, and hepatic intra-arterial administration. *Cancer Chemother Pharmacol* 1998; **42:** 433–40.
3. Ulrich J, *et al.* Management of cerebral metastases from malignant melanoma: results of a combined, simultaneous treatment with fotemustine and irradiation. *J Neurooncol* 1999; **43:** 173–8.
4. Terheyden P, *et al.* Sequential interferon-alpha2b, interleukin-2 and fotemustine for patients with metastatic melanoma. *Melanoma Res* 2000; **10:** 475–82.
5. Frenay M, *et al.* Up-front chemotherapy with fotemustine (F) / cisplatin (CDDP) / etoposide (VP16) regimen in the treatment of 33 non-removable glioblastomas. *Eur J Cancer* 2000; **36:** 1026–31.
6. Mornex F, *et al.* A prospective randomized multicentre phase III trial of fotemustine plus whole brain irradiation versus fotemustine alone in cerebral metastases of malignant melanoma. *Melanoma Res* 2003; **13:** 97–103.
7. Aapro MS, *et al.* Phase II study of fotemustine in patients with advanced ovarian carcinoma: a trial of the EORTC Gynecological Cancer Group. *Eur J Cancer* 2003; **39:** 1141–13.
8. Fazeny-Dorner B, *et al.* Second-line chemotherapy with dacarbazine and fotemustine in nitrosourea-pretreated patients with recurrent glioblastoma multiforme. *Anticancer Drugs* 2003; **14:** 437–42.
9. Avril MF, *et al.* Fotemustine compared with dacarbazine in patients with disseminated malignant melanoma: a phase III study. *J Clin Oncol* 2004; **22:** 1118–25.
10. Ozkan M, *et al.* Post-operative sequential chemo-radiotherapy in high-grade cerebral gliomas with fotemustine. *J Chemother* 2004; **16:** 298–302.
11. Bonenkamp JJ, *et al.* Isolated limb infusion with fotemustine after dacarbazine chemosensitisation for inoperable loco-regional melanoma recurrence. *Eur J Surg Oncol* 2004; **30:** 1107–12.
12. Peters S, *et al.* Intra-arterial hepatic fotemustine for the treatment of liver metastases from uveal melanoma: experience in 101 patients. *Ann Oncol* 2006; **17:** 578–83.
13. Gill S, *et al.* Long-term survival and secondary acute leukemia after fotemustine therapy for metastatic melanoma. *J Clin Oncol* 2007; **25:** 4493–4.
14. Scoccianti S, *et al.* Second-line chemotherapy with fotemustine in temozolomide-pretreated patients with relapsing glioblastoma: a single institution experience. *Anticancer Drugs* 2008; **19:** 613–20.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Muforan†; ***Austral.:*** Muphoran; ***Austria:*** Muphoran; ***Belg.:*** Muphoran; ***Braz.:*** Muphoran; ***Cz.:*** Mustophoran; ***Fr.:*** Muphoran; ***Gr.:*** Muphoran; ***Hung.:*** Mustophoran; ***Israel:*** Muphoran; ***Ital.:*** Muphoran; ***NZ:*** Muphoran; ***Pol.:*** Mustophoran; ***Port.:*** Muphoran; ***Rus.:*** Mustophoran (Мюстофоран); ***Spain:*** Mustoforan; ***Turk.:*** Muphoran.

Fulvestrant *(BAN, USAN, rINN)* ⊗

Fulvestrantum; ICI-182780; ZD-9238. 7α-[9-(4,4,5,5,5-Pentafluoropentylsulfinyl)nonyl]estra-1,3,5(10)-triene-3,17β-diol.

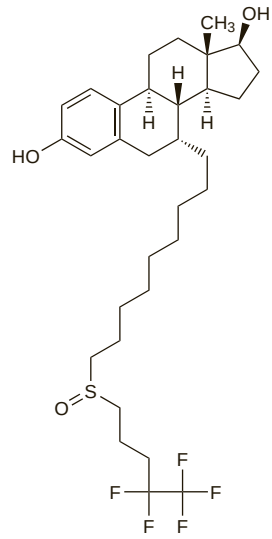
Фульвестрант

$C_{32}H_{47}F_5O_3S$ = 606.8.

CAS — 129453-61-8.

ATC — L02BA03.

ATC Vet — QL02BA03.



Pharmacopoeias. In *US.*

USP 31 (Fulvestrant). A mixture of the diastereoisomers A and B. A white powder. Freely soluble in alcohol. Store at a temperature of 2° to 8°. Protect from light.

Adverse Effects and Precautions

The most commonly reported adverse effects of fulvestrant are nausea, vomiting, constipation, diarrhoea, abdominal pain, headache, back pain, hot flushes, and pharyngitis. Injection site reactions can occur. Other adverse effects include rash, asthenia, urinary-tract infections, venous thromboembolism, and elevations in liver enzyme values. Myalgia, vertigo, and leucopenia have been reported. Hypersensitivity reactions, including angioedema and urticaria, can occur. Vaginal bleeding has been reported rarely. Fulvestrant should be given with caution to those with severe renal impairment (creatinine clearance less than 30 mL/minute) and in those with mild to moderate hepatic impairment; use is contra-indicated in those with severe hepatic impairment. In patients with bleeding tendencies, thrombocytopenia, or taking anticoagulants, fulvestrant should also be used with caution, if at all.

Pharmacokinetics

Fulvestrant is slowly absorbed after intramuscular injection; maximum plasma concentrations are reached after about 7 days. Steady-state concentrations are reached after about 3 to 6 doses (given monthly). Fulvestrant is highly bound to plasma proteins. It is metabolised primarily in the liver to a number of metabolites,