3. Kreis W, Budman D. Daily oral estramustine and intermittent intravenous docetaxel (Taxotere) as chemotherapeutic treatment for metastatic, hormone-refractory prostate cancer. *Semin Oncol* 1999; **26** (suppl 17): 34–8.
4. Kitamura T. Necessity of re-evaluation of estramustine phosphate sodium (EMP) as a treatment option for first-line monotherapy in advanced prostate cancer. *Int J Urol* 2001; **8:** 33–6.
5. Hamilton A, Muggia F. Estramustine potentiates taxane in prostate and refractory breast cancers. *Oncology (Huntingt)* 2001; **15** (suppl 7): 40–3.
6. Kitamura T, *et al.* EMP combination chemotherapy and low-dose monotherapy in advanced prostate cancer. *Expert Rev Anticancer Ther* 2002; **2:** 59–71.
7. Petrylak DP, *et al.* Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004; **351:** 1513–20.
8. Fizazi K, *et al.* Meta-analysis of Estramustine in Prostate Cancer (MECaP) Trialists' Collaborative Group. Addition of estramustine to chemotherapy and survival of patients with castration-refractory prostate cancer: a meta-analysis of individual patient data. *Lancet Oncol* 2007; **8:** 994–1000.

Preparations

BP 2008: Estramustine Phosphate Capsules.

Proprietary Preparations (details are given in Part 3)

Arg.: Amsupros†; Estracyt; ***Austria:*** Estracyt; ***Belg.:*** Estracyt; ***Canad.:*** Emcyt; ***Chile:*** Estracyt; ***Cz.:*** Estracyt; ***Denm.:*** Estracyt; ***Fin.:*** Estracyt; ***Fr.:*** Estracyt; ***Ger.:*** cellmustin; Estracyt; Medactin; Multosin; Prostamustin†; ***Gr.:*** Estracyt; ***Hong Kong:*** Estracyt; ***Hung.:*** Estracyt; ***India:*** X-Trant; ***Irl.:*** Estracyt; ***Israel:*** Estracyt; ***Ital.:*** Estracyt; ***Jpn:*** Estracyt; ***Malaysia:*** Estracyt†; ***Mex.:*** Emcyt; ***Neth.:*** Estracyt; ***Norw.:*** Estracyt; ***Pol.:*** Estracyt; ***Port.:*** Estracyt; ***Rus.:*** Estracyt (Эстрацит); ***S.Afr.:*** Estracyt; ***Singapore:*** Estracyt; ***Spain:*** Estracyt; ***Swed.:*** Estracyt; ***Switz.:*** Estracyt; ***Turk.:*** Estracyt; ***UK:*** Estracyt; ***USA:*** Emcyt; ***Venez.:*** Estracyt.

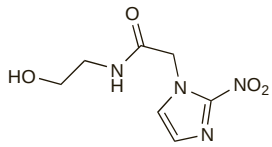
Etanidazole *(USAN, rINN)*

Etanidazol; Étanidazole; Etanidazolum; NSC-301467; SR-2508. *N*-(2-Hydroxyethyl)-2-nitroimidazole-1-acetamide.

Этанидазол

$C_7H_{10}N_4O_4$ = 214.2.

CAS — 22668-01-5.



Profile

Etanidazole is a radiosensitiser, structurally related to metronidazole, that is under investigation as an adjunct to radiotherapy in the treatment of cancer. Peripheral neuropathy may be dose-limiting.

◊ References.

1. Lee DJ, *et al.* Results of an RTOG phase III trial (RTOG 85-27) comparing radiotherapy plus etanidazole with radiotherapy alone for locally advanced head and neck carcinomas. *Int J Radiat Oncol Biol Phys* 1995; **32:** 567–76.
2. Eschwege F, *et al.* Results of a European randomized trial of etanidazole combined with radiotherapy in head and neck carcinomas. *Int J Radiat Oncol Biol Phys* 1997; **39:** 275–81.
3. Marcus KJ, *et al.* A phase I trial of etanidazole and hyperfractionated radiotherapy in children with diffuse brainstem glioma. *Int J Radiat Oncol Biol Phys* 2003; **55:** 1182–5.
4. Drzymala RE, *et al.* Radiation Therapy Oncology Group. A phase I-B trial of the radiosensitizer: etanidazole (SR-2508) with radiosurgery for the treatment of recurrent previously irradiated primary brain tumors or brain metastases (RTOG Study 95-02). *Radiother Oncol* 2008; **87:** 89–92.

Etoposide *(BAN, USAN, rINN)*

EPEG; Etoposid; Étoposide; Etoposidi; Etopósido; Etoposidum; Etopozid; Etopozidas; NSC-141540; VP-16; VP-16-213. 4′-Demethylepipodophyllotoxin 9-[4,6-*O*-(*R*)-ethylidene-β-D-glucopyranoside]; (5*S*,5a*R*,8a*S*,9*R*)-9-(4,6-*O*-Ethylidene-β-D-glucopyranosyloxy)-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-isobenzofuro[5,6-*f*][1,3]benzodioxol-6(5a*H*)-one.

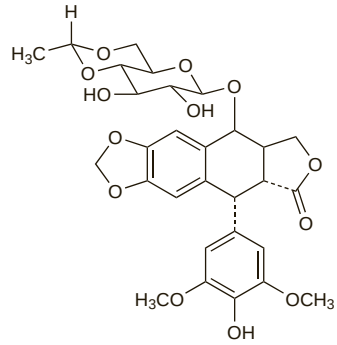
Этопозид

$C_{29}H_{32}O_{13}$ = 588.6.

CAS — 33419-42-0.

ATC — L01CB01.

ATC Vet — QL01CB01.



NOTE. The trivial name epipodophyllotoxin has occasionally been used incorrectly for this derivative.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 6.2 (Etoposide). A white or almost white, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane; sparingly soluble in methyl alcohol. Store in airtight containers.

USP 31 (Etoposide). A fine, white to off-white, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol, in chloroform, in dichloromethane, and in ethyl acetate; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Etoposide Phosphate *(USAN)*

BMY-40481; Etopósido, fosfato de. {5*R*-[5α,5aβ,8aα,9β(*R**)]}-5-[3,5-Dimethoxy-4-(phosphonooxy)phenyl]-9-[(4,6-*O*-ethylidene-β-D-glucopyranosyl)oxy]-5,8,8a,9-tetrahydrofuro-[3′,4′:6,7]naphtho[2,3-*d*]-1,3-dioxol-6(5a*H*)-one; 4′-Demethylepipodophyllotoxin 9-(4,6-*O*-ethylidene-β-D-glucopyranoside) 4′-(dihydrogen phosphate).

$C_{29}H_{33}O_{16}P$ = 668.5.

CAS — 117091-64-2.

ATC — L01CB01.

ATC Vet — QL01CB01.

Incompatibility. For reference to precipitation when mannitol or potassium chloride was added to mixtures of etoposide and cisplatin in sodium chloride injection, see Cisplatin, p.698.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

The dose-limiting toxicity of etoposide is myelosuppression, mainly seen as leucopenia, but also thrombocytopenia, and sometimes anaemia. The nadir of the granulocyte count usually occurs 7 to 14 days after a dose, with recovery by about 21 days. Nausea and vomiting are common; there may also be anorexia, diarrhoea, and mucositis. Gastrointestinal toxicity may be more common after oral dosage. Reversible alopecia occurs in about two-thirds of all patients. Hypersensitivity or anaphylactoid reactions can occur, characterised by flushing, chills, fever, tachycardia, bronchospasm, dyspnoea, and hypotension. Apnoea and fatal reactions associated with bronchospasm have been reported. Peripheral or central neuropathies, including transient cortical blindness, have been reported rarely, as have weakness, fatigue, somnolence, aftertaste, fever, rashes, urticaria, skin pigmentation, pruritus, and dysphagia. Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred rarely. Tumour lysis syndrome, sometimes fatal, has been reported after use of etoposide with other chemotherapeutic drugs. Disturbances of liver function have been reported, mainly at high doses. There have been occasional reports of cardiotoxicity. Local irritation and thrombophlebitis may occur at the site of injection. Care should be taken to avoid extravasation although tissue damage (possibly associated with the vehicle) is rare.

Rapid intravenous doses may cause hypotension; etoposide should be given by infusion over at least 30 minutes. Etoposide should not be given to patients with severe hepatic impairment nor by the intracavitary route.

Some adverse effects associated with intravenous etoposide may be due to the formulation of the vehicle.

There is evidence that etoposide may be associated with the development of secondary leukaemias—see Carcinogenicity, p.635.

Breast feeding. Some licensed product information states that it is not known whether etoposide is excreted into breast milk. However, in breast milk samples from a woman given consolidation therapy, including etoposide,[1] for acute promyelocytic leukaemia, etoposide concentrations were maximal just after a dose, but decreased rapidly to undetectable levels within 24 hours on each of three days. She started to breast feed her baby 3 weeks after the completion of therapy, and no abnormalities were observed in the infant up to 16 months of age.

1. Azuno Y, *et al.* Mitoxantrone and etoposide in breast milk. *Am J Hematol* 1995; **48:** 131–2.

Effects on the gastrointestinal tract. Pneumatosis intestinalis (the presence of gas within the bowel wall), a rare condition, has been reported after intravenous[1] and oral[2] etoposide. It is supposed that myelosuppressive drugs might interfere with the mucosal integrity of the intestinal tract, and that the intestinal mucosa might be highly sensitive to etoposide.

1. Hashimoto S, *et al.* Pneumatosis cystoides intestinalis after chemotherapy for hematological malignancies: report of 4 cases. *Intern Med* 1995; **34:** 212–15.
2. Shih I-L, *et al.* Pneumatosis coli after etoposide chemotherapy for breast cancer. *J Clin Oncol* 2007; **25:** 1623–5.

Effects on the nervous system. A report of an acute dystonic reaction in a child given etoposide as part of a combined maintenance regimen for acute lymphoblastic leukaemia;[1] the patient had been receiving the same regimen uneventfully for over a year but symptoms (which responded to diphenhydramine) recurred on rechallenge with etoposide.

1. Ascher DP, Delaney RA. Acute dystonia from etoposide. *Drug Intell Clin Pharm* 1988; **22:** 41–2.

Handling and disposal. *Urine and faeces* produced for up to 4 and 7 days respectively after a dose of etoposide 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.

Hypersensitivity. Hypersensitivity reactions to intravenous etoposide are characterised by one or more of: hypotension, bronchospasm, flushing, exanthema, dyspnoea, fever, chills, tachycardia, tightness in the chest, cyanosis, and hypertension. Although originally thought rare, some investigators[1] have reported an incidence of up to about 50%, particularly in younger patients. The mechanism is uncertain, but a literature review[1] supported the hypothesis that it might not be antibody-mediated, since reducing the rate of infusion can prevent reactions, as can reducing etoposide concentration in the infusion solution. However, an immunogenic mechanism cannot be excluded as hypersensitivity appears to have been reported less frequently with the oral formulation, which unlike the infusion does not contain polysorbate 80. In addition, there are reports[2-4] of successful use of etoposide phosphate formulations (which do not contain polysorbate 80) after hypersensitivity reactions to etoposide, suggesting that the solvent may be responsible.

1. Hoetelmans RMW, *et al.* Hypersensitivity reactions to etoposide. *Ann Pharmacother* 1996; **30:** 367–71.
2. Bernstein BJ, Troner MB. Successful rechallenge with etoposide phosphate after an acute hypersensitivity reaction to etoposide. *Pharmacotherapy* 1999; **19:** 989–91.
3. Siderov J, *et al.* Safe administration of etoposide phosphate after hypersensitivity reaction to intravenous etoposide. *Br J Cancer* 2002; **86:** 12–13.
4. Collier K, *et al.* Successful treatment with etoposide phosphate in patients with previous etoposide hypersensitivity. *J Oncol Pharm Pract* 2008; **14:** 51–5.

Pregnancy. For a report of hair loss in an infant, attributed to etoposide given to the mother before delivery, see Pregnancy, under Cisplatin, p.699.

Interactions

For a general outline of antineoplastic drug interactions, see p.642. Phenylbutazone, salicylic acid, and sodium salicylate can affect the protein binding of etoposide. Caution is advised when etoposide phosphate is given with drugs such as levamisole hydrochloride that are known to inhibit phosphatase activities.

Antineoplastics. Giving etoposide 2 days after a dose of *cisplatin* was associated with a marked decrease in etoposide clearance and more toxicity, compared with the same dose given 21 days after a dose of cisplatin, in a study involving 17 children.[1] There was no evidence of a persistent decrease in etoposide clearance associated with the cumulative dose of cisplatin, however. In a randomised, crossover study,[2] cisplatin or *carboplatin* were given alternately during 2 courses of etoposide. Although increases in the area under the concentration-time curve of etoposide were seen in the second course, effects were modest

and, given the pharmacokinetic variability seen with etoposide, the authors considered any clinical impact to be small.

1. Relling MV, *et al.* Etoposide pharmacokinetics and pharmacodynamics after acute and chronic exposure to cisplatin. *Clin Pharmacol Ther* 1994; **56:** 503–11.
2. Thomas HD, *et al.* Randomized cross-over clinical trial to study potential pharmacokinetic interactions between cisplatin or carboplatin and etoposide. *Br J Clin Pharmacol* 2002; **53:** 83–91.

Ciclosporin. High-dose ciclosporin therapy was found to increase the exposure to etoposide by 80%, and to reduce etoposide clearance by 38%. Leucopenia was increased. Etoposide doses should be halved when the drug is given with high-dose ciclosporin.[1] In a study[2] of children who received etoposide and mitoxantrone for acute myeloid leukaemia, the addition of ciclosporin with a 40% reduction in the doses of the antineoplastics still resulted in a 71% reduction in the clearance of etoposide, and a 42% reduction for mitoxantrone. However, there was wide interpatient variability, and the rates of stomatitis and infection were similar between the groups, with or without ciclosporin.

1. Lum BL, *et al.* Alteration of etoposide pharmacokinetics and pharmacodynamics by cyclosporine in a phase I trial to modulate drug resistance. *J Clin Oncol* 1992; **10:** 1635–42.
2. Lacayo NJ, *et al.* Pharmacokinetic interactions of cyclosporine with etoposide and mitoxantrone in children with acute myeloid leukemia. *Leukemia* 2002; **16:** 920–7.

Grapefruit juice. In a randomised crossover study[1] of 6 patients, grapefruit juice appeared to reduce the oral bioavailability of etoposide. Initially the authors had expected the opposite since etoposide is demethylated by cytochrome P450 isoenzyme CYP3A4. Although no definite conclusions could be made due to the small number of patients studied, a possible mechanism might have been alteration of P-glycoprotein mediated transport.

1. Reif S, *et al.* Effect of grapefruit juice intake on etoposide bioavailability. *Eur J Clin Pharmacol* 2002; **58:** 491–4.

Pharmacokinetics

Absorption after oral doses is variable, but on average about 50% of the dose of etoposide is absorbed. The pharmacokinetics of etoposide are subject to considerable interindividual variation. It is rapidly distributed, and concentrations in plasma fall in a biphasic manner, with a terminal half-life of 4 to 11 hours. Etoposide is about 94% bound to plasma protein. It is metabolised by the cytochrome P450 isoenzyme CYP3A4. Etoposide is excreted in urine and faeces as unchanged drug and metabolites: about 45% of a dose is reported to be excreted in urine over 72 hours. It crosses the blood-brain barrier poorly; concentrations in CSF are 1 to 10% of those in plasma. It is distributed into breast milk (see Breast Feeding, above).

◊ References.

1. Toffoli G, *et al.* Pharmacokinetic optimisation of treatment with oral etoposide. *Clin Pharmacokinet* 2004; **43:** 441–66.

Metabolism. Studies *in vitro* suggested that metabolic activation of etoposide by oxidation into the *O*-quinone derivative might play an essential role in its activity against DNA.[1]

1. van Maanen JMS, *et al.* Metabolic activation of anti-tumour agent VP 16-213. *Hum Toxicol* 1986; **5:** 136.

Uses and Administration

Etoposide is a semisynthetic derivative of podophyllotoxin with antineoplastic properties; it interferes with the function of topoisomerase II thus inhibiting DNA synthesis, and is most active against cells in the late S and G_2 phases of the cell cycle.

It is used, usually with other antineoplastics, in the treatment of tumours of the testis, small cell cancer of the lung, and in acute leukaemias. It has also been tried in other solid tumours including those of the brain, gastrointestinal tract, ovary, and thymus, and some childhood neoplasms; in lymphomas, and in the treatment of Kaposi's sarcoma associated with AIDS. For further discussion, see the cross-references indicated under Malignant Neoplasms, below.

Etoposide is given by slow intravenous infusion over at least 30 minutes, as a solution in sodium chloride 0.9% or glucose 5% injection. In general, the concentration of the infusion should be between 200 to 400 micrograms/mL, although recommendations vary depending on the preparation; precipitation may occur at higher concentrations. Etoposide phosphate, a prodrug, has improved solubility in water. 113.6 mg of etoposide phosphate is equivalent to 100 mg of etoposide. Intravenous doses are calculated in terms of etoposide, and are identical to those of the base, but it may be given in concentrations up to the equivalent of etoposide 20 mg/mL. Etoposide phosphate solutions may be infused over 5 minutes to 3.5 hours. Etoposide may also be given orally.

Regimens vary; the usual intravenous dose of etoposide ranges from 50 to 120 mg/m^2 daily for 5 days. Somewhat lower doses have been suggested in lung cancer. Alternatively, 100 mg/m^2 has been given on alternate days to a total of 300 mg/m^2. The usual oral dose of etoposide is 100 to 240 mg/m^2 daily for 5 consecutive days. Courses may be repeated after 3 to 4 weeks. Doses should be reduced in renal impairment (see below).

Administration. Although precipitation of etoposide may occur at high infusion concentrations (see Uses and Administration, above), high doses of etoposide have been infused undiluted to avoid giving large volumes of fluid to the patient.[1-3] Etoposide was infused through a central line, and this method has been reported to be safe and effective;[2] pharmacokinetic studies suggested unaltered systemic bioavailability when compared with diluted infusions.[3] However, cracking of plastic syringes and infusion cassettes has been reported, possibly due to the polyethylene glycol component of the formulation. This appears particularly problematic when devices containing ABS plastic (a polymer produced from acrylonitrile, butadiene, and styrene) are used; alternative devices may be preferable.[1]

Etoposide has been injected into the ventricles of the brain in the treatment of patients with neoplastic meningitis.[4]

1. Schwinghammer TL, *et al.* Cracking of ABS plastic devices used to infuse undiluted etoposide injection. *Am J Hosp Pharm* 1988; **45:** 1277.
2. Creger RJ, *et al.* Infusion of high doses of undiluted etoposide through central venous catheters during preparation for bone marrow transplantation. *Cancer Invest* 1990; **8:** 13–16.
3. Ehninger G, *et al.* Unaltered pharmacokinetics after the administration of high-dose etoposide without prior dilution. *Cancer Chemother Pharmacol* 1991; **28:** 214–16.
4. Chamberlain MC, *et al.* Phase II trial of intracerebrospinal fluid etoposide in the treatment of neoplastic meningitis. *Cancer* 2006; **106:** 2021–7.

Administration in renal impairment. Some licensed product information for etoposide or etoposide phosphate recommends that patients with a creatinine clearance of between 15 and 50 mL/minute be given 75% of the recommended dose. No recommendations are given for those patients having a creatinine clearance of below 15 mL/minute, although one product (*Vepesid; BMS, USA*) suggests that further dose reduction in these patients be considered.

Blood disorders, non-malignant. For reference to the use of combination chemotherapy, including etoposide, in a few patients with refractory idiopathic thrombocytopenic purpura, see p.1505.

Histiocytic syndromes. Systemic chemotherapy is often tried in patients with extensive Langerhans-cell histiocytosis (p.650), although its value is uncertain. Etoposide is one of the drugs widely used for this purpose.

Hypereosinophilic syndrome. Etoposide has been reported to produce clinical responses in patients with the hypereosinophilic syndrome.[1]

1. Bourrat E, *et al.* Etoposide for treating the hypereosinophilic syndrome. *Ann Intern Med* 1994; **121:** 899–900.

Malignant neoplasms. Etoposide has been used for a variety of solid tumours: in particular it is part of curative regimens used in the treatment of testicular cancer and germ-cell tumours of the ovary (see p.673 and p.670), and is used with cisplatin and other drugs in the treatment of lung cancer (p.668). Other solid neoplasms in which it is sometimes employed include those of the brain (p.660), stomach (p.664), and thymus (p.674), as well as in neuroblastoma (p.674), Wilms' tumour (p.667), retinoblastoma (p.675), and rhabdomyosarcoma (p.676); it has also formed part of systemic regimens for bone sarcomas (p.675), disseminated Kaposi's sarcoma (see p.675), and gestational trophoblastic tumours (p.650). Etoposide is used in regimens for Hodgkin's disease (see p.655); it is also sometimes used in aggressive intermediate- and high-grade non-Hodgkin's lymphomas (p.656), and may produce short-term responses in mycosis fungoides (p.657). It is also used in Burkitt's lymphoma (p.657). Etoposide may have benefits when added to induction protocols for acute myeloid leukaemia (p.652), and when used as part of intensification therapy in acute lymphoblastic leukaemia (p.651). It has formed part of salvage regimens in multiple myeloma (p.658).

Vasculitic syndromes. For mention of the use of etoposide to induce remission in patients with Wegener's granulomatosis resistant to standard therapy with cyclophosphamide and corticosteroids, see p.1515.

Preparations

BP 2008: Etoposide Capsules; Etoposide Intravenous Infusion;
USP 31: Etoposide Capsules; Etoposide Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Citodox; Etocris; Etopofos†; Euvaxon; Labimion†; Neoplaxol; Optasid†; Percas; Vepesid; VP-Gen; ***Austral.:*** Etopophos; Vepesid; ***Austria:*** Etopofos; Vepesid; ***Belg.:*** Celltop; Eposin; Etopophos†; Vepesid; ***Braz.:*** Eposido; Etopos†; Etopul†; Etosin; Eunades; Evoposdo†; Nexvep; Posidon; Vepesid; ***Canad.:*** Vepesid; ***Chile:*** Epsidox; Lastet†; ***Cz.:*** Etopophos†; Lastet; Vepesid; ***Denm.:*** Etopofos; Vepesid; ***Fin.:*** Eposin†; Etopofos; Exitop†; Vepesid; ***Fr.:*** Celltop; Etopophos; Vepeside; ***Ger.:*** ETO CS; Eto-cell; Eto-Gry; Etomedac; Etopophos; Exitop; Neoposid; Onkoposid; Riboposid; Vepesid; ***Gr.:*** Etobion; Vepesid; ***Hong Kong:*** Vepesid; ***Hung.:*** Lastet; Sintopozid; Vepesid; ***India:*** Bioposide; Etosid; Lastet†; Posid; ***Indon.:*** Posyd; ***Irl.:*** Etopophos†; Vepesid; ***Israel:*** Etopophos†; Vepesid†; ***Ital.:*** Lastet; Vepesid; ***Jpn:*** Lastet; ***Malaysia:*** Eposin; Lastet; Vepesid†; ***Mex.:*** Etonco; Etopos; Kenazol; Lastet†; Vepesid; VP-Tec; ***Neth.:*** Toposin; Vepesid; ***Norw.:*** Eposin; Etopofos; Vepesid; ***NZ:*** Etopophos; Vepesid; ***Philipp.:*** Etopoxan; Etopul; Fytosid; Lastet; Posid; Topresid; Vepesid; ***Pol.:*** Lastet; Sintopozid; Vepesid; ***Port.:*** Eposin; Lastet; Vepesid; ***Rus.:*** Etopos (Этопос)†; Vepesid (Вепезид); ***S.Afr.:*** Eposin; Etopophos; Vepesid; ***Singapore:*** Lastet; Vepesid†; ***Spain:*** Eposin†; Lastet; Vepesid; ***Swed.:*** Eposin; Etopofos; Exitop†; Vepesid; ***Switz.:*** Etopophos; Vepesid; ***Thai.:*** Eposin; Etopos; Fytosid; Lastet; Vepesid; ***Turk.:*** Eposin; Lastet; Vepesid; ***UK:*** Eposin; Etopophos; Vepesid; ***USA:*** Etopophos; Toposar; Vepesid; ***Venez.:*** Etonolver; Etosid; Fytosid.

Exemestane *(BAN, USAN, rINN)* ⊗

Eksemestaani; Eksemestan; Exemestan; Exémestane; Exemestano; Exemestanum; FCE-24304. 6-Methyleneandrosta-1,4-diene-3,17-dione.

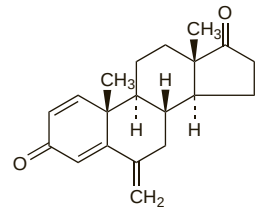
Эксеместан

$C_{20}H_{24}O_2$ = 296.4.

CAS — 107868-30-4.

ATC — L02BG06.

ATC Vet — QL02BG06.



Adverse Effects and Precautions

The most frequently reported adverse effects for exemestane are gastrointestinal disturbances, hot flushes, arthralgia, myalgia, sweating, fatigue, and dizziness. Other reported effects include headache, insomnia, somnolence, depression, skin rashes, alopecia, asthenia, and peripheral and leg oedema. Thrombocytopenia and leucopenia have been reported occasionally. Reductions in bone mineral density can occur with long-term use of exemestane. Density should therefore be assessed at the start of therapy, in those with osteoporosis or at risk of it, and patients monitored during therapy.

The use of exemestane is contra-indicated in premenopausal women (particularly in pregnancy).

Effects on the musculoskeletal system. Exemestane therapy has been found to decrease bone mineral density (BMD) in postmenopausal women with early breast cancer.[1,2] In one study, the decrease in BMD was seen within 6 months of switching therapy from tamoxifen, and was significant at the lumbar spine and hip.[2] In a Scandinavian study, BMD loss with exemestane compared with placebo was modest from the femoral neck, and not significant at the lumbar spine;[1] however, it was noted that the changes in the placebo group were greater than expected, possibly due to the lack of calcium and vitamin D supplementation, and that there is a high incidence of hip fracture in Scandinavia. Patients starting exemestane therapy should be assessed for baseline BMD;[1] while those with normal BMD are considered to not need further assessment beyond lifestyle advice, those with osteopenia should have their BMD monitored, and therapeutic interventions made as appropriate.[2]

1. Lønning PE, *et al.* Effects of exemestane administered for 2 years versus placebo on bone mineral density, bone biomarkers, and plasma lipids in patients with surgically resected early breast cancer. *J Clin Oncol* 2005; **23:** 5126–37.
2. Coleman RE, *et al.* Skeletal effects of exemestane on bone-mineral density, bone biomarkers, and fracture incidence in postmenopausal women with early breast cancer participating in the Intergroup Exemestane Study (IES): a randomised controlled study. *Lancet Oncol* 2007; **8:** 119–27.

Interactions

The metabolism of exemestane is mediated by the cytochrome P450 isoenzyme CYP3A4. Rifampicin, a potent inducer of CYP isoenzymes, can decrease plasma concentrations of exemestane. Use with other drugs that induce this isoenzyme may reduce the efficacy of exemestane. Exemestane should also be used cautiously with drugs that are substrates for CYP3A4