Erlotinib Hydrochloride *(USAN, rINNM)*

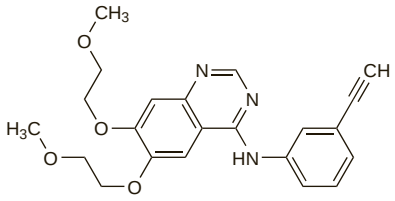
CP-358774-01; Erlotinib, Chlorhydrate d'; Erlotinibi Hydrochloridum; Hidrocloruro de erlotinib; NSC-718781; OSI-774. *N*-(3-Ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine hydrochloride.

Эрльотиниба Гидрохлорид

$C_{22}H_{23}N_3O_4$,HCl = 429.9.

CAS — 183321-74-6 (erlotinib); 183319-69-9 (erlotinib hydrochloride).

ATC — L01XE03.



(erlotinib)

Adverse Effects, Treatment, and Precautions

The most common adverse effects associated with erlotinib hydrochloride are rash and diarrhoea. Moderate or severe diarrhoea should be treated with an appropriate antidiarrhoeal such as loperamide; dose reduction may be needed. In more severe or persistent cases leading to dehydration, therapy should be stopped temporarily. Other common adverse effects include other gastrointestinal disturbances, gastrointestinal bleeding, fatigue, alopecia, stomatitis, pruritus, dry skin, paronychia, conjunctivitis, keratoconjunctivitis sicca, epistaxis, and abdominal pain. Alterations in liver function tests have occurred. Rare cases of hepatic failure, including fatalities, have been reported. Interstitial lung disease has also been reported; fatalities have occurred. Erlotinib treatment should be interrupted if unexplained pulmonary symptoms occur, such as dyspnoea, cough, and fever.

Interactions

Inhibitors of the cytochrome P450 isoenzyme CYP3A4, such as ketoconazole, can increase erlotinib concentrations and use with potent inhibitors should be avoided as increased toxicity may occur. Conversely, CYP3A4 inducers, such as rifampicin, can reduce erlotinib concentrations and may reduce its efficacy. Dose adjustments may be required (see Uses and Administration, below). Caution is also required with ciprofloxacin or potent inhibitors of CYP1A2, as erlotinib exposure may be increased, and dose reductions may be needed if adverse effects occur. Use with P-glycoprotein inhibitors such as ciclosporin and verapamil may cause altered distribution or elimination of erlotinib. Caution is advised when erlotinib is used with antacids, proton pump inhibitors, or histamine H_2-receptor antagonists, as erlotinib absorption may be impaired. Exposure to erlotinib is reduced in smokers compared with non-smokers.

Pharmacokinetics

Erlotinib is absorbed from the gastrointestinal tract, with a bioavailability of about 60%; this may increase up to almost 100% in the presence of food. Peak plasma concentrations are reached about 4 hours after a dose, and it is about 93% bound to plasma proteins. Erlotinib is metabolised predominantly by the cytochrome P450 isoenzyme CYP3A4, and to a lesser extent by CYP1A2. Metabolic pathways include demethylation, to metabolites OSI-420 and OSI-413, oxidation, and aromatic hydroxylation. Erlotinib has an elimination half-life of about 36 hours. More than 80% of a dose is excreted as metabolites in the faeces.

Uses and Administration

Erlotinib inhibits the intracellular phosphorylation of tyrosine kinase associated with the epidermal growth factor receptor. It is used for the management of locally advanced or metastatic non-small cell lung cancer (p.668) that is unresponsive to other therapy. It is also used with gemcitabine in the first-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer (p.671). It is given orally as the hydrochloride but doses are expressed in terms of the base: erlotinib hydrochloride 109 mg is equivalent to about 100 mg of erlotinib.

The usual dose for non-small cell lung cancer is 150 mg daily, taken at least 1 hour before or 2 hours after food. In the treatment of pancreatic cancer, the recommended dose is 100 mg daily, taken at least 1 hour before or 2 hours after food. Treatment is continued until disease progression or unacceptable toxicity occurs. Where dosage adjustment is necessary, reductions are made in 50 mg steps.

If concurrent use of potent inhibitors or inducers of cytochrome P450 isoenzyme CYP3A4 cannot be avoided, dose adjustments of erlotinib are considered necessary. When used with a potent CYP3A4 inhibitor, the dose of erlotinib may need to be reduced, especially if severe adverse effects occur. When given with a potent CYP3A4 inducer, increases in the dose of erlotinib should be considered at 2-week intervals with monitoring. The maximum dose of erlotinib when used with rifampicin is 450 mg. If the inducer is then stopped, the erlotinib dose will need to be immediately reduced to the indicated starting dose.

Erlotinib is also under investigation in the treatment of malignant glioma.

◊ References.

1. Perez-Soler R. The role of erlotinib (Tarceva, OSI 774) in the treatment of non-small cell lung cancer. *Clin Cancer Res* 2004; **10** (suppl): 4238s–4240s.
2. Pérez-Soler R, *et al.* Determinants of tumor response and survival with erlotinib in patients with non—small-cell lung cancer. *J Clin Oncol* 2004; **22:** 3238–47.
3. Anonymous. Erlotinib. *Med Lett Drugs Ther* 2005; **47:** 25–6.
4. Smith J. Erlotinib: small-molecule targeted therapy in the treatment of non-small-cell lung cancer. *Clin Ther* 2005; **27:** 1513–34.
5. Brown ER, Shepherd FA. Erlotinib in the treatment of non-small cell lung cancer. *Expert Rev Anticancer Ther* 2005; **5:** 767–75.
6. Shepherd FA, *et al.* Erlotinib in previously treated non—small-cell lung cancer. *N Engl J Med* 2005; **353:** 123–32.
7. Tang PA, *et al.* A review of erlotinib and its clinical use. *Expert Opin Pharmacother* 2006; **7:** 177–93.
8. Gridelli C, *et al.* Erlotinib in non-small-cell lung cancer. *Expert Opin Pharmacother* 2007; **8:** 2579–92.
9. Saif MW, *et al.* Erlotinib: the first biologic in the management of pancreatic cancer. *Expert Opin Pharmacother* 2008; **9:** 1595–1607.

Administration in hepatic or renal impairment. Erlotinib is metabolised by the liver. UK licensed product information states that although erlotinib exposure was similar in patients with moderate hepatic impairment (Child-Pugh score 7 to 9) compared with those with adequate hepatic function, caution is advised when using erlotinib in hepatic impairment. Dose reduction or interruption of therapy should be considered if adverse effects occur. Use in severe hepatic impairment is not recommended due to a lack of data.

UK licensed product information also states that no dose adjustments appear necessary in patients with mild to moderate renal impairment, but that use of erlotinib in patients with severe renal impairment is not recommended. There are no data available for patients with a creatinine clearance less than 15 mL/minute or those with a serum creatinine concentration greater than 1.5 times the upper normal limit.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Tarceva; ***Austral.:*** Tarceva; ***Belg.:*** Tarceva; ***Canad.:*** Tarceva; ***Chile:*** Tarceva; ***Cz.:*** Tarceva; ***Fin.:*** Tarceva; ***Fr.:*** Tarceva; ***Ger.:*** Tarceva; ***Gr.:*** Tarceva; ***Hong Kong:*** Tarceva; ***Hung.:*** Tarceva; ***Irl.:*** Tarceva; ***Israel:*** Tarceva; ***Malaysia:*** Tarceva; ***Mex.:*** Tarceva; ***Neth.:*** Tarceva; ***NZ:*** Tarceva; ***Philipp.:*** Tarceva; ***Pol.:*** Tarceva; ***Port.:*** Tarceva; ***Rus.:*** Tarceva (Тарцева); ***Singapore:*** Tarceva; ***Swed.:*** Tarceva; ***Switz.:*** Tarceva; ***UK:*** Tarceva; ***USA:*** Tarceva.

Estramustine Sodium Phosphate *(BANM, rINNM)*

Estramustin Fosfat Sodyum; Estramustine, Phosphate Sodique de; Estramustine Phosphate Sodium *(USAN)*; Fosfato sódico de estramustina; Natrii Estramustini Phosphas; NSC-89199 (estramustine phosphate); Ro-21-8837/001; Ro-22-2296/000 (estramustine). Estra-1,3,5(10)-triene-3,17β-diol 3-[bis(2-chloroethyl)carbamate] 17-(disodium phosphate); Disodium 3-[bis(2-chloroethyl)-carbamoyloxy]estra-1,3,5(10)-trien-17β-yl orthophosphate.

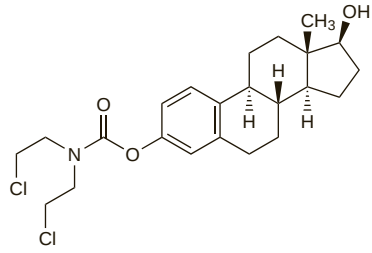
Натрия Эстрамустина Фосфат

$C_{23}H_{30}Cl_2NNa_2O_6P$ = 564.3.

CAS — 2998-57-4 (estramustine); 4891-15-0 (estramustine phosphate); 52205-73-9 (estramustine sodium phosphate).

ATC — L01XX11.

ATC Vet — QL01XX11.



(estramustine)

Pharmacopoeias. In *Br.*

BP 2008 (Estramustine Sodium Phosphate). A white or almost white powder. Freely soluble in water and in methyl alcohol; very slightly soluble in dehydrated alcohol and in chloroform. A 0.5% solution in water has a pH of 8.5 to 10.0. Protect from light.

Adverse Effects, Treatment, and Precautions

Oestrogenic adverse effects are fairly common, and may include gynaecomastia, fluid retention, and cardiovascular effects. Gastrointestinal disturbances, hepatic dysfunction, loss of libido, hypersensitivity reactions, and occasionally leucopenia and thrombocytopenia may occur. Estramustine is contra-indicated in patients with peptic ulceration and severe hepatic or cardiovascular disease. Diabetes mellitus may be exacerbated, and the drug should be given with care to patients with disorders such as congestive heart failure, epilepsy, hypertension, migraine, and renal impairment which may be adversely affected by additional fluid retention. Care is also required in patients with conditions predisposing to hypercalcaemia, and serum calcium should be monitored in hypercalcaemic patients.

Porphyria. Estramustine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

Estramustine sodium phosphate should not be given with milk products or products high in calcium, which may interfere with its absorption. Hypersensitivity reactions including angioedema have occurred rarely in patients given estramustine who were also receiving an ACE inhibitor.

Pharmacokinetics

Up to 75% of a dose of estramustine sodium phosphate is absorbed from the gastrointestinal tract and rapidly dephosphorylated. Estramustine is found in the body mainly as its oxidised isomer estromustine; both forms accumulate in the prostate. Some hydrolysis of the carbamate linkage occurs in the liver, releasing estradiol, estrone, and the normustine group. Estramustine and estromustine have plasma half-lives of 10 to 20 hours, and are excreted with their metabolites mainly in the faeces.

Uses and Administration

Estramustine is a combination of estradiol and normustine and has weaker oestrogenic activity than estradiol and weaker antineoplastic activity than most other alkylating agents. Estramustine phosphate is given orally as the disodium salt. Doses are calculated in terms of estramustine phosphate; 108 mg of estramustine sodium phosphate is equivalent to about 100 mg of estramustine phosphate. Estramustine phosphate with meglumine has been given by intravenous injection.

Estramustine sodium phosphate is licensed for use in the treatment of advanced prostatic carcinoma (p.671). An estramustine phosphate dose of about 14 mg/kg daily in divided doses is used. The usual initial dose is 560 to 840 mg daily, which may be adjusted to between 140 mg and 1.4 g daily according to the response and gastrointestinal tolerance. It should be given not less than 1 hour before or 2 hours after meals.

◊ References.

1. Bergenheim AT, Henriksson R. Pharmacokinetics and pharmacodynamics of estramustine phosphate. *Clin Pharmacokinet* 1998; **34:** 163–72.
2. Sangrajrang S, *et al.* Estramustine resistance. *Gen Pharmacol* 1999; **33:** 107–13.

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.

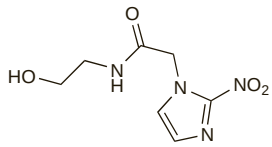
Etanidazole *(USAN, rINN)*

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.

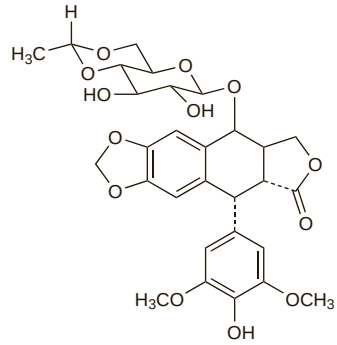
Этопозид

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