Epirubicin Hydrochloride

(BANM, USAN, rINNM)

4′-Epiadriamycin Hydrochloride; 4′-Epidoxorubicin Hydrochloride; Épirubicine, chlorhydrate d'; Epirubicin-hidroklorid; Epirubicin-hydrochlorid; Epirubicinhydroklorid; Epirubicini hydrochloridum; Epirubicino hidrochloridas; Epirubisiinihydrokloridi; Epirubisin Hidroklorür; Hidrocloruro de epirubicina; IMI-28; Pidorubicin Hydrochloride. (8*S*,10*S*)-10-(3-Amino-2,3,6-trideoxy-α-L-*arabino*-hexopyranosyloxy)-8-glycolloyl-7,8,9,10-tetrahydro-6,8,-11-trihydroxy-1-methoxynaphthacene-5,12-dione hydrochloride.

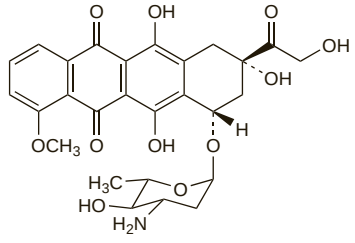
Эпирубицина Гидрохлорид

$C_{27}H_{29}NO_{11}$,HCl = 580.0.

CAS — 56420-45-2 (epirubicin); 56390-09-1 (epirubicin hydrochloride).

ATC — L01DB03.

ATC Vet — QL01DB03.



(epirubicin)

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*

Ph. Eur. 6.2 (Epirubicin Hydrochloride). A substance obtained by chemical transformation of a substance produced by certain strains of *Streptomyces peucetius*. An orange-red powder. Soluble in water and in methyl alcohol; slightly soluble in dehydrated alcohol; practically insoluble in acetone. A 0.5% solution in water has a pH of 4.0 to 5.5. Store at 2° to 8° in airtight containers. Protect from light.

Incompatibility. Licensed product information states that epirubicin hydrochloride is incompatible with heparin or fluorouracil, resulting in precipitation, and that it is hydrolysed in alkaline solutions.

Stability. Epirubicin was not subject to significant photodegradation at clinical concentrations,[1,2] and special precautions to protect solutions from light during use do not appear to be necessary. However, photodegradation may be significant at lower concentrations (below 500 micrograms/mL).[1]

1. Wood MJ, *et al.* Photodegradation of doxorubicin, daunorubicin and epirubicin measured by high-performance liquid chromatography. *J Clin Pharm Ther* 1990; **15:** 291–300.
2. Pujol M, *et al.* Stability study of epirubicin in NaCl 0.9% injection. *Ann Pharmacother* 1997; **31:** 992–5.

Adverse Effects, Treatment, and Precautions

As for Doxorubicin, p.712. Cardiotoxicity and myelotoxicity may be less than with doxorubicin. Cardiotoxicity is more likely when the cumulative dose exceeds 0.9 to 1 g/m^2.

Effects on the heart. For further discussion of the cardiotoxicity of anthracyclines, see under Adverse Effects of Doxorubicin, p.713.

Interactions

As for Doxorubicin, p.713.

Antineoplastics. Increased exposure to epirubicin, and a consequent increase in myelotoxicity, has been reported in patients given epirubicin immediately after *paclitaxel*, compared with patients who received epirubicin before paclitaxel.[1] Similar interactions have been seen when paclitaxel was given before other anthracyclines.[2] These and other studies[3,4] have suggested that paclitaxel given in this way is associated with a reduced conversion of epirubicin to the less myelotoxic metabolite, epirubicinol, although the interaction is complex, and may involve both disposition and pharmacodynamics.

1. Venturini M, *et al.* Sequence effect of epirubicin and paclitaxel treatment on pharmacokinetics and toxicity. *J Clin Oncol* 2000; **18:** 2116–25.
2. Danesi R, *et al.* Pharmacokinetic optimisation of treatment schedules for anthracyclines and paclitaxel in patients with cancer. *Clin Pharmacokinet* 1999; **37:** 195–211.
3. Grasselli G, *et al.* Clinical and pharmacologic study of the epirubicin and paclitaxel combination in women with metastatic breast cancer. *J Clin Oncol* 2001; **19:** 2222–31.
4. Danesi R, *et al.* Pharmacokinetics and pharmacodynamics of combination chemotherapy with paclitaxel and epirubicin in breast cancer patients. *Br J Clin Pharmacol* 2002; **53:** 508–18.

Cimetidine. Cimetidine increased the formation of the active metabolite of epirubicin in a study in 8 patients; there was also a substantial increase in systemic exposure to unchanged epirubicin.[1] The mechanisms and potential clinical significance of the interaction were unclear.

1. Murray LS, *et al.* The effect of cimetidine on the pharmacokinetics of epirubicin in patients with advanced breast cancer: preliminary evidence of a potentially common drug interaction. *Clin Oncol* 1998; **10:** 35–8.

Pharmacokinetics

After intravenous doses epirubicin is rapidly and extensively distributed into body tissues, and undergoes metabolism in the liver, with the formation of epirubicinol (13-hydroxyepirubicin) and appreciable amounts of glucuronide derivatives. Epirubicin is eliminated mainly in bile, with a terminal plasma elimination half-life of about 30 to 40 hours. About 10% of a dose is recovered in urine within 48 hours. Epirubicin does not cross the blood-brain barrier.

◊ References.

1. Morris RG, *et al.* Disposition of epirubicin and metabolites with repeated courses to cancer patients. *Eur J Clin Pharmacol* 1991; **40:** 481–7.
2. Robert J. Clinical pharmacokinetics of epirubicin. *Clin Pharmacokinet* 1994; **26:** 428–38.

Uses and Administration

Epirubicin is an anthracycline antibiotic with antineoplastic actions similar to those of doxorubicin (p.714). It is used, alone or with other antineoplastics, in acute leukaemias, lymphomas, multiple myeloma, and in solid tumours including Wilms' tumour (p.667), cancer of the bladder (p.659), breast (p.661), and stomach (p.664).

Epirubicin hydrochloride is given by intravenous injection of a solution in sodium chloride 0.9% or Water for Injections into a fast-running infusion of sodium chloride 0.9% or glucose 5% over 3 to 5 minutes, or by infusion over up to 30 minutes. It is given as a single agent in usual doses of 60 to 90 mg/m^2 as a single dose every 3 weeks; this dose may be divided over 2 or 3 days if desired. A regimen of 12.5 to 25 mg/m^2 once a week has also been tried in palliative care. High-dose regimens, of 120 mg/m^2 or more every 3 weeks, or 45 mg/m^2 for 3 consecutive days every 3 weeks have been used.

Doses may need to be reduced if epirubicin is given with other antineoplastics. Doses should also be reduced in patients with liver impairment (see below) and in those whose bone-marrow function is impaired by age or previous chemotherapy or radiotherapy.

A total cumulative dose of 0.9 to 1 g/m^2 should not generally be exceeded, because of the risk of cardiotoxicity.

Epirubicin has also been given by intravesical instillation in the local treatment of bladder cancer. Instillation of 50 mg weekly as a 0.1% solution (in sodium chloride 0.9% or sterile water) for 8 weeks has been suggested, reduced to 30 mg in 50 mL weekly if chemical cystitis develops; for carcinoma *in-situ*, the dose may be increased, if tolerated, to 80 mg in 50 mL weekly. For the prophylaxis of recurrence in patients who have undergone transurethral resection, 50 mg weekly for 4 weeks, followed by 50 mg instilled once a month for 11 months is the suggested regimen. The solution should be retained in the bladder for 1 hour.

Blood counts should be made routinely during treatment with epirubicin (see also Bone-marrow Depression, p.639) and cardiac function should be carefully monitored. Liver function should be assessed before and if possible during therapy.

◊ References.

1. Plosker GL, Faulds D. Epirubicin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in cancer chemotherapy. *Drugs* 1993; **45:** 788–856.
2. Coukell AJ, Faulds D. Epirubicin: an updated review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of breast cancer. *Drugs* 1997; **53:** 453–82.
3. Onrust SV, *et al.* Epirubicin: a review of its intravesical use in superficial bladder cancer. *Drugs Aging* 1999; **15:** 307–33.
4. Ormrod D, *et al.* Epirubicin: a review of its efficacy as adjuvant therapy and in the treatment of metastatic disease in breast cancer. *Drugs Aging* 1999; **15:** 389–416.
5. Earl H, Iddawela M. Epirubicin as adjuvant therapy in breast cancer. *Expert Rev Anticancer Ther* 2004; **4:** 189–95.

Administration in hepatic impairment. Doses of epirubicin should be halved in patients with moderate liver dysfunction (serum bilirubin concentrations of 12 to 30 micrograms/mL), while those with severe liver impairment (serum bilirubin greater than 30 micrograms/mL) should be given a quarter of the usual dose.

Amyloidosis. For reference to a regimen including epirubicin used to control disease in a patient with amyloidosis, see p.743.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Crisabon; Cuatroepi; Epidoxo; Epifil; Epikebir; EPR†; Farmorubicin; Robanul; Rubifarm†; ***Austral.:*** Pharmorubicin; ***Austria:*** Epi-Cell; Farmorubicin; ***Belg.:*** Farmorubicine; ***Braz.:*** Farmorubicina; Nuovodox; Rubina; Tecnomax; ***Canad.:*** Pharmorubicin; ***Chile:*** Farmorrubicina; ***Cz.:*** Farmorubicin; ***Denm.:*** Farmorubicin; ***Fin.:*** Farmorubicin; ***Fr.:*** Farmorubicine; ***Ger.:*** Epi-Cell; Epi-NC; Farmorubicin; Riboepi; ***Gr.:*** Ciazil; Epirub; Farmorubicin; Megarubicin; ***Hong Kong:*** Pharmorubicin; ***Hung.:*** Farmorubicin; ***Irl.:*** Pharmorubicin; ***Israel:*** Farmorubicin; ***Ital.:*** Farmorubicina; ***Jpn:*** Farmorubicin; ***Malaysia:*** Pharmorubicin; ***Mex.:*** Binarin; Epilem; Farmorubicin; ***Neth.:*** Farmorubicine; ***Norw.:*** Farmorubicin; ***NZ:*** Pharmorubicin; ***Philipp.:*** Pharmorubicin; ***Pol.:*** Bioepicyna; Farmorubicin; ***Port.:*** Epi-cell; Farmorubicina; ***Rus.:*** Epilem (Эпилем)†; Farmorubicin (Фарморубицин); ***S.Afr.:*** Farmorubicin; ***Singapore:*** Pharmorubicin; ***Spain:*** Farmorubicina; ***Swed.:*** Farmorubicin; ***Switz.:*** Farmorubicin; ***Thai.:*** Anthracin; E.P.Mycin; Epilem; Pharmorubicin; ***Turk.:*** Farmorubicin; ***UK:*** Pharmorubicin; ***USA:*** Ellence; ***Venez.:*** Farmorubicin.

Epratuzumab *(rINN)*

Épratuzumab; Epratuzumabum. Immunoglobulin G (human-mouse monoclonal IMMU-hLL2 γ-chain anti-human antigen CD22), disulfide with human-mouse monoclonal IMMU-hLL2 κ-chain, dimer.

Эпратузумаб

CAS — 205923-57-5.

Profile

Epratuzumab is a humanised anti-CD22 monoclonal antibody under investigation, alone or conjugated with yttrium-90, for the treatment of non-Hodgkin's lymphoma. It is also under investigation for the treatment of moderate to severe SLE.

◊ References.

1. Davies SL, Martin L. Epratuzumab. *Drugs Of The Future* 2005; **30:** 683–7.
2. Leonard JP, *et al.* Combination antibody therapy with epratuzumab and rituximab in relapsed or refractory non-Hodgkin's lymphoma. *J Clin Oncol* 2005; **23:** 5044–51.
3. Lindén O, *et al.* Dose-fractionated radioimmunotherapy in non-Hodgkin's lymphoma using DOTA-conjugated, Y-radiolabeled, humanized anti-CD22 monoclonal antibody, epratuzumab. *Clin Cancer Res* 2005; **11:** 5215–22.
4. Goldenberg DM. Epratuzumab in the therapy of oncological and immunological diseases. *Expert Rev Anticancer Ther* 2006; **6:** 1341–53.
5. Leonard JP, Goldenberg DM. Preclinical and clinical evaluation of epratuzumab (anti-CD22 IgG) in B-cell malignancies. *Oncogene* 2007; **26:** 3704–13.

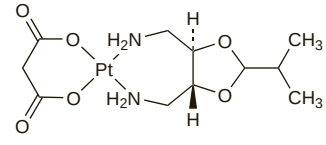
Eptaplatin *(rINN)*

Eptaplatine; Eptaplatino; Eptaplatinum; Heptaplatin; SKI-2053R. *cis*-[(4*R*,5*R*)-2-Isopropyl-1,3-dioxolane-4,5-bis(methylamine)-*N*,*N*′][malonato(2–)-*O*,*O*′]platinum.

Эптаплатин

$C_{11}H_{20}N_2O_6Pt$ = 471.4.

CAS — 146665-77-2.



Profile

Eptaplatin is a platinum derivative that is used as an antineoplastic in the treatment of gastric cancer. Nephrotoxicity is the main adverse effect.

◊ References.

1. Ahn JH, *et al.* Nephrotoxicity of heptaplatin: a randomized comparison with cisplatin in advanced gastric cancer. *Cancer Chemother Pharmacol* 2002; **50:** 104–10.
2. Min YJ, *et al.* Combination chemotherapy with 5-fluorouracil and heptaplatin as first-line treatment in patients with advanced gastric cancer. *J Korean Med Sci* 2004; **19:** 369–73.

Preparations

Proprietary Preparations (details are given in Part 3)
Kor.: Sunpla.

Erlotinib Hydrochloride *(USAN, rINNM)*

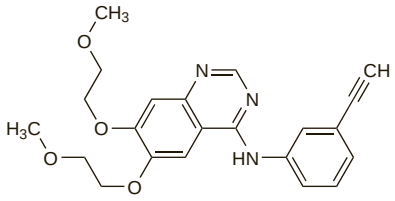
CP-358774-01; Erlotinib, Chlorhydrate d'; Erlotinibi Hydrochloridum; Hidrocloruro de erlotinib; NSC-718781; OSI-774. *N*-(3-Ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine hydrochloride.

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.

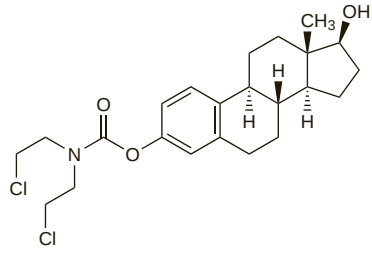
Натрия Эстрамустина Фосфат

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