Erlotinib Hydrochloride *(USAN, rINNM)*

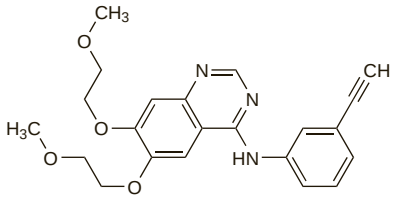
CP-358774-01; Erlotinib, Chlorhydrate d'; Erlotinibi Hydrochloridum; Hidrocloruro de erlotinib; NSC-718781; OSI-774. *N*-(3-Ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine hydrochloride.

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.

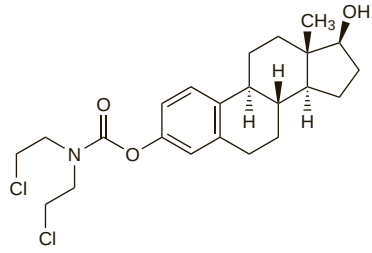
Натрия Эстрамустина Фосфат

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