## Formestane *(BAN, rINN)* ⊗

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

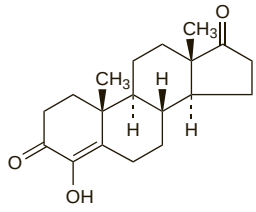
Форместан

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

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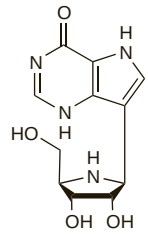
## Forodesine Hydrochloride *(USAN, rINNM)*

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.

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## Fotemustine *(BAN, rINN)*

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

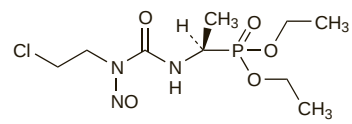
Фотемустин

$C_9H_{19}ClN_3O_5P$ = 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.

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## 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.

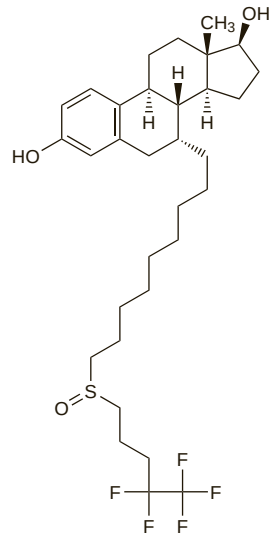
Фульвестрант

$C_{32}H_{47}F_5O_3S$ = 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,

some of which have oestrogen antagonist activity, and is excreted in the faeces. After intramuscular injection fulvestrant has a half-life of about 40 to 50 days.

◊ References.


1. Robertson JFR, *et al.* Pharmacokinetic profile of intramuscular fulvestrant in advanced breast cancer. *Clin Pharmacokinet* 2004; **43:** 529–38.


### Uses and Administration

Fulvestrant is an oestrogen antagonist that downregulates the oestrogen receptor and is used for the treatment of oestrogen-receptor positive, locally advanced or metastatic breast cancer in postmenopausal women (p.661); it is given when disease has relapsed or progressed during or after treatment with anti-oestrogens. The recommended dose is 250 mg, given intramuscularly at monthly intervals. It is injected into the buttock, either as a single injection or as two concurrent doses.

◊ References.


1. Osborne CK, *et al.* Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial. *J Clin Oncol* 2002; **20:** 3386–95.
2. Howell A, *et al.* Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. *J Clin Oncol* 2002; **20:** 3396–3403.
3. Bross PF, *et al.* Fulvestrant in postmenopausal women with advanced breast cancer. *Clin Cancer Res* 2003; **9:** 4309–17.
4. Howell A, *et al.* Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: a multinational, double-blind, randomized trial. *J Clin Oncol* 2004; **22:** 1605–13.
5. McKeage K, *et al.* Fulvestrant: a review of its use in hormone receptor-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. *Drugs* 2004; **64:** 633–48.
6. Buzdar AU. Fulvestrant: a new type of estrogen receptor antagonist for the treatment of advanced breast cancer. *Drugs Today* 2004; **40:** 751–64.
7. Robertson JF, *et al.* Endocrine treatment options for advanced breast cancer—the role of fulvestrant. *Eur J Cancer* 2005; **41:** 346–56.
8. Howell A, *et al.* Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma: a prospectively planned combined survival analysis of two multicenter trials. *Cancer* 2005; **104:** 236–9.
9. Bundred N. Preclinical and clinical experience with fulvestrant (Faslodex) in postmenopausal women with hormone receptor-positive advanced breast cancer. *Cancer Invest* 2005; **23:** 173–81.
10. Buzdar AU, Robertson JFR. Fulvestrant: pharmacologic profile versus existing endocrine agents for the treatment of breast cancer. *Ann Pharmacother* 2006; **40:** 1572–83.


### Preparations

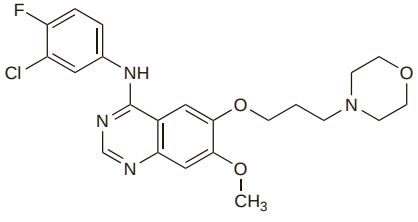
**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Faslodex; ***Austral.:*** Faslodex; ***Belg.:*** Faslodex; ***Braz.:*** Faslodex; ***Canad.:*** Faslodex; ***Cz.:*** Faslodex; ***Denm.:*** Faslodex; ***Fin.:*** Faslodex; ***Fr.:*** Faslodex; ***Ger.:*** Faslodex; ***Gr.:*** Faslodex; ***Hung.:*** Faslodex; ***Irl.:*** Faslodex; ***Israel:*** Faslodex; ***Ital.:*** Faslodex; ***Malaysia:*** Faslodex; ***Mex.:*** Faslodex; ***Neth.:*** Faslodex; ***Norw.:*** Faslodex; ***NZ:*** Faslodex; ***Pol.:*** Faslodex; ***Port.:*** Faslodex; ***Rus.:*** Faslodex (Фазлодекс); ***Spain:*** Faslodex; ***Swed.:*** Faslodex; ***Switz.:*** Faslodex; ***UK:*** Faslodex; ***USA:*** Faslodex; ***Venez.:*** Faslodex.

## Gefitinib *(BAN, USAN, rINN)*

Géfitinib; Gefitinibum; ZD-1839. *N*-(3-Chloro-4-fluorophenyl)-7-methoxy-6-[3-(morpholin-4-yl)propoxy]quinazolin-4-amine.

Гефитиниб

$C_{22}H_{24}ClFN_4O_3$ = 446.9.
*CAS — 184475-35-2.*
*ATC — L01XE02.*
*ATC Vet — QL01XE02.*



### Profile

Gefitinib is a selective inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor. It blocks signal transduction pathways implicated in the growth of tumour cells. It is given orally for the management of locally advanced or metastatic non-small cell lung cancer (p.668) unresponsive to other therapy; the usual dose is 250 mg daily. In the USA, use is restricted to those patients who are currently receiving and benefiting from gefitinib, or to those who have previously benefited from therapy. Adverse effects include rashes and diarrhoea. There have been reports of severe diffuse parenchymal lung disease, including fatalities. There are also reports of tumour haemorrhage, sometimes fatal, after use of gefitinib in patients with head and neck cancer. Gefitinib is under investigation in the management of other solid tumours.

◊ References.


1. Culy CR, Faulds D. Gefitinib. *Drugs* 2002; **62:** 2237–48.
2. Inoue A, *et al.* Severe acute interstitial pneumonia and gefitinib. *Lancet* 2003; **361:** 137–9.
3. Kris MG, *et al.* Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non–small cell lung cancer: a randomized trial. *JAMA* 2003; **290:** 2149–58.
4. Liu CY, Seen S. Gefitinib therapy for advanced non–small-cell lung cancer. *Ann Pharmacother* 2003; **37:** 1644–53.
5. Cersosimo RJ. Gefitinib: a new antineoplastic for advanced non-small-cell lung cancer. *Am J Health-Syst Pharm* 2004; **61:** 889–98.
6. Forsythe B, Faulkner K. Overview of the tolerability of gefitinib (IRESSA ) monotherapy: clinical experience in non-small-cell lung cancer. *Drug Safety* 2004; **27:** 1081–92.
7. Frampton JE, Easthope SE. Gefitinib: a review of its use in the management of advanced non-small-cell lung cancer. *Drugs* 2004; **64:** 2475–92.
8. Tanovic A, Alfaro V. Gefitinib: current status in the treatment of non-small cell lung cancer. *Drugs Today* 2004; **40:** 809–27.
9. Birnbaum A, Ready N. Gefitinib therapy for non-small cell lung cancer. *Curr Treat Options Oncol* 2005; **6:** 75–81.
10. Shah NT, *et al.* Practical management of patients with non-small-cell lung cancer treated with gefitinib. *J Clin Oncol* 2005; **23:** 165–74.
11. Swaisland HC, *et al.* Pharmacokinetic drug interactions of gefitinib with rifampicin, itraconazole and metoprolol. *Clin Pharmacokinet* 2005; **44:** 1067–81.
12. Swaisland HC, *et al.* Single-dose clinical pharmacokinetic studies of gefitinib. *Clin Pharmacokinet* 2005; **44:** 1165–77.
13. Blackhall F, *et al.* Where next for gefitinib in patients with lung cancer? *Lancet Oncol* 2006; **7:** 499–507.


**Effects on survival.** In chemotherapy-naive patients with advanced non-small cell lung cancer, gefitinib, given with gemcitabine plus cisplatin,[1] or paclitaxel plus carboplatin,[2] showed no survival advantage over chemotherapy without gefitinib. In a large study in patients with non-small cell lung cancer given gefitinib or placebo, after failure of one or two previous treatment regimens, no survival benefit was shown with gefitinib;[3] recommendations restricting the use of gefitinib to selected patients have been made in the USA (see above).[4] However, a subset analysis of study data found an improvement in survival in a subgroup of patients of Asian origin.[5] In reports of the IMEX study in patients with head and neck cancer, no survival advantage for gefitinib was found when compared with methotrexate; an increased incidence of tumour haemorrhage was seen in those treated with gefitinib.[6] Studies have suggested that there are subgroups of patients with non-small cell lung cancer who have specific biomarkers or mutations in the epidermal growth factor receptor gene which correlate with clinical response to gefitinib.[7-10]

A small retrospective study found that further treatment with gefitinib prolonged survival in patients who were initially responsive, but who had subsequent disease progression upon stopping therapy.[11]


1. Giaccone G, *et al.* Gefitinib in combination with gemcitabine and cisplatin in advanced non–small-cell lung cancer: a phase III trial—INTACT 1. *J Clin Oncol* 2004; **22:** 777–84.
2. Herbst RS, *et al.* Gefitinib in combination with paclitaxel and carboplatin in advanced non–small-cell lung cancer: a phase III trial—INTACT 2. *J Clin Oncol* 2004; **22:** 785–94.
3. Thatcher N, *et al.* Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet* 2005; **366:** 1527–37.
4. FDA Public Health Advisory. New labeling and distribution program for gefitinib (Iressa) (issued 17/06/05). Available at: http://www.fda.gov/cder/drug/advisory/iressa.htm (accessed 13/03/06)
5. Chang A, *et al.* Gefitinib (IRESSA) in patients of Asian origin with refractory advanced non-small cell lung cancer: subset analysis from the ISEL study. *J Thorac Oncol* 2006; **1:** 847–55.
6. AstraZeneca, Canada. Health Canada endorsed important safety information on Iressa (gefitinib): lack of survival benefit and increased incidence of tumour haemorrhage in association with IRESSA in patients with squamous cell carcinoma of the head and neck (SCCHN) (issued 1st December 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2006/iressa_4_hpc-cps-eng.php (accessed 01/08/08)
7. Lynch TJ, *et al.* Activating mutations in the epidermal growth factor receptor underlying responsiveness of non–small-cell lung cancer to gefitinib. *N Engl J Med* 2004; **350:** 2129–39.
8. Paez JG, *et al.* EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004; **304:** 1497–1500.
9. Pao W, Miller VA. Epidermal growth factor receptor mutations, small-molecule kinase inhibitors, and non–small-cell lung cancer: current knowledge and future directions. *J Clin Oncol* 2005; **23:** 2556–68.
10. Hirsch FR, *et al.* Molecular predictors of outcome with gefitinib in a phase III placebo-controlled study in advanced non-small-cell lung cancer. *J Clin Oncol* 2006; **24:** 5034–42.
11. Yokouchi H, *et al.* Clinical benefit of readministration of gefitinib for initial gefitinib-responders with non-small cell lung cancer. *BMC Cancer* 2007; **7:** 51.


### Preparations

**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Iressa; ***Austral.:*** Iressa; ***Canad.:*** Iressa; ***Chile:*** Iressa; ***Fr.:*** Iressa†; ***Hong Kong:*** Iressa; ***India:*** Geftinat; ***Indon.:*** Iressa; ***Israel:*** Iressa; ***Malaysia:*** Iressa; ***Mex.:*** Iressa; ***NZ:*** Iressa; ***Philipp.:*** Iressa; ***Rus.:*** Iressa (Иресса); ***Singapore:*** Iressa; ***Switz.:*** Iressa; ***Thai.:*** Iressa; ***UK:*** Iressa; ***USA:*** Iressa; ***Venez.:*** Iressa.

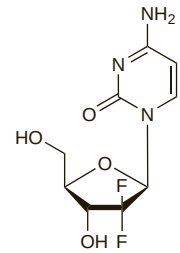
## Gemcitabine Hydrochloride

*(BANM, USAN, rINNM)*

Gemcitabine, chlorhydrate de; Gemcitabini hydrochloridum; Hidrocloruro de gemcitabina; LY-188011 (gemcitabine). 4-Amino-1-(2-deoxy-2,2-difluoro-β-D-ribofuranosyl)pyrimidin-2(1*H*)-one hydrochloride; 2′-Deoxy-2′,2′-difluorocytidine hydrochloride.

Гемцитабина Гидрохлорид

$C_9H_{11}F_2N_3O_4$,HCl = 299.7.
*CAS — 95058-81-4 (gemcitabine); 122111-03-9 (gemcitabine hydrochloride).*
*ATC — L01BC05.*
*ATC Vet — QL01BC05.*



*(gemcitabine)*

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

**Ph. Eur. 6.2** (Gemcitabine Hydrochloride). A white or almost white powder. Soluble in water; slightly soluble in methyl alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 2.0 to 3.0.

**USP 31** (Gemcitabine Hydrochloride). A white to off-white solid. Soluble in water; practically insoluble in alcohol and in polar organic solvents; slightly soluble in methyl alcohol. pH of a 1% solution in water is between 2.0 and 3.0. Store in airtight containers.

**Incompatibility.** Gemcitabine hydrochloride was reported to be physically incompatible with aciclovir sodium, amphotericin B, cefoperazone sodium, cefotaxime sodium, furosemide, ganciclovir sodium, imipenem with cilastatin sodium, irinotecan, methotrexate sodium, methylprednisolone sodium succinate, mezlocillin sodium, mitomycin, piperacillin sodium, piperacillin sodium with tazobactam, and prochlorperazine edisilate during simulated Y-site administration.[1]


1. Trissel LA, *et al.* Compatibility of gemcitabine hydrochloride with 107 selected drugs during simulated Y-site injection. *J Am Pharm Assoc* 1999; **39:** 514–18.


### Adverse Effects, Treatment, and Precautions

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

The major dose-limiting adverse effect of gemcitabine is bone-marrow depression, although this is reported to be modest and rarely requires stopping therapy. Gastrointestinal disturbances occur, especially nausea and vomiting, but these are usually of mild to moderate severity. Rashes, often associated with pruritus, and flu-like symptoms are relatively common. Oedema, dyspnoea, and alopecia are also commonly reported. Pulmonary oedema has been reported infrequently; interstitial pneumonitis, pulmonary fibrosis, and acute respiratory distress syndrome have occurred. Therapy should be stopped if pulmonary toxicity occurs. There are rare cases of hypotension, anaphylactoid reactions, and severe desquamative and bullous skin eruptions. Haematuria, proteinuria, transient liver enzyme elevations, and serious hepatotoxicity, including liver failure and death, have been reported. It should therefore be used with caution in patients with impaired renal or hepatic function. Haemolytic-uraemic syndrome and/or thrombocytopenic purpura have been reported and have led to irreversible renal failure; gemcitabine