and that have a narrow therapeutic index. Significant effects on exemestane clearance by cytochrome P450 isoenzyme inhibitors are considered unlikely. Exemestane should not be given with oestrogen-containing drugs as these would negate its pharmacological action.

Pharmacokinetics

Exemestane is rapidly absorbed from the gastrointestinal tract. Its bioavailability is limited by first-pass metabolism, but is increased when taken with food. Exemestane is widely distributed, and is extensively bound to plasma proteins. It is metabolised via oxidation by the cytochrome P450 isoenzyme CYP3A4, and via reduction by aldoketoreductase. Metabolites are excreted in the urine and faeces, and less than 1% of a dose is excreted unchanged in the urine. Exemestane has a terminal elimination half-life of about 24 hours.

Uses and Administration

Exemestane is a selective inhibitor of the aromatase (oestrogen synthase) system, similar to formestane (p.726). It is used in the treatment of advanced breast cancer (p.661), in postmenopausal women who are no longer responsive to anti-oestrogen therapy. It is also used for adjuvant treatment of postmenopausal women with oestrogen-receptor positive early breast cancer, after 2 to 3 years of initial adjuvant tamoxifen treatment; a total of 5 years of adjuvant hormonal therapy should be given. The recommended oral dose is 25 mg once daily, preferably after a meal.

In patients receiving potent inducers of the cytochrome P450 isoenzyme CYP3A4 (such as rifampicin or phenytoin), the recommended oral dose of exemestane is 50 mg once daily, after a meal.

◊ References.

1. Clemett D, Lamb HM. Exemestane: a review of its use in postmenopausal women with advanced breast cancer. *Drugs* 2000; **59:** 1279–96.
2. Kaufmann M, *et al.* Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: results of a phase III randomized double-blind trial. *J Clin Oncol* 2000; **18:** 1399–1411.
3. Lønning PE, *et al.* Activity of exemestane in metastatic breast cancer after failure of nonsteroidal aromatase inhibitors: a phase II trial. *J Clin Oncol* 2000; **18:** 2234–44.
4. Coombes RC, *et al.* A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med* 2004; **350:** 1081–92. Corrections. *ibid.*; **351:** 2461 and *ibid.* 2006; **355:** 1746.
5. Bertelli G, *et al.* Sequential treatment with exemestane and nonsteroidal aromatase inhibitors in advanced breast cancer. *Oncology* 2006; **69:** 471–7.
6. Bundred N. The evolving role of exemestane in the management of breast cancer. *Br J Hosp Med* 2006; **67:** 427–30.
7. Coombes RC, *et al.* Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. *Lancet* 2007; **369:** 559–70. Correction. *ibid.*; 906.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Aromasin; ***Austral.:*** Aromasin; ***Austria:*** Aromasin; ***Belg.:*** Aromasin; ***Braz.:*** Aromasin; ***Canad.:*** Aromasin; ***Chile:*** Aromasin; ***Cz.:*** Aromasin; ***Denm.:*** Aromasin; ***Fin.:*** Aromasin; ***Fr.:*** Aromasine; ***Ger.:*** Aromasin; ***Gr.:*** Aromasin; ***Hong Kong:*** Aromasin; ***Hung.:*** Aromasin; ***Indon.:*** Aromasin; ***Irl.:*** Aromasin; ***Israel:*** Aromasin; ***Ital.:*** Aromasin; ***Malaysia:*** Aromasin; ***Neth.:*** Aromasin; ***Norw.:*** Aromasin; ***NZ:*** Aromasin; ***Philipp.:*** Aromasin; ***Pol.:*** Aromasin; ***Port.:*** Aromasin; ***Rus.:*** Aromasin (Аромазин); ***S.Afr.:*** Aromasin; ***Singapore:*** Aromasin; ***Spain:*** Aromasil; ***Swed.:*** Aromasin; ***Switz.:*** Aromasin; ***Thai.:*** Aromasin; ***Turk.:*** Aromasin; ***UK:*** Aromasin; ***USA:*** Aromasin; ***Venez.:*** Aromasin.

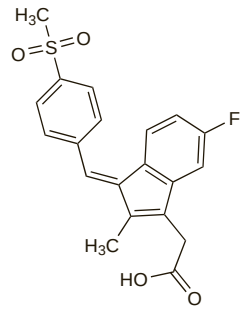
Exisulind *(rINN)*

Exisulindum; FGN-1; Sulindac Sulfone. 5-Fluoro-2-methyl-1-[(*Z*)-*p*-(methylsulfonyl)benzylidene]indene-3-acetic acid.

Эксисулинд

$C_{20}H_{17}FO_4S$ = 372.4.

CAS — 59973-80-7.



Profile

Exisulind is a sulfone metabolite of sulindac (p.126) that is reported to induce apoptosis in cancerous and precancerous cells. It has been studied for the treatment of familial adenomatous polyposis, with variable results. It is also being investigated for the prevention and treatment of malignant neoplasms, including those of the breast, prostate, and lung.

◊ References.

1. Goluboff ET. Exisulind, a selective apoptotic antineoplastic drug. *Expert Opin Invest Drugs* 2001; **10:** 1875–82.
2. Webster WS, Leibovich BC. Exisulind in the treatment of prostate cancer. *Expert Rev Anticancer Ther* 2005; **5:** 957–62.
3. Arber N, *et al.* Sporadic adenomatous polyp regression with exisulind is effective but toxic: a randomised, double blind, placebo controlled, dose-response study. *Gut* 2006; **55:** 367–73.

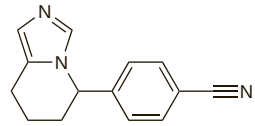
Fadrozole Hydrochloride *(USAN, rINNM)* ⊗

CGS-16949 (fadrozole); CGS-16949A; Fadrozole, Chlorhydrate de; Fadrozoli Hydrochloridum; Hidrocloruro de fadrozol. (±)-*p*-(5,6,7,8-Tetrahydroimidazo[1,5-*a*]pyridin-5-yl)benzonitrile monohydrochloride.

Фадрозола Гидрохлорид

$C_{14}H_{13}N_3HCl$ = 259.7.

CAS — 102676-47-1 (fadrozole); 102676-96-0 (fadrozole hydrochloride).



(fadrozole)

Profile

Fadrozole hydrochloride is a selective nonsteroidal inhibitor of the aromatase (oestrogen synthetase) system, similar to anastrozole (p.681). It is used for the treatment of breast cancer. It has been given in oral doses of 1 mg twice daily.

◊ References.

1. Buzdar AU, *et al.* Fadrozole HCl (CGS-16949A) versus megestrol acetate treatment of postmenopausal patients with metastatic breast carcinoma: results of two randomized double blind controlled multiinstitutional trials. *Cancer* 1996; **77:** 2503–13.
2. Miller AA, *et al.* Fadrozole hydrochloride in postmenopausal patients with metastatic breast carcinoma. *Cancer* 1996; **78:** 789–93.
3. Falkson CI, Falkson HC. A randomised study of CGS 16949A (fadrozole) versus tamoxifen in previously untreated postmenopausal patients with metastatic breast cancer. *Ann Oncol* 1996; **7:** 465–9.
4. Thurlimann B, *et al.* First-line fadrozole HCl (CGS 16949A) versus tamoxifen in postmenopausal women with advanced breast cancer: prospective randomised trial of the Swiss Group for Clinical Cancer Research SAKK 20/88. *Ann Oncol* 1996; **7:** 471–9.
5. Tominaga T, *et al.* Double-blind randomised trial comparing the non-steroidal aromatase inhibitors letrozole and fadrozole in postmenopausal women with advanced breast cancer. *Ann Oncol* 2003; **14:** 62–70.

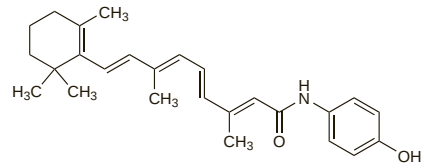
Fenretinide *(USAN, rINN)*

Fenretinida; Fenrétinide; Fenretinidum; 4-HPR; 4-Hydroxyphenylretinamide; McN-R-1967. *all-trans*-4′-Hydroxyretinanilide.

Фенретинид

$C_{26}H_{33}NO_2$ = 391.5.

CAS — 65646-68-6.



Profile

Fenretinide is a retinoid derivative that is given orally and is being studied in the management of breast and prostate cancer, malignant bone tumours, soft-tissue sarcoma, and some other malignancies. It has also been tried in oral lichen planus and leucoplakia. Fenretinide has been investigated in the treatment of psoriasis, but was associated with unacceptable adverse effects such as night blindness and severe toxic erythema.

◊ Fenretinide has been studied for the treatment of breast cancer and cutaneous malignancies but early results were disappointing and night blindness and mucocutaneous effects have been associated with this use.[1] Fenretinide has been investigated for the prevention of breast cancer (p.662), but a large randomised study of secondary prevention failed to show any benefit.[2] A follow-up of the same study[3] found that patients receiving fenretinide had a lower incidence of ovarian carcinoma during the 5-year treatment period, but that this apparently protective effect disappeared after treatment was stopped. Combinations of tamoxifen and fenretinide, given intermittently (for treatment or prevention), have been reported to be well tolerated.[4-6]

1. Modiano MR, *et al.* Phase II study of fenretinide (N-[4-hydroxyphenyl]retinamide) in advanced breast cancer and melanoma. *Invest New Drugs* 1990; **8:** 317–19.
2. Veronesi U, *et al.* Randomized trial of fenretinide to prevent second breast malignancy in women with early breast cancer. *J Natl Cancer Inst* 1999; **91:** 1847–56.
3. De Palo G, *et al.* Effect of fenretinide on ovarian carcinoma occurrence. *Gynecol Oncol* 2002; **86:** 24–7.
4. Cobleigh MA, *et al.* Phase I/II trial of tamoxifen with or without fenretinide, an analog of vitamin A, in women with metastatic breast cancer. *J Clin Oncol* 1993; **11:** 474–7.
5. Conley B, *et al.* Pilot trial of the safety, tolerability, and retinoid levels of N-(4-hydroxyphenyl) retinamide in combination with tamoxifen in patients at high risk for developing invasive breast cancer. *J Clin Oncol* 2000; **18:** 275–83.
6. Guerrieri-Gonzaga A. *et al.* Preliminary results on safety and activity of a randomized, double-blind, 2 x 2 trial of low-dose tamoxifen and fenretinide for breast cancer prevention in premenopausal women. *J Clin Oncol* 2006; **24:** 129–35.

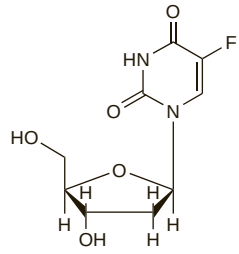
Floxuridine *(USAN, rINN)*

Floxuridina; Floxuridinum; 5-Fluorouracil Deoxyriboside; FUDR; NSC-27640; WR-138720. 2′-Deoxy-5-fluorouridine; 5-Fluoro-2′-deoxyuridine; 1-(2-Deoxy-β-D-ribofuranosyl)-5-fluoropyrimidine-2,4(1*H*,3*H*)-dione.

Флоксуридин

$C_9H_{11}FN_2O_5$ = 246.2.

CAS — 50-91-9.



Pharmacopoeias. In *US.*

USP 31 (Floxuridine). Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Fluorouracil, p.722. Adverse reactions after intra-arterial infusion often include local reactions, thromboembolic complications, and infection or bleeding at the catheter site, or blockage of the catheter. Erythema, stomatitis, and gastrointestinal disturbances are relatively common. There have also been signs of liver dysfunction.

Effects on the liver. Serious biliary toxicity has been reported in over half of all patients receiving hepatic arterial infusions of floxuridine, usually manifesting as sclerosing cholangitis or acalculous cholecystitis;[1] as a result some surgeons routinely remove the gallbladder at the time of infusion pump implantation.[2] Extrahepatic biliary stenosis with jaundice and cholestasis has also been described;[3] the authors suggest that this could lead to intrahepatic biliary damage from bile stasis and infection, recurrent