Bexarotene *(BAN, USAN, rINN)*

Beksaroteeni; Beksaroten; Bexaroten; Bexarotène; Bexaroteno; Bexarotenum; LG-100069; LGD-1069. *p*-[1-(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthyl)vinyl]benzoic acid.

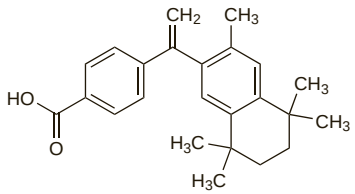
Бексаротен

$C_{24}H_{28}O_2$ = 348.5.

CAS — 153559-49-0.

ATC — L01XX25.

ATC Vet — QL01XX25.



Adverse Effects and Precautions

The main adverse effects noted after oral therapy with bexarotene include hyperlipidaemia, hypothyroidism, leucopenia, headache, oedema, altered liver function, rash, and pruritus. Exfoliative dermatitis, alopecia, and skin disorders may occur. Other common adverse effects include anaemia, insomnia, dizziness, eye or ear disorders, gastrointestinal disturbances, arthralgia, and myalgia. Acute pancreatitis has been associated with hypertriglyceridaemia, and patients with risk factors for pancreatitis should generally not be given bexarotene. If triglyceride concentrations rise during therapy, dose reductions are recommended, and lipid-lowering therapy may be instituted (with the exception of gemfibrozil, see below). The most common adverse events associated with topical therapy are rash, pruritus, and pain. Bexarotene capsules and gel should not be used during pregnancy because of the risk of fetal malformation.

◊ References.

1. Assaf C, *et al.* Minimizing adverse side-effects of oral bexarotene in cutaneous T-cell lymphoma: an expert opinion. *Br J Dermatol* 2006; **155:** 261–6.

Interactions

Gemfibrozil. Gemfibrozil inhibits clearance of bexarotene, resulting in extremely high triglyceride levels and pancreatitis.[1]

1. Talpur R, *et al.* Optimizing bexarotene therapy for cutaneous T-cell lymphoma. *J Am Acad Dermatol* 2002; **47:** 672–84.

Uses and Administration

Bexarotene is an agonist at the retinoid X receptor, which is involved in the regulation of cell differentiation and proliferation. It is used in the treatment of cutaneous T-cell lymphoma (see Mycosis Fungoides, p.657), in a usual initial oral dose of 300 mg/m^2 daily as a single dose taken with a meal. Dosage is adjusted according to toxicity. For the topical treatment of refractory disease a 1% gel may be applied on alternate days for the first week, gradually increased at weekly intervals to up to 4 times daily, depending on tolerance.

◊ References.

1. Anonymous. Bexarotene (Targretin) for cutaneous T-cell lymphoma. *Med Lett Drugs Ther* 2000; **42:** 31–2.
2. Lowe MN, Plosker GL. Bexarotene. *Am J Clin Dermatol* 2000; **1:** 245–50.
3. Duvic M, *et al.* Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. *J Clin Oncol* 2001; **19:** 2456–71.
4. Wong S-F. Oral bexarotene in the treatment of cutaneous T-cell lymphoma. *Ann Pharmacother* 2001; **35:** 1056–65.
5. Heald P, *et al.* Topical bexarotene therapy for patients with refractory or persistent early-stage cutaneous T-cell lymphoma: results of the phase III clinical trial. *J Am Acad Dermatol* 2003; **49:** 801–15.
6. Hanifin JM, *et al.* Novel treatment of chronic severe hand dermatitis with bexarotene gel. *Br J Dermatol* 2004; **150:** 545–53.
7. Farol LT, Hymes KB. Bexarotene: a clinical review. *Expert Rev Anticancer Ther* 2004; **4:** 180–8.
8. Gniadecki R, *et al.* The optimal use of bexarotene in cutaneous T-cell lymphoma. *Br J Dermatol* 2007; **157:** 433–40.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Targretin; ***Chile:*** Targretin; ***Cz.:*** Targretin; ***Denm.:*** Targretin; ***Fr.:*** Targretin; ***Ger.:*** Targretin; ***Gr.:*** Targretin; ***Hung.:*** Targretin; ***Irl.:*** Targretin; ***Ital.:*** Targretin; ***Neth.:*** Targretin; ***Port.:*** Targretin; ***Spain:*** Targretin; ***UK:*** Targretin; ***USA:*** Targretin.

Bicalutamide *(BAN, USAN, rINN)*

Bicalutamida; Bicalutamidum; Bikalutamid; Bikalutamidi; ICI-176334. (*RS*)-4′-Cyano-α′,α′,α′-trifluoro-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methylpropiono-*m*-toluidide.

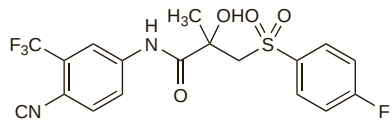
Бикалутамид

$C_{18}H_{14}F_4N_2O_4S$ = 430.4.

CAS — 90357-06-5.

ATC — L02BB03.

ATC Vet — QL02BB03.



Pharmacopoeias. In *US.*

USP 31 (Bicalutamide). A fine, white to off-white powder. Sparingly to slightly soluble in alcohol; freely soluble in acetone and in tetrahydrofuran; soluble in acetonitrile. Store in airtight containers.

Adverse Effects and Precautions

As for Flutamide, p.725. Pruritus, asthenia, alopecia, hair regrowth, and dry skin occur commonly with bicalutamide. Hypersensitivity reactions, including angioedema and urticaria, have been reported infrequently.

Cardiovascular effects including angina, heart failure, arrhythmias, and ECG changes have been reported rarely. Interstitial pneumonitis and pulmonary fibrosis have also been reported rarely.

Effects on the gastrointestinal tract. There is some evidence that bicalutamide is associated with a lower incidence of diarrhoea than flutamide.[1]

1. Schellhammer P, *et al.* A controlled trial of bicalutamide versus flutamide, each in combination with luteinizing hormone-releasing hormone analogue therapy, in patients with advanced prostate cancer. *Urology* 1995; **45:** 745–52.

Effects on the lungs. For a review of cases of pneumonitis associated with anti-androgens including bicalutamide, see under Flutamide, p.725.

Gynaecomastia. For a discussion of gynaecomastia, a frequent adverse effect of anti-androgen therapy, and its management, see under Flutamide, p.725.

Interactions

Bicalutamide inhibits various cytochrome P450 isoenzymes, particularly CYP3A4, *in vitro*, and licensed product information recommends that terfenadine, astemizole, and cisapride should not be given with bicalutamide, and that other drugs with a narrow therapeutic index that are metabolised by cytochrome P450 isoenzymes should be used with caution. *In vitro* studies have shown that bicalutamide can displace warfarin from its protein binding sites (see also Antineoplastics, p.1429).

Pharmacokinetics

Bicalutamide is well absorbed after oral doses. It undergoes extensive metabolism in the liver, the active *R*-enantiomer mainly by oxidation, the inactive *S*-enantiomer mainly by glucuronidation. It is excreted as metabolites in urine and faeces. The half-life of the *R*-enantiomer is about 6 to 7 days, and may be prolonged still further in severe hepatic impairment. The *S*-enantiomer is cleared more rapidly. Bicalutamide is about 96% bound to plasma proteins.

◊ References.

1. Cockshott ID. Bicalutamide: clinical pharmacokinetics and metabolism. *Clin Pharmacokinet* 2004; **43:** 855–78.

Uses and Administration

Bicalutamide is a nonsteroidal anti-androgen with actions and uses similar to those of flutamide (p.725). It is used orally in the treatment of prostatic cancer (p.671). When used with a gonadorelin analogue in the palliative treatment of advanced prostatic cancer the usual dose is 50 mg daily. In the UK treatment is started at least 3 days before starting the gonadorelin analogue to suppress any flare reaction, but in the USA treatment is started at the same time. A similar dose is used with surgical castration, starting on the same day as surgery.

Bicalutamide in a dose of 150 mg daily may be given as monotherapy or adjuvant therapy to surgery or radiotherapy in men with locally advanced disease at high risk for disease progression. It has been used as monotherapy in localised disease, but there is some evidence to suggest that in men without high risk of disease progression, who would otherwise be managed with watchful waiting, the immediate use of bicalutamide may increase the risk of death.

◊ References.

1. Wirth M, *et al.* Bicalutamide (Casodex) 150 mg as immediate therapy in patients with localized or locally advanced prostate cancer significantly reduces the risk of disease progression. *Urology* 2001; **58:** 146–51.
2. Boccardo F, *et al.* Bicalutamide monotherapy versus flutamide plus goserelin in prostate cancer: updated results of a multicentric trial. *Eur Urol* 2002; **42:** 481–90.
3. See WA, *et al.* Bicalutamide as immediate therapy either alone or as adjuvant to standard care of patients with localized or locally advanced prostate cancer: first analysis of the early prostate cancer program. *J Urol (Baltimore)* 2002; **168:** 429–35.
4. See W, *et al.* Immediate treatment with bicalutamide 150 mg as adjuvant therapy significantly reduces the risk of PSA progression in early prostate cancer. *Eur Urol* 2003; **44:** 512–17.
5. Fradet Y. Bicalutamide (Casodex) in the treatment of prostate cancer. *Expert Rev Anticancer Ther* 2004; **4:** 37–48.
6. Schellhammer PF, Davis JW. An evaluation of bicalutamide in the treatment of prostate cancer. *Clin Prostate Cancer* 2004; **2:** 213–19.
7. Wirth MP, *et al.* Bicalutamide 150 mg in addition to standard care in patients with localized or locally advanced prostate cancer: results from the second analysis of the early prostate cancer program at median followup of 5.4 years. *J Urol (Baltimore)* 2004; **172:** 1865–70.
8. Iversen P, *et al.* Bicalutamide (150 mg) versus placebo as immediate therapy alone or as adjuvant to therapy with curative intent for early nonmetastatic prostate cancer: 5.3-year median followup from the Scandinavian Prostate Cancer Group Study Number 6. *J Urol (Baltimore)* 2004; **172:** 1871–6.
9. Klotz L, Schellhammer P. Combined androgen blockade: the case for bicalutamide. *Clin Prostate Cancer* 2005; **3:** 215–19.
10. Wirth M, *et al.* Bicalutamide ('Casodex') 150 mg in addition to standard care in patients with nonmetastatic prostate cancer: updated results from a randomised double-blind phase III study (median follow-up 5.1 y) in the early prostate cancer programme. *Prostate Cancer Prostatic Dis* 2005; **8:** 194–200.
11. Tyrell CJ, *et al.* Bicalutamide ('Casodex') 150 mg as adjuvant to radiotherapy in patients with localised or locally advanced prostate cancer: results from the randomised Early Prostate Cancer Programme. *Radiother Oncol* 2005; **76:** 4–10.
12. McLeod DG, *et al.* Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. *BJU Int* 2006; **97:** 247–54.
13. Wellington K, Keam SJ. Bicalutamide 150mg: a review of its use in the treatment of locally advanced prostate cancer. *Drugs* 2006; **66:** 837–50.
14. Iversen P, Roder MA. The Early Prostate Cancer program: bicalutamide in nonmetastatic prostate cancer. *Expert Rev Anticancer Ther* 2008; **8:** 361–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Androxinon†; Bicaprost†; Bidrostat; Biolutam; Bitakebir; Bosconar; Casodex; Codebup; Dimalan; Finaband; Gepeprostin; Imda†; Liberprost; Raffolutil; ***Austral.:*** Cosudex; ***Austria:*** Casodex; ***Belg.:*** Casodex; ***Braz.:*** Casodex; Gepeprostin; Lutamidal; ***Canad.:*** Casodex; ***Chile:*** Casodex; Lutamidal; ***Cz.:*** Bicaluplex; Calumid; Casodex; Lanbica; ***Denm.:*** Casodex; ***Fin.:*** Casodex; ***Fr.:*** Casodex; ***Ger.:*** Casodex; ***Gr.:*** Bicalut; Bicamide; Casodex; Verodex; ***Hong Kong:*** Casodex; ***Hung.:*** Bicatlon; Bilutamid; Calumid; Casodex; ***India:*** Caluran; Calutide; ***Indon.:*** Casodex; ***Irl.:*** Casodex; ***Israel:*** Casodex; ***Ital.:*** Casodex; ***Malaysia:*** Casodex; ***Mex.:*** Casodex; ***Neth.:*** Casodex; ***Norw.:*** Casodex; ***NZ:*** Cosudex; ***Philipp.:*** Casodex; ***Pol.:*** Casodex; ***Port.:*** Casodex; ***Rus.:*** Bilumid (Билумид); Calumid (Калумид); Casodex (Касодекс); ***S.Afr.:*** Casodex; ***Singapore:*** Casodex; ***Spain:*** Casodex; ***Swed.:*** Casodex; ***Switz.:*** Casodex; ***Thai.:*** Casodex; ***Turk.:*** Casodex; ***UK:*** Casodex; ***USA:*** Casodex; ***Venez.:*** Calutol; Casodex.

Multi-ingredient: ***Austral.:*** Zolacos CP.