Preparations

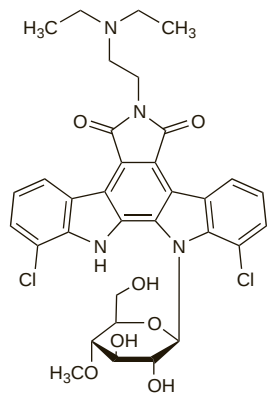
Proprietary Preparations (details are given in Part 3)
USA: Vidaza.

Becatecarin *(USAN, rINN)*

Becatecarina; Bécatécarine; Becatecarinum; BMS-181176; BMY-27557; NSC-655649; XL-119. 1,11-Dichloro-6-[2-(diethylamino)ethyl]-12-(4-*O*-methyl-β-D-glucopyranosyl)-12,13-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione.

Бекатекарин

$C_{33}H_{34}Cl_2N_4O_7$ = 669.6.
CAS — 119673-08-4.



Profile

Becatecarin is an antineoplastic under investigation in the treatment of bile-duct and other tumours.

◊ References.

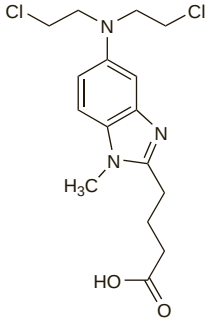
1. Merchant J, *et al.* Phase I clinical and pharmacokinetic study of NSC 655649, a rebeccamycin analogue, given in both single-dose and multiple-dose formats. *Clin Cancer Res* 2002; **8:** 2193–2201.
2. Goel S, *et al.* A phase II study of rebeccamycin analog NSC 655649 in patients with metastatic colorectal cancer. *Invest New Drugs* 2003; **21:** 103–7.
3. Langevin AM, *et al.* Phase I trial of rebeccamycin analog (NSC #655649) in children with refractory solid tumors: a pediatric oncology group study. *J Pediatr Hematol Oncol* 2003; **25:** 526–33.
4. Hussain M, *et al.* A phase II study of rebeccamycin analog (NSC-655649) in metastatic renal cell cancer. *Invest New Drugs* 2003; **21:** 465–71.
5. Ricart AD, *et al.* Phase I and pharmacokinetic study of sequences of the rebeccamycin analogue NSC 655649 and cisplatin in patients with advanced solid tumors. *Clin Cancer Res* 2005; **11:** 8728–36.
6. Langevin AM, *et al.* Children's Oncology Group. A phase II trial of rebeccamycin analogue (NSC #655649) in children with solid tumors: a Children's Oncology Group study. *Pediatr Blood Cancer* 2008; **50:** 577–80.

Bendamustine Hydrochloride *(USAN, rINNM)*

Bendamustine, Chlorhydrate de; Bendamustini Hydrochloridum; Hidrocloruro de bendamustina; IMET-3393; SDX-105. 5-[Bis(2-chloroethyl)amino]-1-methyl-2-benzimidazolebutyric acid hydrochloride.

Бендамустина Гидрохлорид

$C_{16}H_{21}Cl_2N_3O_2$, HCl = 394.7.
CAS — 16506-27-7 (bendamustine); 3543-75-7 (bendamustine hydrochloride).



(bendamustine)

Stability. US licensed product information for bendamustine hydrochloride states that, once reconstituted as directed and further diluted with sodium chloride 0.9%, the final infusion solution is stable for 24 hours when refrigerated (2° to 8°) or for 3 hours when stored at room temperature (15° to 30°) and exposed to light.

Adverse Effects, Treatment, and Precautions

Bendamustine commonly causes myelosuppression and doses may need to be reduced (see Uses and Administration, below); patients are therefore susceptible to infection. Other common adverse effects include gastrointestinal disturbances, fever, asthenia, fatigue, malaise, dry mouth, somnolence, cough, headache, mucosal inflammation, and stomatitis. Infusion reactions are common; symptoms include fever, chills, pruritus, and rash. Anaphylactic reactions have been reported rarely, especially during the second and subsequent cycles of therapy. Prophylactic antihistamines, antipyretics, and corticosteroids should be considered. If severe infusion reactions occur, stopping therapy should be considered. Tumour lysis syndrome has been reported, usually within the first treatment cycle, and may lead to acute renal failure and death. Adequate volume status should be maintained and potassium and uric acid concentrations should be monitored; allopurinol may be used in patients at high risk. Skin reactions such as bullous exanthema can occur with bendamustine; therapy may need to be withheld or stopped. Worsening hypertension, including hypertensive crisis, has also occurred. Increases in creatinine concentrations and liver enzyme values have been reported; bendamustine should be used with caution in patients with renal or hepatic impairment.

Interactions

Bendamustine is extensively metabolised by cytochrome P450 isoenzyme CYP1A2. Inhibitors of CYP1A2, such as fluvoxamine and ciprofloxacin, may increase exposure to bendamustine. Conversely, CYP1A2 inducers, such as omeprazole, can reduce exposure to bendamustine; tobacco smoking also may increase exposure to bendamustine.

Pharmacokinetics

Bendamustine is about 95% bound to plasma proteins; data suggest it is not likely to displace nor to be displaced by highly protein-bound drugs. Bendamustine distributes freely into human red blood cells. It is mainly metabolised by hydrolysis via the cytochrome P450 isoenzyme CYP1A2. Little or no accumulation in plasma is anticipated for intravenous doses of bendamustine given on days 1 and 2 of a 28-day cycle. About 90% of the drug is eliminated, mainly via the faeces.

Uses and Administration

Bendamustine is an antineoplastic alkylating agent. It is given intravenously as the hydrochloride for the treatment of chronic lymphocytic leukaemia (p.653); it may also be used in non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, and breast cancer.

For the treatment of chronic lymphocytic leukaemia, bendamustine hydrochloride is given in a dose of 100 mg/m^2, in 500 mL of sodium chloride 0.9%, infused over 30 minutes on days 1 and 2 of a 28-day cycle, for up to 6 cycles.

Doses are modified if toxicity occurs; dose delays may be warranted until neutrophils and platelets have recovered to acceptable concentrations. For severe haematological or non-haematological toxicity, doses should be reduced to 50 mg/m^2 on days 1 and 2 of each cycle. If severe haematological toxicity recurs, the dose should be further reduced to 25 mg/m^2. Dose re-escalation in subsequent cycles may be considered.

◊ References.

1. Barman Balfour JA, Goa KL. Bendamustine. *Drugs* 2001; **61:** 631–8.
2. Gandhi V. Metabolism and mechanisms of action of bendamustine: rationales for combination therapies. *Semin Oncol* 2002; **29** (4 suppl 13): 4–11.
3. Rummel MJ, *et al.* Bendamustine in the treatment of non-Hodgkin's lymphoma: results and future perspectives. *Semin Oncol* 2002; **29** (4 suppl 13): 27–32.
4. Rummel MJ, *et al.* Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's lymphoma. *J Clin Oncol* 2005; **23:** 3383–9.
5. von Minckwitz G, *et al.* Bendamustine prolongs progression-free survival in metastatic breast cancer (MBC): a phase III prospective, randomized, multicenter trial of bendamustine hydrochloride, methotrexate and 5-fluorouracil (BMF) versus cyclophosphamide, methotrexate and 5-fluorouracil (CMF) as first-line treatment of MBC. *Anticancer Drugs* 2005; **16:** 871–7.
6. Herold M, *et al.* Bendamustine, vincristine and prednisone (BOP) versus cyclophosphamide, vincristine and prednisone (COP) in advanced indolent non-Hodgkin's lymphoma and mantle cell lymphoma: results of a randomised phase III trial (OSHO 19). *J Cancer Res Clin Oncol* 2006; **132:** 105–12.
7. Ponisch W, *et al.* Treatment of bendamustine and prednisone in patients with newly diagnosed multiple myeloma results in superior complete response rate, prolonged time to treatment failure and improved quality of life compared to treatment with melphalan and prednisone—a randomized phase III study of the East German Study Group of Hematology and Oncology (OSHO). *J Cancer Res Clin Oncol* 2006; **132:** 205–12.
8. Eichbaum MH, *et al.* Weekly administration of bendamustine as salvage therapy in metastatic breast cancer: final results of a phase II study. *Anticancer Drugs* 2007; **18:** 963–8.
9. Friedberg JW, *et al.* Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin's lymphoma: results from a phase II multicenter, single-agent study. *J Clin Oncol* 2008; **26:** 204–10. Correction. *ibid.*; 1911.
10. Apostolopoulos C, *et al.* Bendamustine as a model for the activity of alkylating agents. *Future Oncol* 2008; **4:** 323–32.

Administration in hepatic impairment. US licensed product information states that, although no meaningful effect on the pharmacokinetics of bendamustine was seen in mild hepatic impairment, data are limited, and therefore caution should be exercised when using bendamustine in these patients. Bendamustine should not be used in moderate or severe hepatic impairment due to a lack of data.

Administration in renal impairment. US licensed product information states that, although no meaningful effect on the pharmacokinetics of bendamustine was seen in renal impairment, data are limited, and therefore caution should be exercised in patients with mild or moderate renal impairment. Bendamustine should not be used in patients with creatinine clearance less than 40 mL/minute, due to a lack of data.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Ribomustin; ***USA:*** Treanda.

Bevacizumab *(rINN)*

Bévacizumab; Bevacizumabum; rhuMAb-VEGF. Immunoglobulin G1 (human-mouse monoclonal rhuMAb-VEGF γ-chain anti-human vascular endothelial growth factor), disulfide with human-mouse monoclonal rhuMAb-VEGF light chain, dimer.

Бевацизумаб

CAS — 216974-75-3.
ATC — L01XC07.
ATC Vet — QL01XC07.

Stability. UK licensed product information states that bevacizumab is chemically and physically stable for 48 hours at 2° to 30° in sodium chloride 0.9%, although immediate use is recommended from a microbiological point of view. If the solution is not used immediately, storage for longer than 24 hours at 2° to 8° cannot be recommended, unless dilution has taken place in controlled and validated aseptic conditions. In the USA, licensed product information states that bevacizumab solutions for infusion may be stored at 2° to 8° for up to 8 hours.

Bevacizumab should not be mixed with glucose.

Adverse Effects, Treatment, and Precautions

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

Bevacizumab may impair wound healing; therapy should not be started for at least 28 days after major surgery or until the surgical incision is fully healed; it should also be withheld before elective surgery. Gastrointestinal perforation complicated by intra-abdominal abscesses or fistula formation is more common in patients receiving bevacizumab; fatalities have been reported. Bevacizumab should be stopped permanently in patients who develop gastrointestinal perforation, or fistulas, or wound dehiscence needing medical intervention. Very rare cases of nasal septum perforation have been reported.

Leucopenia, anaemia, neutropenia, thrombocytopenia, and febrile neutropenia have also occurred; severe neutropenia with infection has caused fatalities. Haemorrhage may occur; fatal pulmonary haemorrhage presenting as haemoptysis has been reported. There is an increased risk of serious thromboembolic events associated with the use of bevacizumab including stroke, transient ischaemic attacks, myocardial infarction, angina, and death. Bevacizumab may cause congestive heart failure; the risk is higher in those patients who have concurrent or previous treatment with anthracyclines. Hypertension, possibly dose-dependent, has occurred; blood pressure should be monitored, and therapy stopped in patients who develop hypertensive crisis or hypertensive encephalopathy.

Proteinuria may develop; bevacizumab should be stopped in patients who develop nephrotic syndrome. Other adverse effects include asthenia, pain, abdominal pain, gastrointestinal disturbances, stomatitis, headache, epistaxis, dyspnoea, upper respiratory infection, and exfoliative dermatitis. Peripheral sensory neuropathy, syncope, somnolence, supraventricular tachycardia, palmar-plantar erythrodysesthesia syndrome, and muscular weakness have been commonly reported. Infusion reactions, manifesting as hypertension, wheezing, chest pain, headaches, rigors, and dia-

phoresis may occur rarely with the first dose of bevacizumab; treatment should be interrupted.

There have been rare reports of reversible posterior leukoencephalopathy syndrome, a neurological disorder; this may present as seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Bevacizumab therapy should be stopped, and patients treated symptomatically.

◊ References.

1. Hurwitz H, Saini S. Bevacizumab in the treatment of metastatic colorectal cancer: safety profile and management of adverse events. *Semin Oncol* 2006; **33** (suppl 10): S26–S34.
2. Saif MW, Mehra R. Incidence and management of bevacizumab-related toxicities in colorectal cancer. *Expert Opin Drug Saf* 2006; **5:** 553–66.

Effects on the cardiovascular system. For a discussion of the incidence of hypertension associated with use of bevacizumab, see Effects on the Kidneys, below.

Effects on the kidneys. A systematic review and subsequent meta-analysis of 7 studies in 1850 patients with various cancers estimated the incidence and risk of developing hypertension and proteinuria with bevacizumab therapy.[1] The relative risk (RR) of developing proteinuria was 1.4 with low-dose bevacizumab (95% confidence interval 1.1 to 1.7) and even higher with high-dose therapy (RR 2.2; 95% confidence interval 1.6 to 2.9). For hypertension, the RR was 3.0 for low-dose bevacizumab (95% confidence interval 2.2 to 4.2) and 7.5 for high-dose therapy (95% confidence interval 4.2 to 13.4). US licensed product information states that hypertension can persist after stopping bevacizumab; therapy should be stopped permanently in those with hypertensive crisis or hypertensive encephalopathy. (For the suggestion that hypertension is a problem with angiogenesis inhibitors in general see Effects on the Cardiovascular System in Sorafenib, p.770.) The safety of continued treatment in patients with moderate to severe proteinuria has not been evaluated; therapy should be interrupted if proteinuria is equal to or greater than 2 g per 24 hours, and may be resumed when it is less than this.

Nephrotic syndrome has also been reported with use of bevacizumab;[2,3] therapy should be stopped in these patients. In one case,[3] there was evidence of a haemolytic-uraemic syndrome; renal biopsy revealed a glomerular thrombotic microangiopathy. Bevacizumab was stopped, with favourable response; however, sunitinib therapy was started but had to be stopped due to a recurrence of severe haemolytic-uraemic syndrome.

A patient who received 3 doses of bevacizumab was diagnosed with acute renal failure secondary to interstitial nephritis. His renal function resolved slowly after stopping therapy; haemodialysis was required.[4]

1. Zhu X, *et al.* Risks of proteinuria and hypertension with bevacizumab, an antibody against vascular endothelial growth factor: systematic review and meta-analysis. *Am J Kidney Dis* 2007; **49:** 186–93.
2. George BA, *et al.* Nephrotic syndrome after bevacizumab: case report and literature review. *Am J Kidney Dis* 2007; **49:** e23–e29.
3. Frangié C, *et al.* Renal thrombotic microangiopathy caused by anti-VEGF-antibody treatment for metastatic renal-cell carcinoma. *Lancet Oncol* 2007; **8:** 177–8.
4. Barakat RK, *et al.* Interstitial nephritis secondary to bevacizumab treatment in metastatic leiomyosarcoma. *Ann Pharmacother* 2007; **41:** 707–10.

Effects on the nervous system. There are reports of reversible posterior leukoencephalopathy syndrome (RPLS) attributed to bevacizumab.[1,2] Presenting symptoms included lethargy, seizures, hypertension, acute bilateral loss of vision, headache, and confusion. Recovery was rapid after symptomatic treatment.

The symptoms of RPLS may be difficult to distinguish from those of uncontrolled hypertension, and patients presenting with the above signs and symptoms should be examined neurologically.[3]

1. Glusker P, *et al.* Reversible posterior leukoencephalopathy syndrome and bevacizumab. *N Engl J Med* 2006; **354:** 980–1.
2. Ozcan C, *et al.* Reversible posterior leukoencephalopathy syndrome and bevacizumab. *N Engl J Med* 2006; **354:** 981–2.
3. Health Canada. Association of AVASTIN (bevacizumab) with hypertensive encephalopathy and reversible posterior leukoencephalopathy syndrome (RPLS) (issued 24th October 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/public/_2006/avastin_pc-cp-eng.php (accessed 30/07/08)

Effects on the spleen. Splenic infarction has been reported in a patient given bevacizumab, fluorouracil, folinic acid, and irinotecan. Bevacizumab was stopped. Four further chemotherapy cycles were given. The splenic infarcts partially regressed, although the patient died from metastatic progression. The authors attributed the splenic infarction to bevacizumab, which has been associated with arterial thromboembolic events.[1]

1. Malka D, *et al.* Splenic infarction and bevacizumab. *Lancet Oncol* 2006; **7:** 1038.

Fistula formation. US licensed product information for bevacizumab states that the incidence of gastrointestinal perforation, including fistula formation and/or intra-abdominal abscess, in bevacizumab-treated patients with colorectal cancer or non-small cell lung cancer was 2.4% and 0.9%, respectively. The Canadian manufacturer (*Roche, Canada*) has stated that there have been uncommon reports of other types of fistulas such as bronchopleural, urogenital, and biliary fistulas, across various indications. While cancer itself might have been a risk factor for fistula formation, a role for bevacizumab could not be excluded; most events occurred within the first 6 months of therapy.[1] There have been reports of tracheo-oesophageal fistula formation in association with use of bevacizumab, including some fatalities.[1,2] Therapy should be permanently stopped in patients with tracheo-oesophageal or gastrointestinal fistulas.

1. Roche, Canada. Health Canada endorsed important safety information on AVASTIN (bevacizumab): association of AVASTIN (bevacizumab) with tracheo-esophageal fistula (issued June 2007). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/avastin_hpc-cps_2_e.pdf (accessed 13/06/07)
2. Genentech, USA. Important drug warning regarding AVASTIN (bevacizumab) (issued April 2007). Available at: http://www.fda.gov/medwatch/safety/2007/Avastin_DHCP_TEF_Final_April2007.pdf (accessed 13/06/07)

Interactions

◊ The US manufacturer of bevacizumab has recommended that it should not be used with *sunitinib* after several patients receiving the combination had developed microangiopathic haemolytic anaemia.[1]

1. Genentech, USA. Important drug warning subject: microangiopathic hemolytic anemia (MAHA) in patients treated with Avastin (bevacizumab) and sunitinib malate (issued July 2008). Available at: http://www.fda.gov/medwatch/safety/2008/MAHA_DHCP.pdf (accessed 30/07/08)

Pharmacokinetics

Bevacizumab has an initial half-life of 1.4 days and a terminal half-life of about 20 days. The predicted time to steady state is about 100 days. Male patients and those with a higher tumour burden have higher clearances of bevacizumab than females and those with tumour burdens below the median, respectively; although no evidence of lesser efficacy has been seen due to this higher clearance, the relationship between exposure to bevacizumab and clinical outcome is not known.

Uses and Administration

Bevacizumab is a recombinant humanised monoclonal antibody that binds to vascular endothelial growth factor (VEGF), thereby inhibiting the angiogenesis that occurs during tumour growth. Bevacizumab is used with fluoropyrimidine-based chemotherapy in the treatment of metastatic colorectal cancer (p.665). It is also used with paclitaxel for the first-line treatment of patients with metastatic breast cancer (p.661), and with platinum-based chemotherapy in the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic, non-squamous, non-small cell lung cancer (p.668). Bevacizumab is used with interferon alfa for the first-line treatment of advanced and/or metastatic renal cell cancer (p.667).

Bevacizumab is usually given diluted in 100 mL of sodium chloride 0.9%; the final concentration should be kept within the range of 1.4 to 16.5 mg/mL. The first dose should be given as an intravenous infusion over 90 minutes; if this is well tolerated the second dose should be given over 60 minutes, and if this is well tolerated then subsequent doses may be given over 30 minutes.

In the treatment of **colorectal cancer**, bevacizumab is given in a dose of 5 or 10 mg/kg once every 2 weeks, or 7.5 or 15 mg/kg once every 3 weeks; doses depend on the combination of drugs used in the regimen.

For **breast cancer**, the recommended dose of bevacizumab is 10 mg/kg given once every 2 weeks, or 15 mg/kg given once every 3 weeks.

For **non-small cell lung cancer**, the recommended dose of bevacizumab is 7.5 or 15 mg/kg given once every 3 weeks. In the UK, combination therapy is given for up to 6 cycles, followed by bevacizumab monotherapy until disease progression.

For **renal cell carcinoma**, bevacizumab is given in a dose of 10 mg/kg once every 2 weeks.

There are no recommended dose reduction regimens should adverse effects occur with bevacizumab; therapy should either be permanently stopped or temporarily suspended.

Bevacizumab is under investigation for various other neoplasms, such as head and neck, ovarian, and prostate cancer. A related monoclonal antibody, ranibizumab (p.2377) has been developed for the treatment of neovascular (wet) age-related macular degeneration, and it has been suggested that bevacizumab might also be of benefit.

◊ References.

1. Hurwitz H, *et al.* Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; **350:** 2335–42.
2. Johnson DH, *et al.* Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non–small-cell lung cancer. *J Clin Oncol* 2004; **22:** 2184–91.
3. Zondor SD, Medina PJ. Bevacizumab: an angiogenesis inhibitor with efficacy in colorectal and other malignancies. *Ann Pharmacother* 2004; **38:** 1258–64.
4. Motl S. Bevacizumab in combination chemotherapy for colorectal and other cancers. *Am J Health-Syst Pharm* 2005; **62:** 1021–32. Correction. *ibid.*; 1241.
5. Kabbinavar FF, *et al.* Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. *J Clin Oncol* 2005; **23:** 3706–12.
6. Midgley R, Kerr D. Bevacizumab—current status and future directions. *Ann Oncol* 2005; **16:** 999–1004.
7. Lyseng-Williamson KA, Robinson DM. Spotlight on bevacizumab in advanced colorectal cancer, breast cancer, and non-small cell lung cancer. *BioDrugs* 2006; **20:** 193–5.
8. Shih T, Lindley C. Bevacizumab: an angiogenesis inhibitor for the treatment of solid malignancies. *Clin Ther* 2006; **28:** 1779–1802.
9. Pañares RL, Garcia AA. Bevacizumab in the management of solid tumors. *Expert Rev Anticancer Ther* 2007; **7:** 433–45.
10. Cilley JC, *et al.* Bevacizumab in the treatment of colorectal cancer. *Expert Opin Biol Ther* 2007; **7:** 739–49.
11. Burger RA. Experience with bevacizumab in the management of epithelial ovarian cancer. *J Clin Oncol* 2007; **25:** 2902–8.
12. Escudier B, *et al.* AVOREN Trial investigators. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet* 2007; **370:** 2103–11.
13. Miller K, *et al.* Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med* 2007; **357:** 2666–76.
14. Scott LJ. Bevacizumab: in first-line treatment of metastatic breast cancer. *Drugs* 2007; **67:** 1793–9.
15. McCormack PL, Keam SJ. Bevacizumab: a review of its use in metastatic colorectal cancer. *Drugs* 2008; **68:** 487–506.
16. Di Costanzo F, *et al.* Bevacizumab in non-small cell lung cancer. *Drugs* 2008; **68:** 737–46.
17. Norden AD, *et al.* Bevacizumab for recurrent malignant gliomas: efficacy, toxicity, and patterns of recurrence. *Neurology* 2008; **70:** 779–87.

Administration. It has been suggested that bevacizumab may be safely given at an infusion rate of 500 micrograms/kg per minute; this means a dose of 5 mg/kg could be given over 10 minutes.[1]

1. Reidy DL, *et al.* Bevacizumab 5 mg/kg can be infused safely over 10 minutes. *J Clin Oncol* 2007; **25:** 2691–5.

Age-related macular degeneration. Short-term results with intravenous[1] or intravitreal[2-7] bevacizumab to treat age-related macular degeneration (p.785) are promising, although it is unlicensed for this use. Ranibizumab (p.2377) is a humanised antibody fragment derived from bevacizumab that is used for the treatment of this disease.

1. Michels S, *et al.* Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration: twelve-week results of an uncontrolled open-label clinical study. *Ophthalmology* 2005; **112:** 1035–47.
2. Avery RL, *et al.* Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmology* 2006; **113:** 363–72.
3. Bashshur ZF, *et al.* Intravitreal bevacizumab for the management of choroidal neovascularization in age-related macular degeneration. *Am J Ophthalmol* 2006; **142:** 1–9.
4. Spaide RF, *et al.* Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. *Retina* 2006; **26:** 383–90.
5. Fung AE, *et al.* The International Intravitreal Bevacizumab Safety Survey: using the internet to assess drug safety worldwide. *Br J Ophthalmol* 2006; **90:** 1344–9.
6. Lynch SS, Cheng CM. Bevacizumab for neovascular ocular diseases. *Ann Pharmacother* 2007; **41:** 614–25.
7. Madhusudhana KC, *et al.* Intravitreal bevacizumab (Avastin) for the treatment of choroidal neovascularization in age-related macular degeneration: results from 118 cases. *Br J Ophthalmol* 2007; **91:** 1716–17.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Avastin; ***Austral.:*** Avastin; ***Belg.:*** Avastin; ***Braz.:*** Avastin; ***Canad.:*** Avastin; ***Chile:*** Avastin; ***Cz.:*** Avastin; ***Denm.:*** Avastin; ***Fin.:*** Avastin; ***Fr.:*** Avastin; ***Ger.:*** Avastin; ***Gr.:*** Avastin; ***Hong Kong:*** Avastin; ***Hung.:*** Avastin; ***Indon.:*** Avastin; ***Irl.:*** Avastin; ***Israel:*** Avastin; ***Ital.:*** Avastin; ***Jpn:*** Avastin; ***Mex.:*** Avastin; ***Neth.:*** Avastin; ***Norw.:*** Avastin; ***NZ:*** Avastin; ***Philipp.:*** Avastin; ***Pol.:*** Avastin; ***Port.:*** Avastin; ***Rus.:*** Avastin (Авастин); ***S.Afr.:*** Avastin; ***Singapore:*** Avastin; ***Spain:*** Avastin; ***Swed.:*** Avastin; ***Switz.:*** Avastin; ***Thai.:*** Avastin; ***UK:*** Avastin; ***USA:*** Avastin.

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.

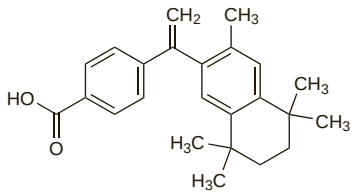
Бексаротен

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

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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.

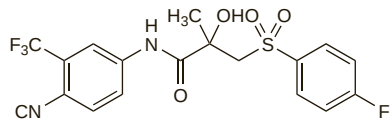
Бикалутамид

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