travenous infusion over 1 hour, at a dose of 650 mg/m^2 daily for 5 days, and repeated every 21 days.

◊ References.

1. Gandhi V, *et al.* Evaluation of the combination of nelarabine and fludarabine in leukemias: clinical response, pharmacokinetics, and pharmacodynamics in leukemia cells. *J Clin Oncol* 2001; **19:** 2142–52.
2. Kisor DF. Nelarabine: a nucleoside analog with efficacy in T-cell and other leukemias. *Ann Pharmacother* 2005; **39:** 1056–63.
3. Sanford M, Lyseng-Williamson KA. Nelarabine. *Drugs* 2008; **68:** 439–47.

Preparations

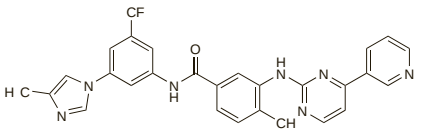
Proprietary Preparations (details are given in Part 3)
Cz.: Atriance; ***UK:*** Atriance; ***USA:*** Arranon.

Nilotinib *(USAN, rINN)*

AMN-107; Nilotinibum. 4-Methyl-*N*-[3-(4-methyl-1*H*-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]-amino}benzamide.

Нильотиниб

$C_{28}H_{22}F_3N_7O$ = 529.5.
CAS — 641571-10-0.
ATC — L01XE08.
ATC Vet — QL01XE08.



Nilotinib Hydrochloride *(rINNM)*

Hidrocloruro de nilotinib; Nilotinib, Chlorhydrate d'; Nilotinibi Hydrochloridum. Nilotinib Hydrochloride Monohydrate.

Нильотиниба Гидрохлорид

$C_{28}H_{22}F_3N_7O,HCl,H_2O$ = 584.0.
CAS — 923288-90-8.
ATC — L01XE08.
ATC Vet — QL01XE08.

Adverse Effects, Treatment, and Precautions

The most common adverse effects of nilotinib are rash, pruritus, nausea, fatigue, headache, and gastrointestinal disturbances. Myelosuppression occurs, but is generally reversible and can be managed by temporary cessation of therapy or dose reduction. Complete blood counts should be performed every fortnight for the first 2 months and monthly thereafter. Nilotinib can prolong the QT interval, which may result in ventricular tachycardia (torsade de pointes), causing syncope, seizures, and/or death; nilotinib should not be used in patients with hypokalaemia or hypomagnesaemia or long QT syndrome. Electrolyte abnormalities including hypophosphataemia, hypokalaemia, hyperkalaemia, hypocalcaemia, and hyponatraemia can occur, and should be monitored during therapy. Hepatotoxicity has been reported. Serum lipase should be monitored as increases can occur, and caution is recommended in patients with a history of pancreatitis.

Interactions

Nilotinib is a competitive inhibitor of several cytochrome P450 isoenzymes, particularly CYP3A4, which plays an important role in its metabolism. Use of nilotinib with strong inhibitors or inducers of CYP3A4 should be avoided. If they are used, dose adjustments may be required (see Uses and Administration, below). Grapefruit juice may also increase plasma concentrations of nilotinib and should be avoided. St John's wort should also be avoided. Nilotinib should not be given with drugs that prolong the QT interval.

Pharmacokinetics

Peak plasma concentrations occur about 3 hours after an oral dose of nilotinib; bioavailability is increased almost twofold when given with food, especially a high-fat meal. Plasma protein binding is about 98%. The apparent elimination half-life is about 17 hours. It is metabolised in the liver via oxidation and hydroxylation, in which cytochrome P450 isoenzyme CYP3A4 plays an important role.

Uses and Administration

Nilotinib is a tyrosine kinase inhibitor that is used for the treatment of chronic myeloid leukaemia. In patients who are resistant or intolerant to prior treatment that included imatinib, nilotinib hydrochloride is given in an oral dose equivalent to nilotinib 400 mg every 12 hours, at least 1 hour before or 2 hours after food. Therapy is interrupted if toxicity occurs; treatment may be re-started at a lower dose of 400 mg once daily.

Nilotinib is a competitive inhibitor of cytochrome P450 isoenzymes, including CYP3A4. Use with strong CYP3A4 inhibitors or inducers should be avoided. If no alternative is available, a dose reduction to nilotinib 400 mg once daily should be considered if it is given with a strong CYP3A4 inhibitor. Once the inhibitor is stopped, a washout period should be allowed before nilotinib is increased to the original dose. A dose increase of nilotinib may be needed if a strong CYP3A4 inducer is given; this depends on patient tolerability, and the nilotinib dose will need to be decreased once the inducer is stopped.

Nilotinib is also under investigation for the treatment of gastrointestinal stromal tumours.

◊ References.

1. Weisberg E, *et al.* AMN107 (nilotinib): a novel and selective inhibitor of BCR-ABL. *Br J Cancer* 2006; **94:** 1765–9.
2. Kantarjian H, *et al.* Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. *N Engl J Med* 2006; **354:** 2542–51.
3. Kantarjian HM, *et al.* Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. *Blood* 2007; **110:** 3540–6.
4. Plosker GL, Robinson DM. Nilotinib. *Drugs* 2008; **68:** 449–59.

Preparations

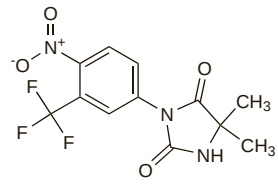
Proprietary Preparations (details are given in Part 3)
Cz.: Tasigna; ***Port.:*** Tasigna; ***Switz.:*** Tasigna; ***UK:*** Tasigna; ***USA:*** Tasigna.

Nilutamide *(BAN, USAN, rINN)*

Nilutamid; Nilutamida; Nilutamidi; Nilutamidum; RU-23908. 5,5-Dimethyl-3-(α,α,α-trifluoro-4-nitro-*m*-tolyl)-imidazolidine-2,4-dione.

Нилутамид

$C_{12}H_{10}F_3N_3O_4$ = 317.2.
CAS — 63612-50-0.
ATC — L02BB02.
ATC Vet — QL02BB02.



Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Nilutamide). A white or almost white powder. Very slightly soluble in water; freely soluble in acetone; soluble in anhydrous ethanol. Protect from light.

Adverse Effects and Precautions

As for Flutamide, p.725. Interstitial pneumonitis has occurred in patients receiving nilutamide, and the drug is contra-indicated in those with severe respiratory insufficiency.

Effects on the eyes. Reversible visual disturbances, particularly delayed dark adaptation, have been associated with nilutamide.[1,2] Although some consider such visual disturbances to be mild and generally well tolerated,[3] others suggest that these, together with alcohol intolerance and, more seriously, effects on the lung, mean that other nonsteroidal anti-androgens should be preferred.[4]

1. Harnois C, *et al.* Ocular toxicity of Anandron in patients treated for prostatic cancer. *Br J Ophthalmol* 1986; **70:** 471–3.
2. Brisset JM, *et al.* Ocular toxicity of Anandron. *Br J Ophthalmol* 1987; **71:** 639.
3. Dijkman GA, *et al.* Comment: clinical experiences of visual disturbances with nilutamide. *Ann Pharmacother* 1997; **31:** 1550–1.
4. Dole EJ, Holdsworth MT. Comment: clinical experiences of visual disturbances with nilutamide. *Ann Pharmacother* 1997; **31:** 1551–2.

Interactions

Patients receiving nilutamide may exhibit intolerance to alcohol.

Pharmacokinetics

Nilutamide is rapidly and completely absorbed from the gastrointestinal tract. It is extensively metabolised although it may inhibit its own metabolism to some extent after multiple doses. About 60% of an oral dose of nilutamide is eliminated in the urine and less than 10% in the faeces, with an elimination half-life of 41 to 49 hours.

Uses and Administration

Nilutamide is a nonsteroidal anti-androgen that is used similarly to flutamide (p.725) in the treatment of prostatic carcinoma (p.671). It is given orally in a dose of 300 mg daily, usually starting on the same day that the patient undergoes orchidectomy or receives treatment with a gonadorelin analogue. Dosage may be reduced to 150 mg daily after 1 month.

◊ References.

1. Dole EJ, Holdsworth MT. Nilutamide: an antiandrogen for the treatment of prostate cancer. *Ann Pharmacother* 1997; **31:** 65–75.
2. Desai A, *et al.* Nilutamide: possible utility as a second-line hormonal agent. *Urology* 2001; **58:** 1016–20.
3. Kassouf W, *et al.* Nilutamide as second line hormone therapy for prostate cancer after androgen ablation fails. *J Urol (Baltimore)* 2003; **169:** 1742–4.
4. Nakabayashi M, *et al.* Efficacy of nilutamide as secondary hormonal therapy in androgen-independent prostate cancer. *BJU Int* 2005; **96:** 783–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Anandron†; ***Austral.:*** Anandron; ***Braz.:*** Anandron; ***Canad.:*** Anandron; ***Cz.:*** Anandron†; ***Fr.:*** Anandron; ***Gr.:*** Anandron; ***Hung.:*** Anandron; ***Mex.:*** Anandron; ***Neth.:*** Anandron; ***Port.:*** Anandron; ***Swed.:*** Anandron; ***USA:*** Nilandron.

Nimotuzumab *(rINN)*

Cimazumab; h-R3; Nimotutsumabi; Nímótúzúmab; Nimotuzumabas; Nimotuzumabs; Nimotuzumabum. Immunoglobulin G1, anti-(humanized mouse monoclonal hR3 β1 chain anti-human epidermal growth factor receptor), disulfide with humanized mouse monoclonal hR3 κ-chain, dimer.

Нимотузумаб

CAS — 828933-51-3.

Profile

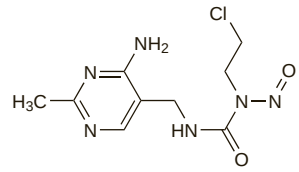
Nimotuzumab is a monoclonal antibody that binds to the epidermal growth factor receptor (EGFR). It is used in some countries for the treatment of glioma and cancers of the head and neck and pancreas.

Nimustine Hydrochloride *(rINNM)*

ACNU; Hidrocloruro de nimustina; Nimustiinihydrokloridi; Nimustine, Chlorhydrate de; Nimustinhydrokloridi; Nimustini Hydrochloridum; NSC-245382; Pimustine Hydrochloride. 3-[(4-Amino-2-methylpyrimidin-5-yl)methyl]-1-(2-chloroethyl)-1-nitrosourea hydrochloride.

Нимустина Гидрохлорид

$C_9H_{13}ClN_6O_2,HCl$ = 309.2.
CAS — 42471-28-3 (nimustine); 55661-38-6 (nimustine hydrochloride).
ATC — L01AD06.
ATC Vet — QL01AD06.



(nimustine)

Profile

Nimustine is a nitrosourea antineoplastic with actions and uses similar to those of carmustine (p.694). It is licensed for use in the treatment of malignant glioma. Nimustine hydrochloride is given in doses of 2 to 3 mg/kg or 90 to 100 mg/m^2 as a single dose by slow intravenous injection, repeated at intervals of 6 weeks depending on haematological response.

◊ References.

1. Anders K, *et al.* Accelerated radiotherapy with concomitant ACNU/Ara-C for the treatment of malignant glioma. *J Neurooncol* 2000; **48:** 63–73.
2. Kochii M, *et al.* Randomized comparison of intra-arterial versus intravenous infusion of ACNU for newly diagnosed patients with glioblastoma. *J Neurooncol* 2000; **49:** 63–70.