

travenous infusion over 1 hour, at a dose of 650 mg/m² daily for 5 days, and repeated every 21 days.

◇ References.

- 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.
- Kisor DF. Nelarabine: a nucleoside analog with efficacy in T-cell and other leukemias. *Ann Pharmacother* 2005; **39**: 1056–63.
- Sanford M, Lyseng-Williamson KA. Nelarabine. *Drugs* 2008; **68**: 439–47.

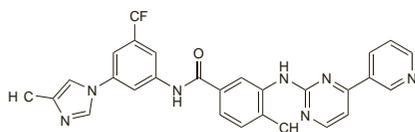
Preparations

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-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino]benzamide.

Нильотиниб
 C₂₈H₂₂F₃N₇O = 529.5.
 CAS — 641571-10-0.
 ATC — L01XE08.
 ATC Vet — QL01XE08.



Nilotinib Hydrochloride (rINN)

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

Нильотиниба Гидрохлорида
 C₂₈H₂₂F₃N₇O₂·HCl·H₂O = 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 me-

tabolised 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.

- Weisberg E, et al. AMN107 (nilotinib): a novel and selective inhibitor of BCR-ABL. *Br J Cancer* 2006; **94**: 1765–9.
- Kantarjian H, et al. Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. *N Engl J Med* 2006; **354**: 2542–51.
- 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.
- Plosker GL, Robinson DM. Nilotinib. *Drugs* 2008; **68**: 449–59.

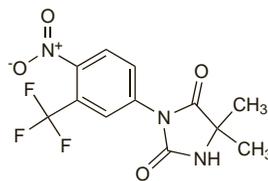
Preparations

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 -trifluoro-4-nitro-*m*-tolyl)-imidazolidine-2,4-dione.

Нилутамида
 C₁₂H₁₀F₃N₃O₄ = 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

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

- Dole EJ, Holdsworth MT. Nilutamide: an antiandrogen for the treatment of prostate cancer. *Ann Pharmacother* 1997; **31**: 65–75.
- Desai A, et al. Nilutamide: possible utility as a second-line hormonal agent. *Urology* 2001; **58**: 1016–20.
- Kassouf W, et al. Nilutamide as second line hormone therapy for prostate cancer after androgen ablation fails. *J Urol (Baltimore)* 2003; **169**: 1742–4.
- 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: Anadron; **Austral:** Anadron; **Braz:** Anadron; **Canad:** Anadron; **Cz:** Anadron; **Fr:** Anadron; **Gr:** Anadron; **Hung:** Anadron; **Mex:** Anadron; **Neth:** Anadron; **Port:** Anadron; **Swed:** Anadron; **USA:** Nilandron.

Nimotuzumab (rINN)

Cimazumab; h-R3; Nimotutsumabi; Nímótúzumáb; Nimotuzumabas; Nimotuzumabs; Nimotuzumabum. Immunoglobulin G1, anti-(humanized mouse monoclonal hR3 β 1 chain anti-human epidermal growth factor receptor), disulfide with humanized mouse monoclonal hR3 κ -chain, dimer.

Нимотузумаб
 CAS — 828933-51-3.

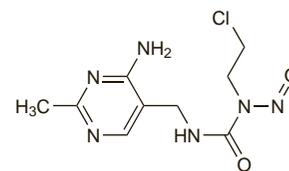
Profile

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 (rINN)

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

Нимустина Гидрохлорида
 C₉H₁₃ClN₅O₂·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/m² as a single dose by slow intravenous injection, repeated at intervals of 6 weeks depending on haematological response.

◇ References.

- Anders K, et al. Accelerated radiotherapy with concomitant ACNU/Ara-C for the treatment of malignant glioma. *J Neurooncol* 2000; **48**: 63–73.
- 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.

- Silvani A, et al. Intra-arterial ACNU and carboplatin versus intravenous chemotherapy with cisplatin and BCNU in newly diagnosed patients with glioblastoma. *Neurol Sci* 2002; **23**: 219–24.
- Weller M, et al. Neuro-Oncology Working Group 01 trial of nimustine plus teniposide versus nimustine plus cytarabine chemotherapy in addition to involved-field radiotherapy in the first-line treatment of malignant glioma. *J Clin Oncol* 2003; **21**: 3276–84.
- Watanabe T, et al. Human interferon beta, nimustine hydrochloride, and radiation therapy in the treatment of newly diagnosed malignant astrocytomas. *J Neurooncol* 2005; **72**: 57–62.

Preparations

Proprietary Preparations (details are given in Part 3)

Ger.: ACNU; Jpn.: Nidran†; Neth.: ACNU†; Switz.: ACNU†.

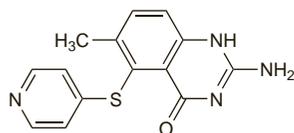
Nolatrexed (rINN)

AG-337 (nolatrexed dihydrochloride); Nolatrexedum. 2-Amino-6-methyl-5-(4-pyridylthio)-4(3H)-quinazolinone.

Нолатрексад

C₁₄H₁₂N₄OS = 284.3.

CAS — 147149-76-6 (nolatrexed); 152946-68-4 (nolatrexed dihydrochloride).



Profile

Nolatrexed is, like raltitrexed (p.766), a selective inhibitor of thymidylate synthase. It has been investigated as an antimetabolite antineoplastic for the treatment of hepatocellular carcinoma, although results of single-agent studies have been disappointing. It is also under investigation in combination therapy for other solid tumours.

References

- Mok TS, et al. A multi-centre randomized phase II study of nolatrexed versus doxorubicin in treatment of Chinese patients with advanced hepatocellular carcinoma. *Cancer Chemother Pharmacol* 1999; **44**: 307–11.
- Hughes AN, et al. Clinical pharmacokinetic and in vitro combination studies of nolatrexed dihydrochloride (AG337, Thymitaq) and paclitaxel. *Br J Cancer* 2000; **82**: 1519–27.
- Estlin EJ, et al. A phase I study of nolatrexed dihydrochloride in children with advanced cancer. *Br J Cancer* 2001; **84**: 11–18.
- Pivot X, et al. Result of two randomized trials comparing nolatrexed (Thymitaq) versus methotrexate in patients with recurrent head and neck cancer. *Ann Oncol* 2001; **12**: 1595–9.
- Jhawer M, et al. Phase II trial of nolatrexed dihydrochloride [Thymitaq, AG 337] in patients with advanced hepatocellular carcinoma. *Invest New Drugs* 2007; **25**: 85–94.
- Gish RG, et al. Phase III randomized controlled trial comparing the survival of patients with unresectable hepatocellular carcinoma treated with nolatrexed or doxorubicin. *J Clin Oncol* 2007; **25**: 3069–75.

Oblimersen Sodium (USAN, rINN)

G-3139; Natrii Oblimersenum; Oblimersén sodico; Oblimersen Sodique.

Натрий Облимерсен

C₁₇₂H₂₀₄N₆₂-Na₁₇O₉₁P₁₇S₁₇ = 6058.3.

CAS — 190977-41-4.

Profile

Oblimersen sodium is an antisense oligonucleotide that blocks the production of BCL-2, a mitochondrial protein that prevents apoptosis. It is under investigation for the treatment of various malignant neoplasms, including leukaemias, lung cancer, and malignant melanoma.

References

- Frankel SR. Oblimersen sodium (G3139 Bcl-2 antisense oligonucleotide) therapy in Waldenström's macroglobulinemia: a targeted approach to enhance apoptosis. *Semin Oncol* 2003; **30**: 300–304.
- Büchtele T. Proapoptische Therapie mit Oblimersen (bcl-2-Antisense-Oligonucleotid)—Übersicht über präklinische und klinische Daten. *Onkologie* 2003; **26** (suppl 7): 60–9.
- Herbst RS, Frankel SR. Oblimersen sodium (Genasense bcl-2 antisense oligonucleotide): a rational therapeutic to enhance apoptosis in therapy of lung cancer. *Clin Cancer Res* 2004; **10** (suppl): 4245s–4248s.
- Chi KN. Targeting Bcl-2 with oblimersen for patients with hormone refractory prostate cancer. *World J Urol* 2005; **23**: 33–7.
- O'Brien SM, et al. Phase I to II multicenter study of oblimersen sodium, a Bcl-2 antisense oligonucleotide, in patients with advanced chronic lymphocytic leukemia. *J Clin Oncol* 2005; **23**: 7697–7702.

The symbol † denotes a preparation no longer actively marketed

- Mita MM, et al. A phase I, pharmacokinetic and biologic correlative study of oblimersen sodium (Genasense, G3139) and irinotecan in patients with metastatic colorectal cancer. *Ann Oncol* 2006; **17**: 313–21.
- Bedikian AY, et al. Bcl-2 antisense (oblimersen sodium) plus dacarbazine in patients with advanced melanoma: the Oblimersen Melanoma Study Group. *J Clin Oncol* 2006; **24**: 4738–45.
- O'Brien S, et al. Randomized phase III trial of fludarabine plus cyclophosphamide with or without oblimersen sodium (Bcl-2 antisense) in patients with relapsed or refractory chronic lymphocytic leukemia. *J Clin Oncol* 2007; **25**: 1114–20. Correction. *ibid.* 2008; **26**: 820.

Ofatumumab (rINN)

HuMax-CD20; Ofatumumabum. Immunoglobulin G1, anti-(human CD20 (antigen))(human monoclonal HuMax-CD20 heavy chain), disulfide with human monoclonal HuMax-CD20 κ-chain, dimer.

Офатумумаб

CAS — 679818-59-8.

Profile

Ofatumumab is an anti-CD20 monoclonal antibody that is under investigation for the treatment of non-Hodgkin's lymphoma and chronic lymphocytic leukaemia.

References

- Coiffier B, et al. Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: a phase 1-2 study. *Blood* 2008; **111**: 1094–1100.
- Hagenbeek A, et al. First clinical use of ofatumumab, a novel fully human anti-CD20 monoclonal antibody in relapsed or refractory follicular lymphoma: results of a phase 1/2 trial. *Blood* 2008; **111**: 5486–95.
- Robak T. Ofatumumab, a human monoclonal antibody for lymphoid malignancies and autoimmune disorders. *Curr Opin Mol Ther* 2008; **10**: 294–309.

Olaparib (rINN)

Olaparibum. 4-[[3-[[4-(Cyclopropylcarbonyl)piperazin-1-yl]carbonyl]-4-fluorophenyl]methyl]phthalazin-1(2H)-one.

Олапариб

C₂₄H₂₃FN₄O₃ = 434.5.

CAS — 763113-22-0.



Profile

Olaparib is an antineoplastic that is under investigation for the treatment of ovarian cancer.

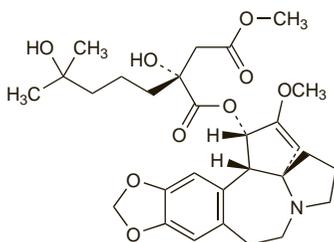
Omacetaxine Mepesuccinate (rINN)

CGX-635; HHT; Homoharringtonine; Mepesuccinato de omacetaxina; NSC-141633; Omacetaxine, Mepésuccinate d'; Omacetaxini mepesuccinas. 1-[[[(1S,3aR,14bS)-2-Methoxy-1,5,6,8,9,14b-hexahydro-4H-cyclopenta[a][1,3]dioxolo[4,5-h]pyrrolo[2,1-b][3]hazepin-1-yl]] 4-methyl (2R)-2-hydroxy-2-(4-hydroxy-4-methylpentyl)butanedioate.

Омацетаксин Мепесукцинат

C₂₉H₃₉NO₉ = 545.6.

CAS — 26833-87-4.



Pharmacopeias. In Chin.

Profile

Omacetaxine mepesuccinate is a semisynthetic formulation of homoharringtonine, which is an alkaloid derived from the tree *Cephalotaxus harringtonia*, and related species. It is thought to induce apoptosis by inhibition of protein synthesis. It is under investigation for the treatment of chronic myeloid leukaemia

(p.653). It has also been tried in the treatment of acute leukaemias and other neoplastic disorders.

The related compounds harringtonine, isoharringtonine, and deoxyharringtonine have also been investigated.

Adverse effects of omacetaxine mepesuccinate may include severe hypotension, cardiac arrhythmias, myelosuppression, gastrointestinal disturbances, chest pain, headache, fatigue, alopecia, rashes, and hyperglycaemia.

References

- Kantarjian HM, et al. Homoharringtonine and low-dose cytarabine in the management of late chronic-phase chronic myelogenous leukemia. *J Clin Oncol* 2000; **18**: 3513–21.
- Kantarjian HM, et al. Homoharringtonine: history, current research, and future direction. *Cancer* 2001; **92**: 1591–1605.
- O'Brien S, et al. Simultaneous homoharringtonine and interferon-alpha in the treatment of patients with chronic-phase chronic myelogenous leukemia. *Cancer* 2002; **94**: 2024–32.
- Tang J, et al. A homoharringtonine-based regimen for childhood acute myelogenous leukemia. *Med Pediatr Oncol* 2003; **41**: 70–2.
- O'Brien S, et al. Results of triple therapy with interferon-alpha, cytarabine, and homoharringtonine, and the impact of adding imatinib to the treatment sequence in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in early chronic phase. *Cancer* 2003; **98**: 888–93.
- Luo CY, et al. Homoharringtonine: a new treatment option for myeloid leukemia. *Hematology* 2004; **9**: 259–70.
- Quintás-Cardama A, Cortes J. Homoharringtonine for the treatment of chronic myelogenous leukemia. *Expert Opin Pharmacother* 2008; **9**: 1029–37.
- Quintás-Cardama A, Cortes J. Omacetaxine mepesuccinate - a semisynthetic formulation of the natural antitumor alkaloid homoharringtonine, for chronic myelocytic leukemia and other myeloid malignancies. *IDrugs* 2008; **11**: 356–72.

Oregovomab (USAN, rINN)

MAB-B43.13; Oregovomab; Oregovomabum. Immunoglobulin G1, anti-(human CA125 (carbohydrate antigen)) (mouse monoclonal B43.13 γ1-chain), disulfide with mouse monoclonal B43.13 κ-chain, dimer.

ОрегОВОмаб

CAS — 213327-37-8.

Profile

Oregovomab is a murine monoclonal antibody that binds to CA-125, an antigen that is overexpressed in the majority of ovarian cancer patients, and stimulates an immune response to the tumour cells. It is under investigation for the treatment of ovarian cancer.

Oxaliplatin (BAN, USAN, rINN)

JM-83; NSC-266046; l-OHP; Oksaliplatiini; Oksaliplatin; Oksalipatina; Oxaliplatina; Oxaliplatino; Oxaliplatinum; RP-54780; SR-96669. [(1R,2R)-1,2-Cyclohexanediamine-N,N']-[oxalato(2-)-O,O']platinum.

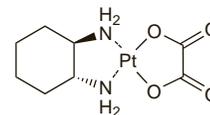
ОксАлИПЛАТИН

C₈H₁₄N₂O₄Pt = 397.3.

CAS — 61825-94-3.

ATC — L01XA03.

ATC Vet — QL01XA03.



Pharmacopeias. In Eur. (see p.vii).

Ph. Eur. 6.2 (Oxaliplatin). A white or almost white, crystalline powder. Slightly soluble in water; practically insoluble in dehydrated alcohol; very slightly soluble in methyl alcohol.

Incompatibility. Licensed product information states that oxaliplatin should not be mixed with chloride-containing solutions (including sodium chloride) or alkaline drugs or solutions. In particular, oxaliplatin should not be mixed with fluorouracil or any trometamol salts. While oxaliplatin may be infused through a Y-site with folic acid (in glucose 5% solution), they may not be mixed in the same infusion bag, and folic acid must not contain trometamol as an excipient. The infusion line should be flushed with glucose 5% before giving any other medication. Oxaliplatin may degrade on contact with aluminium, and injection equipment containing aluminium should not be used.

Stability. UK licensed product information states that oxaliplatin must be diluted in glucose 5% to give a concentration not less than 200 micrograms/mL. From a microbiological point of view, the infusion preparation should be used immediately; the infusion should not be stored for longer than 24 hours at 2° to 8° unless it has been prepared in controlled and validated aseptic conditions. Chemical and physical stability has been shown for 48 hours at 2° to 8°, and for 24 hours at 25°. US licensed product information states that, after dilution in 250 to 500 mL of glucose