be given as pegaspargase, in doses of 2500 units/m^2 every 14 days, preferably by intramuscular injection although the intravenous route may also be used.

Asparaginase is not generally used alone as an induction agent but doses of 200 units/kg daily have been given intravenously for 28 days to adults and children. If pegaspargase is used alone doses are the same as for combination regimens. Children appear to tolerate asparaginase better than adults.

Although not entirely reliable, an intradermal test dose of about 2 units has been recommended in the USA, to test for hypersensitivity, before treatment with colaspase or where more than a week has elapsed between doses. Desensitisation has been advocated if no alternative antineoplastic treatment is available. Anaphylaxis with crisantaspase is stated to be rare; however, in the UK if there has been an interruption in treatment, therapy should be resumed with a low dose of 10 units/kg daily and increased to the full dose over 5 days if tolerated. A test dose is not advocated, although reference to local leukaemia protocols is recommended. The incidence of hypersensitivity is also lower in patients given pegaspargase, and again a test dose is not advocated. Pegaspargase has been successfully used in patients hypersensitive to the native enzyme.

For intravenous use a solution of asparaginase in Water for Injections or sodium chloride 0.9% should be given over not less than 30 minutes through a running infusion of sodium chloride 0.9% or glucose 5%. When given intramuscularly no more than 2 mL of a solution in sodium chloride 0.9% should be injected at a single site.

◊ References.

1. Muller HJ, Boos J. Use of L-asparaginase in childhood ALL. *Crit Rev Oncol Hematol* 1998; **28:** 97–113.
2. Asselin BL. The three asparaginases: comparative pharmacology and optimal use in childhood leukemia. *Adv Exp Med Biol* 1999; **457:** 621–9.
3. Abshire TC, *et al.* Weekly polyethylene glycol conjugated L-asparaginase compared with biweekly dosing produces superior induction remission rates in childhood relapsed acute lymphoblastic leukemia: a Pediatric Oncology Group study. *Blood* 2000; **96:** 1709–15.
4. Avramis VI, Panosyan EH. Pharmacokinetic/pharmacodynamic relationships of asparaginase formulations: the past, the present and recommendations for the future. *Clin Pharmacokinet* 2005; **44:** 367–93.
5. Fu CH, Sakamoto KM. PEG-asparaginase. *Expert Opin Pharmacother* 2007; **8:** 1977–84.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Kidrolase; L-Asp†; Oncaspar; ***Austral.:*** Leunase; ***Belg.:*** Paronal; ***Braz.:*** Elspar; ***Canad.:*** Kidrolase; ***Cz.:*** Erwinase†; Kidrolase; ***Denm.:*** Erwinase†; ***Fin.:*** Erwinase†; ***Fr.:*** Kidrolase; ***Ger.:*** Erwinase†; Oncaspar; ***Gr.:*** Erwinase; Oncaspar; ***Hong Kong:*** Elspar†; Leunase; ***India:*** Leunase; ***Indon.:*** Leunase; ***Irl.:*** Erwinase; ***Israel:*** Kidrolase; ***Jpn:*** Leunase; ***Malaysia:*** Erwinase†; Leunase; ***Mex.:*** Leunase; ***Neth.:*** Erwinase; Paronal; ***NZ:*** Erwinase; Leunase; ***Philipp.:*** Leunase; ***Pol.:*** Oncaspar; ***Port.:*** Erwinase; ***Rus.:*** Oncaspar (Онкаспар); ***S.Afr.:*** Laspar; ***Singapore:*** Erwinase†; Leunase; ***Swed.:*** Erwinase; ***Thai.:*** Erwinase†; Leunase; ***Turk.:*** Leunase; ***UK:*** Erwinase; ***USA:*** Elspar; Oncaspar.

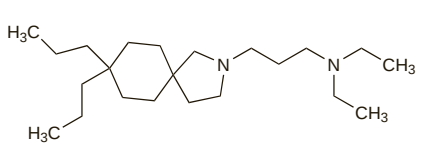
Atiprimod *(rINN)*

Atiprimodum. 2-[3-(Diethylamino)propyl]-8,8-dipropyl-2-azaspiro[4.5]decane.

Атипримод

$C_{22}H_{44}N_2$ = 336.6.

CAS — 123018-47-3 (atiprimod); 130065-61-1 (atiprimod hydrochloride); 183063-72-1 (atiprimod maleate).



Profile

Atiprimod is an antineoplastic that is under investigation for the treatment of carcinoid tumours and multiple myeloma.

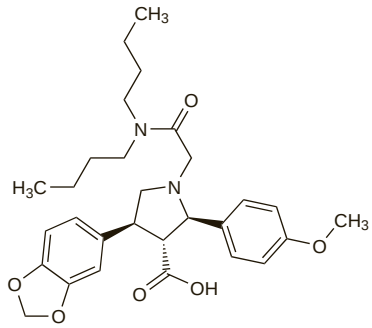
Atrasentan Hydrochloride *(USAN, rINNM)*

A-147627.1; Abbott-147627; ABT-627; Atrasentan, Chlorhydrate d'; Atrasentani Hydrochloridum; Hidrocloruro de atrasentán. (2*R*,3*R*,4*S*)-1-[(Dibutylcarbamoyl)methyl]-2-(*p*-methoxyphenyl)-4-[3,4-(methylenedioxy)phenyl]-3-pyrrolidinecarboxylic acid hydrochloride.

Атразентана Гидрохлорид

$C_{29}H_{38}N_2O_6$,HCl = 547.1.

CAS — 173937-91-2 (atrasentan); 195733-43-8 (atrasentan hydrochloride).



(atrasentan)

Profile

Atrasentan hydrochloride is a selective endothelin-A receptor antagonist that inhibits the effect of endothelin-1, a protein that may be involved in cancer progression. It is under investigation in the treatment of prostate cancer, and has been tried in other malignant neoplasms.

◊ References.

1. Samara E, *et al.* Single-dose pharmacokinetics of atrasentan, an endothelin-A receptor antagonist. *J Clin Pharmacol* 2001; **41:** 397–403.
2. Carducci MA, *et al.* Atrasentan, an endothelin-receptor antagonist for refractory adenocarcinomas: safety and pharmacokinetics. *J Clin Oncol* 2002; **20:** 2171–80.
3. Carducci MA, *et al.* Effect of endothelin-A receptor blockade with atrasentan on tumor progression in men with hormone-refractory prostate cancer: a randomized, phase II, placebo-controlled trial. *J Clin Oncol* 2003; **21:** 679–89.
4. Zonnenberg BA, *et al.* Phase I dose-escalation study of the safety and pharmacokinetics of atrasentan: an endothelin receptor antagonist for refractory prostate cancer. *Clin Cancer Res* 2003; **9:** 2965–72.
5. Ryan CW, *et al.* Dose-ranging study of the safety and pharmacokinetics of atrasentan in patients with refractory malignancies. *Clin Cancer Res* 2004; **10:** 4406–11.
6. Michaelson MD, *et al.* Randomized phase II study of atrasentan alone or in combination with zoledronic acid in men with metastatic prostate cancer. *Cancer* 2006; **107:** 530–5.
7. Carducci MA, *et al.* Atrasentan Phase III Study Group Institutions. A phase 3 randomized controlled trial of the efficacy and safety of atrasentan in men with metastatic hormone-refractory prostate cancer. *Cancer* 2007; **110:** 1959–66.
8. Chiappori AA, *et al.* Phase I/II study of atrasentan, an endothelin A receptor antagonist, in combination with paclitaxel and carboplatin as first-line therapy in advanced non-small cell lung cancer. *Clin Cancer Res* 2008; **14:** 1464–9.
9. Phuphanich S, *et al.* New Approaches to Brain Tumor Therapy (NABTT) CNS Consortium. Phase I safety study of escalating doses of atrasentan in adults with recurrent malignant glioma. *Neuro-oncol* 2008; **10:** 617–623.

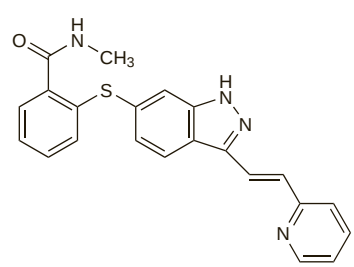
Axitinib *(USAN, rINN)*

AG-013736; Axitinibum. *N*-Methyl-2-({3-[(1*E*)-2-(pyridin-2-yl)ethenyl]-1*H*-indazol-6-yl}sulfanyl)benzamide.

Акситиниб

$C_{22}H_{18}N_4OS$ = 386.5.

CAS — 319460-85-0.



Profile

Axitinib is a tyrosine kinase inhibitor that is under investigation as an antineoplastic for the treatment of various cancers, including pancreatic, lung, gastrointestinal, and breast cancer, as well as melanoma.

◊ Reviews.

1. Sonpavde G, *et al.* Axitinib for renal cell carcinoma. *Expert Opin Invest Drugs* 2008; **17:** 741–8.
2. Choueiri TK. Axitinib, a novel anti-angiogenic drug with promising activity in various solid tumors. *Curr Opin Investig Drugs* 2008; **9:** 658–71.

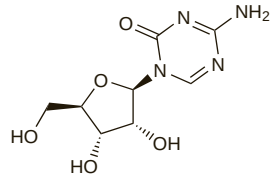
Azacitidine *(USAN, rINN)*

Azacitidina; 5-Azacitidina; Azacitidinum; 5-Azacytidine; Ladakamycin; NSC-102816; U-18496. 4-Amino-1-β-D-ribofuranosyl-1,3,5-triazin-2(1*H*)-one.

Азацитидин

$C_8H_{12}N_4O_5$ = 244.2.

CAS — 320-67-2.



Adverse Effects and Precautions

The adverse effects of azacitidine are generally similar to those seen with cytarabine (p.705). Hypokalaemia, dyspnoea, and bruising are common.

Pharmacokinetics

Azacitidine is rapidly absorbed after subcutaneous use; the bioavailability relative to intravenous use is about 89%. The mean plasma half-life after subcutaneous injection is about 40 minutes. Azacitidine and its metabolites are excreted primarily in the urine; about 50% and 85% is recovered after subcutaneous and intravenous dosing, respectively. The mean elimination half-life is about 4 hours after subcutaneous or intravenous use.

◊ References.

1. Marcucci G, *et al.* Bioavailability of azacitidine subcutaneous versus intravenous in patients with the myelodysplastic syndromes. *J Clin Pharmacol* 2005; **45:** 597–602.
2. Tsao CF, *et al.* Azacitidine pharmacokinetics in an adolescent patient with renal compromise. *J Pediatr Hematol Oncol* 2007; **29:** 330–3.

Uses and Administration

Azacitidine is an antimetabolite antineoplastic with general properties similar to those of cytarabine (p.705). It also inhibits cellular pyrimidine synthesis. Azacitidine is used in myelodysplastic syndromes (p.654); it has also been used in the treatment of acute myeloid leukaemia (p.652).

For the treatment of myelodysplastic syndromes, azacitidine is given subcutaneously or intravenously in a dose of 75 mg/m^2 daily for 7 days, in 4-week cycles. If there is no benefit after 2 cycles, and no toxicity other than nausea and vomiting has occurred, the dose may be increased to 100 mg/m^2 daily. Treatment for at least 4 cycles is usually needed.

Azacitidine should be used with caution in renal impairment and doses adjusted accordingly (see below).

◊ References.

1. Anonymous. Azacitidine (Vidaza) for myelodysplastic syndrome. *Med Lett Drugs Ther* 2005; **47:** 11.
2. Sullivan M, *et al.* Azacitidine: a novel agent for myelodysplastic syndromes. *Am J Health-Syst Pharm* 2005; **62:** 1567–73.
3. Kuykendall JR. 5-Azacytidine and decitabine monotherapies of myelodysplastic disorders. *Ann Pharmacother* 2005; **39:** 1700–9.
4. Siddiqui MAA, Scott LJ. Azacitidine: in myelodysplastic syndromes. *Drugs* 2005; **65:** 1781–9.
5. Kaminskas E, *et al.* FDA drug approval summary: azacitidine (5-azacytidine, Vidaza) for injectable suspension. *Oncologist* 2005; **10:** 176–82.
6. Silverman LR, *et al.* Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. *J Clin Oncol* 2006; **24:** 3895–3903.
7. Abdulhaq H, Rossetti JM. The role of azacitidine in the treatment of myelodysplastic syndromes. *Expert Opin Invest Drugs* 2007; **16:** 1967–75.
8. O'Dwyer K, Maslak P. Azacitidine and the beginnings of therapeutic epigenetic modulation. *Expert Opin Pharmacother* 2008; **9:** 1981–6.

Administration in renal impairment. Adverse renal effects of azacitidine include abnormalities in renal-function tests, renal tubular acidosis, renal failure, and death. US licensed product information recommends that if serum-bicarbonate concentrations fall to below 20 mEq/litre, the dose of azacitidine should be halved for the next course. If there are rises in serum concentrations of urea or creatinine, the next cycle of azacitidine should be delayed until these return to normal or baseline, and the dose should be halved on the next treatment course.