for 6 months. Dysmenorrhoea improved significantly although chronic pelvic pain was unchanged. Adverse effects were mild.

1. Amsterdam LL, *et al.* Anastrazole [sic] and oral contraceptives: a novel treatment for endometriosis. *Fertil Steril* 2005; **84:** 300–4.
2. Hefler LA, *et al.* Role of the vaginally administered aromatase inhibitor anastrozole in women with rectovaginal endometriosis: a pilot study. *Fertil Steril* 2005; **84:** 1033–6.

Gynaecomastia. Anastrozole has been reported[1] to be under investigation for the treatment of gynaecomastia, but controlled studies suggest that it may be no better than placebo—see Gynaecomastia (p.2092) and Gynaecomastia under Adverse Effects and Precautions of Flutamide (p.725).

1. Gruntmanis U, Braunstein GD. Treatment of gynecomastia. *Curr Opin Investig Drugs* 2001; **2:** 643–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Anaskebir; Anastraze; Anebol; Arimidex; Aromenal; Asiolex†; Distalene; Gondonar; Leprofen; Lezole†; Pantestone; Puricap; Trozolite; ***Austral.:*** Arimidex; ***Austria:*** Arimidex; ***Belg.:*** Arimidex; ***Braz.:*** Arimidex; ***Canad.:*** Arimidex; ***Chile:*** Arimidex; Trozolet; ***Cz.:*** Anabrest; Anaya; Arimidex; Egistrozol; OncoFem; Zynzol; ***Denm.:*** Arimidex; ***Fin.:*** Arimidex; ***Fr.:*** Arimidex; ***Ger.:*** Arimidex; ***Gr.:*** Arimidex; ***Hong Kong:*** Arimidex; ***Hung.:*** Arimidex; ***India:*** Altraz; Armotraz; ***Indon.:*** Arimidex; ***Irl.:*** Arimidex; ***Israel:*** Arimidex; ***Ital.:*** Arimidex; ***Malaysia:*** Arimidex; ***Mex.:*** Arimidex; ***Neth.:*** Arimidex; ***Norw.:*** Arimidex; ***NZ:*** Arimidex; ***Philipp.:*** Arimidex; ***Pol.:*** Arimidex; Atrozol; ***Port.:*** Arimidex; Remidex; ***Rus.:*** Arimidex (Аримидекс); ***S.Afr.:*** Arimidex; ***Singapore:*** Arimidex; ***Spain:*** Arimidex; ***Swed.:*** Arimidex; ***Switz.:*** Arimidex; ***Thai.:*** Arimidex; ***Turk.:*** Arimidex; ***UK:*** Arimidex; ***USA:*** Arimidex; ***Venez.:*** Arimidex; Trozolet.

Antineoplaston A10

3-Phenylacetylamino-2,6-piperidinedione.
$C_{13}H_{14}N_2O_3$ = 246.3.

Profile
Antineoplaston A10, one of a group of peptide derivatives isolated from blood and urine, has been investigated for the treatment of breast cancer, brain stem glioma, and other malignant neoplasms although its value has been questioned (see below).

◊ A critical review of the antineoplastons[1] noted that most work had been done with antineoplaston A10, which is insoluble in aqueous solutions, and its derivatives antineoplaston AS2.5 (phenylacetylglutamine), and antineoplaston AS2.1 (a 4:1 mixture of phenylacetic acid and phenylacetylglutamine), which had not been independently shown to be active against cancer. However, some interest in the antineoplastons subsequently continued.[2-4]

1. Green S. Antineoplastons: an unproved cancer therapy. *JAMA* 1992; **267:** 2924–8.
2. Buckner JC, *et al.* Phase II study of antineoplastons A10 (NSC 648539) and AS2-1 (NSC 620261) in patients with recurrent glioma. *Mayo Clin Proc* 1999; **74:** 137–45.
3. Badria F, *et al.* Immune modulatory potentials of antineoplaston A-10 in breast cancer patients. *Cancer Lett* 2000; **157:** 57–63.
4. Burzynski SR, *et al.* Targeted therapy with antineoplastons A10 and AS2-1 of high-grade, recurrent, and progressive brainstem glioma. *Integr Cancer Ther* 2006; **5:** 40–7.

AP-12009

TGF-β2 antisense oligonucleotide; Transforming growth factor-β2-specific phosphorothioate antisense oligodeoxynucleotide.

Profile
AP-12009 is an antisense oligonucleotide that specifically suppresses the production of transforming growth factor-beta-2, an immunosuppressive protein produced by tumour cells. It is under investigation for the treatment of high-grade glioma (see Malignant Neoplasms of the Brain, p.660).

AS-1411

AGRO-100.

Profile
AS-1411 is a selective oligonucleotide ligand (aptamer) that binds to the protein nucleolin, inducing apoptosis in cancer cells. It is under investigation for the treatment of renal cell carcinoma, pancreatic cancer, and acute myelogenous leukaemia.

Asparaginase *(USAN)*

Asparaginasa; L-Asparaginase; L-Asparagine Amidohydrolase; L-Asparaginaz; L-Asparaginaasi; L-Asparaginas; L-Asparaginasum; MK-965; NSC-109229; Re-82-TAD-15.
CAS — 9015-68-3.
ATC — L01XX02.
ATC Vet — QL01XX02.

NOTE. Asparaginase (*USAN*) is an enzyme isolated from *Escherichia coli*, or obtained from other sources. See also Colaspase and Crisantaspase, below.

Incompatibility. Asparaginase is incompatible with rubber. Licensed product information recommends that it should not be mixed with other drugs.

Storage. Asparaginase should be stored at 2° to 8° (see also Stability, below).

Colaspase *(BAN)*

CAS — 9015-68-3.
ATC — L01XX02.
ATC Vet — QL01XX02.

NOTE. Colaspase (*BAN*) is asparaginase obtained from selected strains of *Escherichia coli*, such as ATCC 9637.

Pharmacopoeias. *Chin.* includes Asparaginase obtained from *Escherichia coli* ASI 357.

Crisantaspase *(BAN)*

Crisantaspasum; Erwinia L-asparaginase; Krisantaspaasi; Krisantaspas.
CAS — 9015-68-3.
ATC — L01XX02.
ATC Vet — QL01XX02.

NOTE. Crisantaspase (*BAN*) is asparaginase obtained from cultures of *Erwinia chrysanthemi* (*E. carotovora*).

Pegaspargase *(USAN, rINN)*

PEG-L-asparaginase; Pegaspargasa; Pégaspargase; Pegaspargasum. A conjugate of colaspase with a polyethylene glycol of molecular weight 5000; Monomethoxypolyethylene glycol succinimidyl L-asparaginase.

Пэгаспаргаза
CAS — 130167-69-0.
ATC — L01XX24.
ATC Vet — QL01XX24.

Stability. Although asparaginase was routinely kept under refrigeration,[1] information from a manufacturer (*Merck Sharp & Dohme*) indicated that it would remain stable for 48 hours at 15° to 30°. Licensed product information for pegaspargase states it should not be used if stored at room temperature for more than 48 hours.

1. Vogenberg FR, Souney PF. Stability guidelines for routinely refrigerated drug products. *Am J Hosp Pharm* 1983; **40:** 101–2.

Storage. Pegaspargase should be stored at 2° to 8°.

Units
One international unit of asparaginase splits 1 micromole of ammonia from L-asparagine in 1 minute under standard conditions.

Adverse Effects
Asparaginase is a protein and may produce anaphylaxis and other hypersensitivity reactions including fever, rashes, and bronchospasm; there does not appear to be cross-sensitivity between asparaginase derived from *Escherichia coli* and that from *Erwinia chrysanthemi*. Hypersensitivity to pegaspargase is less common, but about 30% of patients hypersensitive to the native enzyme experience hypersensitivity to pegaspargase treatment.

Liver function abnormalities occur in many patients, and there may be decreased blood concentrations of fibrinogen and clotting factors, alterations in blood lipids and cholesterol, and hypoalbuminaemia. Hyperammonaemia, due to the production of ammonia from asparagine, may occur. Uraemia, and occasionally renal failure, have been reported. Pancreatitis may occur and may be fatal: there may also be hyperglycaemia due to decreased insulin production, and death from ketoacidosis has occurred.

Gastrointestinal disturbances, including nausea and vomiting, and CNS disturbances, including drowsiness, depression, coma, hallucinations, and a Parkinson-like syndrome, have also been reported. Transient bone-marrow depression has occurred rarely, as has marked leucopenia.

Effects on the blood. Central thrombosis or intracranial haemorrhage as well as peripheral thrombosis and haemorrhage have been reported after asparaginase therapy.[1-4] Although the precise mechanism for this effect remains unclear, asparaginase appears to deplete certain clotting factors as well as antithrombin III, plasminogen, and fibrinogen.[4] These decreases may be dependent on the formulation and resultant asparaginase activity of preparations,[5] and there is some suggestion that crisantaspase may affect coagulation factors less severely than colaspase.[6] A multicentre, retrospective survey[3] of paediatric patients with acute lymphoblastic leukaemia found that use of corticosteroids with colaspase may be an additional risk factor for thromboembolic events.

1. Priest JR, *et al.* A syndrome of thrombosis and hemorrhage complicating L-asparaginase therapy for childhood acute lymphoblastic leukemia. *J Pediatr* 1982; **100:** 984–9.
2. Ott N, *et al.* Sequelae of thrombotic or hemorrhagic complications following L-asparaginase therapy for childhood lymphoblastic leukemia. *Am J Pediatr Hematol Oncol* 1988; **10:** 191–5.
3. Sutor AH, *et al.* Bleeding and thrombosis in children with acute lymphoblastic leukaemia, treated according to the ALL-BFM-90 protocol. *Klin Padiatr* 1999; **211:** 201–4.
4. Alberts SR, *et al.* Thrombosis related to the use of L-asparaginase in adults with acute lymphoblastic leukemia: a need to consider coagulation monitoring and clotting factor replacement. *Leuk Lymphoma* 1999; **32:** 489–96.
5. Nowak-Göttl U, *et al.* Influence of two different Escherichia coli asparaginase preparations on fibrinolytic proteins in childhood ALL. *Haematologica* 1996; **81:** 127–31.
6. Carlsson H, *et al.* Effects of Erwinia-asparaginase on the coagulation system. *Eur J Haematol* 1995; **55:** 289–93.

Precautions
Asparaginase is contra-indicated in patients with pancreatitis, and should be avoided in pregnancy. It should be given cautiously to patients with hepatic impairment. Facilities for the management of anaphylaxis (see p.1205) should be available during treatment. Some manufacturers recommend an intradermal test dose at the start of asparaginase treatment to check for hypersensitivity, as described under Uses, below, although such tests may not always be predictive. Retreatment with asparaginase may be associated with an increased risk of allergic reactions. Serum amylase concentrations should be monitored regularly as should blood glucose concentrations. Asparaginase has been reported to interfere with tests of thyroid function by transient reduction of concentrations of thyroxine-binding globulin.

Interactions
If asparaginase is given before, rather than after, methotrexate the activity of the latter may be reduced (see below). Vincristine neurotoxicity may possibly be increased by use with intravenous asparaginase (see p.787).

Methotrexate. Asparaginase inhibits protein synthesis and cell replication, and therefore may interfere with the action of drugs such as methotrexate that require cell replication for their antineoplastic effect.[1] It has been suggested that a 24-hour interval between methotrexate and a subsequent dose of asparaginase permits at least an additive therapeutic effect.[2]

1. Jolivet J, *et al.* Prevention of methotrexate cytotoxicity by asparaginase inhibition of methotrexate polyglutamate formation. *Cancer Res* 1985; **45:** 217–20.
2. Capizzi RL. Asparaginase-methotrexate in combination chemotherapy: schedule-dependent differential effects on normal versus neoplastic cells. *Cancer Treat Rep* 1981; **65** (suppl 4): 115–21.

Pharmacokinetics
After intravenous injection the plasma half-life of the native enzyme has varied from about 8 to 30 hours; half-lives of up to 49 hours may be seen after intramuscular dosage. The mean half-life of pegaspargase is reported to be between 6 and 14 days. Asparaginase is found in the lymph at about 20% of the concentration in plasma. There is virtually no diffusion into the CSF. Little is excreted in the urine.

Uses and Administration
Asparaginase is an enzyme that acts by breaking down the amino acid L-asparagine to aspartic acid and ammonia. It interferes with the growth of those malignant cells which, unlike most healthy cells, are unable to synthesise L-asparagine for their metabolism, but resistance to its action develops fairly rapidly. Its action is reportedly specific for the G_1 phase of the cell cycle.

Asparaginase is used mainly for the induction of remissions in acute lymphoblastic leukaemia (p.651). Regimens vary, and dosage should follow local protocols, but it may be given intravenously in a dose of 1000 units/kg daily for 10 days after treatment with vincristine and prednisone or prednisolone, or intramuscularly in a dose of 6000 units/m^2 given every third day for 9 doses during treatment with vincristine and prednisone or prednisolone. Alternatively it may

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.

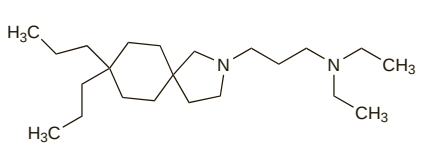
Atiprimod *(rINN)*

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.

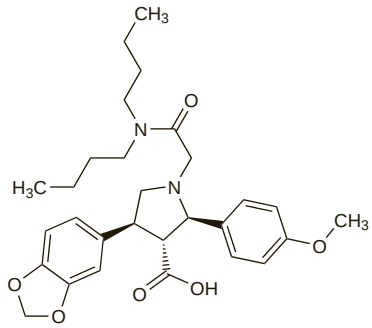
Atrasentan Hydrochloride *(USAN, rINNM)*

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.

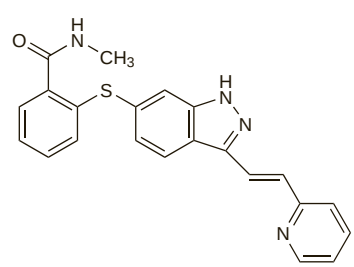
Axitinib *(USAN, rINN)*

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.

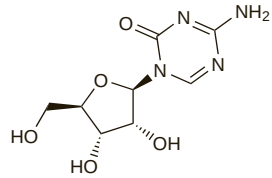
Azacitidine *(USAN, rINN)*

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.