formed during treatment and courses should not be repeated until blood counts have recovered (see also Bone-marrow Depression, p.639).

In the management of multiple sclerosis, the recommended dose is the equivalent of mitoxantrone 12 mg/m^2 by intravenous infusion over 5 to 15 minutes. This dose may be given once every 3 months initially provided that neutrophil counts are above 1500 cells/mm^3 and that LVEF is greater than 50%. Blood counts should be monitored before each dose. LVEF should be evaluated before beginning mitoxantrone therapy and before all subsequent doses; a total cumulative lifetime dose in excess of 140 mg/m^2 should be avoided. LVEF should also be measured if signs or symptoms of heart failure develop.

◊ References.

1. Faulds D, *et al.* Mitoxantrone: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in the chemotherapy of cancer. *Drugs* 1991; **41:** 400–49.
2. Fox EJ. Mechanism of action of mitoxantrone. *Neurology* 2004; **63** (suppl): S15–S18.

Multiple sclerosis. Mitoxantrone has produced clear benefit[1-4] in terms of reduced relapse rate and a slowing of disease progression in patients with multiple sclerosis (p.892). It has been given intravenously in doses of 5 or 12 mg/m^2 every 3 months, or 8 mg/m^2 every month. Patients with progressive relapsing disease may benefit from rapid induction with 12 mg/m^2 monthly for 3 months.[5] Benefit has also been shown in combination with corticosteroids,[6] although the combination was not compared with mitoxantrone alone. However, cardiotoxicity limits the dose that can be given.[7,8] Because of this and other adverse effects, such as possible secondary malignancy or potentially permanent amenorrhoea, some consider the use of mitoxantrone in multiple sclerosis to be unproven[9] and others have cautioned[10] that it should not be used before other immunomodulators. A systematic review[11] concluded that mitoxantrone was moderately effective in the short-term treatment of multiple sclerosis, but that information on its long-term effects was lacking; use should be limited to patients with worsening relapsing-remitting or secondary progressive disease with evidence of worsening disability.

1. Millefiorini E, *et al.* Randomized placebo-controlled trial of mitoxantrone in relapsing-remitting multiple sclerosis: 24-month clinical and MRI outcome. *J Neurol* 1997; **244:** 153–9.
2. van de Wyngaert FA, *et al.* A double-blind clinical trial of mitoxantrone versus methylprednisolone in relapsing, secondary progressive multiple sclerosis. *Acta Neurol Belg* 2001; **101:** 210–16.
3. Hartung H-P, *et al.* Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. *Lancet* 2002; **360:** 2018–25.
4. Jeffery DR, Herndon R. Review of mitoxantrone in the treatment of multiple sclerosis. *Neurology* 2004; **63** (suppl): S19–S24.
5. Rizvi SA, *et al.* Mitoxantrone for multiple sclerosis in clinical practice. *Neurology* 2004; **63** (suppl): S25–S27.
6. Edan G, *et al.* Therapeutic effect of mitoxantrone combined with methylprednisolone in multiple sclerosis: a randomised multicentre study of active disease using MRI and clinical criteria. *J Neurol Neurosurg Psychiatry* 1997; **62:** 112–118.
7. Ghalie RG, *et al.* Cardiac adverse effects associated with mitoxantrone (Novantrone) therapy in patients with MS. *Neurology* 2002; **59:** 909–13.
8. Cohen BA, Mikol DD. Mitoxantrone treatment of multiple sclerosis: safety considerations. *Neurology* 2004; **63** (suppl): S28–S32.
9. Chaudhuri A, Behan PO. Mitoxantrone trial in multiple sclerosis. *Lancet* 2003; **361:** 1133–4.
10. Goodin DS, *et al.* The use of mitoxantrone (Novantrone) for the treatment of multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2003; **61:** 1332–8.
11. Martinelli Boneschi F, *et al.* Mitoxantrone for multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 01/03/06).

Preparations

BP 2008: Mitoxantrone Intravenous Infusion;
USP 31: Mitoxantrone Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Batinel; Micraleve; Mitoxgen; Mitoxmar; ***Austral.:*** Novantrone; Onkotrone; ***Austria:*** Novantron; ***Belg.:*** Novantrone; Xantrosin; ***Braz.:*** Misostol; Mitaxis†; Mitoxal; ***Canad.:*** Novantrone†; ***Chile:*** Neotalem†; ***Cz.:*** Novantrone†; Onkotrone; Refador; ***Denm.:*** Novantrone; ***Fin.:*** Novantrone; ***Fr.:*** Elsep; Novantrone; ***Ger.:*** Neoxantron; Novantron; Onkotrone; Onkoxantron; Ralenova; ***Gr.:*** Genefadrone; Mitoxan; Novantrone; Zyneva; ***Hong Kong:*** Novantrone; ***Hung.:*** Novantrone; Onkotrone; Refador; ***India:*** Oncotron; ***Indon.:*** Norexan; ***Irl.:*** Novantrone; ***Israel:*** Novantrone; ***Ital.:*** Novantrone; Onkotrone; ***Malaysia:*** Novantrone†; ***Mex.:*** Formyxan; Mitoxgen; Mitroxone; Neotalem; ***Neth.:*** Novantrone†; ***Norw.:*** Novantrone; ***NZ:*** Novantrone; ***Philipp.:*** Domitrone; Onkotrone; ***Port.:*** Mitroxene; Novantrone; ***S.Afr.:*** Novantrone; ***Singapore:*** Novantrone; ***Spain:*** Novantrone; Pralifan; ***Swed.:*** Novantrone; ***Switz.:*** Novantron; ***Thai.:*** Neotalem; Novantrone†; ***Turk.:*** Neotalem; Novantrone; ***UK:*** Novantrone†; Onkotrone; ***USA:*** Novantrone; ***Venez.:*** Misostol.

Multialchilpeptide

Multialquilpéptido.

CAS — 9076-25-9.

Profile

Multialchilpeptide is a complex of metamelfalan, an analogue of melphalan (p.742), with peptides. It has been used in the treatment of malignant neoplasms of the blood and lymphatic systems.

Naptumomab Estafenatox *(rINN)*

ABR-217620; Naptumomab Estafénatox; Naptumomabum Estafenatoxum. Immunoglobulin fragment, anti-[trophoblast glycoprotein (TPBG, 5T4)] monoclonal 5T4 gamma1 heavy chain fragment fusion protein [*Mus musculus* VH (5T4V14: H41>P, S44>G, I69>T, V113>G)-IGHG1_CH1] - [Glycyl-Glycyl-Prolyl] - superantigen SEA/E-120 (synthetic), non-disulfide linked with monoclonal 5T4 kappa light chain [*Mus musculus* V-KAPPA (5T4V18: F10>S, T45>K, I63>S, F73>L, T77>S, L78>V, L83>A)-IGKC].

Наптумомаб Эстафенатокс

CAS — 676258-98-3.

Profile

Naptumomab estafenatox is a murine monoclonal antibody conjugated with a bacterial superantigen, a modified variant of Staphylococcal enterotoxin A that acts as a target for T-cell activation. The antibody is directed against a tumour-specific antigen 5T4. Naptumomab estafenatox is under investigation for the treatment of renal cell carcinoma.

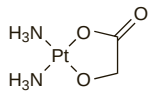
Nedaplatin *(rINN)*

Nédaplatine; Nedaplatino; Nedaplatinum. *cis*-Diammine(glycolato-O^1,O^2)platinum.

Недаплатин

$C_2H_8N_2O_3Pt$ = 303.2.

CAS — 95734-82-0.



Profile

Nedaplatin is a platinum derivative with general properties similar to those of cisplatin (p.698) although it may be associated with less nephrotoxicity. It is used in the treatment of a variety of malignant neoplasms. It is given by intravenous infusion over 1 hour or more, dissolved in at least 300 mL of an appropriate infusion solution, in doses of 80 to 100 mg/m^2. The infusion should be followed by infusion of at least 1 litre of fluid to ensure adequate hydration and reduce the risk of renal damage.

◊ References.

1. Yoshioka T, *et al.* A new combination chemotherapy with cis-diammine-glycolatoplatinum (Nedaplatin) and 5-fluorouracil for advanced esophageal cancers. *Intern Med* 1999; **38:** 844–8.
2. Adachi S, *et al.* Intravenous nedaplatin and intraarterial cisplatin with transcatheter arterial embolization for patients with locally advanced uterine cervical cancer. *Int J Clin Pharmacol Res* 2001; **21:** 105–10.
3. Kato H, *et al.* Efficacy and toxicity of nedaplatin and 5-FU with radiation treatment for advanced esophageal carcinomas. *Anticancer Res* 2003; **23:** 3493–8.
4. Ishibashi T, *et al.* Determination of optimal dosage for nedaplatin based on pharmacokinetic and toxicodynamic analysis. *Anticancer Res* 2005; **25:** 1273–81.
5. Shirai T, *et al.* Phase II study of the combination of gemcitabine and nedaplatin for advanced non-small-cell lung cancer. *Lung Cancer* 2006; **52:** 181–7.
6. Fuwa N, *et al.* Chemoradiation therapy using radiotherapy, systemic chemotherapy with 5-fluorouracil and nedaplatin, and intra-arterial infusion using carboplatin for locally advanced head and neck cancer–Phase II study. *Oral Oncol* 2007; **43:** 1014–20.
7. Oshita F, *et al.* Phase II study of nedaplatin and irinotecan followed by gefitinib for elderly patients with unresectable non-small cell lung cancer. *Cancer Chemother Pharmacol* 2008; **62:** 465–70.
8. Yokoyama Y, *et al.* A phase II multicenter trial of concurrent chemoradiotherapy with weekly nedaplatin in advanced uterine cervical carcinoma: Tohoku Gynecologic Cancer Unit Study. *Oncol Rep* 2008; **19:** 1551–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Aqupla.

Nelarabine *(BAN, USAN, rINN)*

GW-506U; GW-506U78; MAY; Nelarabina; Nélarabine; Nelarabinum; Nelzarabine; 506U; 506U78. 2-Amino-9-β-D-arabinofuranosyl-6-methoxy-9*H*-purine.

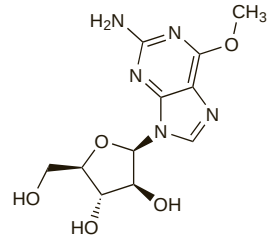
Неларабин

$C_{11}H_{15}N_5O_5$ = 297.3.

CAS — 121032-29-9.

ATC — L01BB07.

ATC Vet — QL01BB07.



Adverse Effects, Treatment, and Precautions

Neurotoxicity is common with nelarabine and may be dose-limiting. Signs and symptoms include somnolence, confusion, convulsions, ataxia, paraesthesias, and hypoaesthesia. Severe toxicity can manifest as coma, status epilepticus (which may be fatal), craniospinal demyelination, or ascending neuropathy. Risk of neurotoxicity is increased by previous or current intrathecal chemotherapy or previous radiation to the spine or brain. Leucopenia, thrombocytopenia, anaemia, and neutropenia are common, especially in children. Full blood counts should be regularly monitored. Other common adverse events include fatigue, gastrointestinal disorders, respiratory disorders, pyrexia, headache, hypokalaemia, hypoalbuminaemia, hyperbilirubinaemia, and increased liver enzyme values. Fatal cerebral haemorrhage has been reported. Appropriate measures to avoid hyperuricaemia (especially in patients considered at risk for tumour lysis syndrome) include adequate hydration, urinary alkalinisation, and possible prophylaxis with allopurinol.

Pharmacokinetics

In adult patients with leukaemia or lymphoma, nelarabine is rapidly eliminated from the plasma, with a half-life of about 30 minutes; no data are available for paediatric patients although the mean clearance is reported to be about 30% higher in children. Nelarabine is rapidly and extensively converted by demethylation to the active metabolite 9-β-D-arabinofuranosylguanine (ara-G; arabinosylguanine; arabinofuranosylguanine; guanine arabinoside); both nelarabine and ara-G are widely distributed throughout the body. Ara-G has an elimination half-life from plasma of about 3 hours. Plasma protein binding is not significant. Nelarabine also undergoes hydrolysis to form methylguanine. Both methylguanine and ara-G undergo further metabolism to guanine, which is deaminated to form xanthine, itself further oxidised to uric acid. Nelarabine and ara-G are partially eliminated by the kidneys; mean apparent clearance is lower in patients with mild to moderate renal impairment.

◊ References.

1. Kisor DF, *et al.* Pharmacokinetics of nelarabine and 9-beta- -arabinofuranosyl guanine in pediatric and adult patients during a phase I study of nelarabine for the treatment of refractory hematologic malignancies. *J Clin Oncol* 2000; **18:** 995–1003.

Uses and Administration

Nelarabine is a prodrug of ara-G, a purine nucleoside analogue that is used as an antimetabolite antineoplastic in the treatment of relapsed or refractory T-cell acute lymphoblastic leukaemia and lymphoma. A dose of 1.5 g/m^2 is given undiluted by intravenous infusion over 2 hours in adults, on days 1, 3, and 5 of a 21-day cycle. In children, nelarabine is given undiluted by in-

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

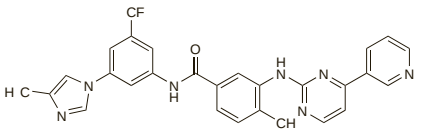
Proprietary Preparations (details are given in Part 3)
Cz.: Atriance; ***UK:*** Atriance; ***USA:*** Arranon.

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

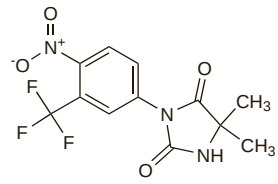
Proprietary Preparations (details are given in Part 3)
Cz.: Tasigna; ***Port.:*** Tasigna; ***Switz.:*** Tasigna; ***UK:*** Tasigna; ***USA:*** Tasigna.

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

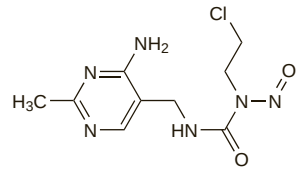
Nimotuzumab is a monoclonal antibody that binds to the epidermal growth factor receptor (EGFR). It is used in some countries for the treatment of glioma and cancers of the head and neck and pancreas.

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.