in did not necessarily correlate with clinical improvement. Conversely, sustained responses have been seen in other studies.[19-22] Use with sodium phenylbutyrate has produced conflicting results.[23-25]

1. Halsey C, Roberts IAG. The role of hydroxyurea in sickle cell disease. *Br J Haematol* 2003; **120:** 177–86.
2. Charache S, *et al.* Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. *N Engl J Med* 1995; **332:** 1317–22.
3. Steinberg MH, *et al.* Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. *JAMA* 2003; **289:** 1645–51. Correction. *ibid.*; **290:** 756.
4. Claster S, Vichinsky E. First report of reversal of organ dysfunction in sickle cell anemia by the use of hydroxyurea: splenic regeneration. *Blood* 1996; **88:** 1951–3.
5. Lanzkron S, *et al.* Systematic review: hydroxyurea for the treatment of adults with sickle cell disease. *Ann Intern Med* 2008; **148:** 939–55.
6. Zimmerman SA, *et al.* Sustained long-term hematologic efficacy of hydroxyurea at maximum tolerated dose in children with sickle cell disease. *Blood* 2004; **103:** 2039–45.
7. Scott JP, *et al.* Hydroxyurea therapy in children severely affected with sickle cell disease. *J Pediatr* 1996; **128:** 820–8.
8. Gulbis B, *et al.* Hydroxyurea for sickle cell disease in children and for prevention of cerebrovascular events: the Belgian experience. *Blood* 2005; **105:** 2685–90.
9. Jayabose S, *et al.* Clinical and hematologic effects of hydroxyurea in children with sickle cell anemia. *J Pediatr* 1996; **129:** 559–65.
10. Ware RE, *et al.* Hydroxyurea as an alternative to blood transfusions for the prevention of recurrent stroke in children with sickle cell disease. *Blood* 1999; **94:** 3022–6.
11. Ware RE, *et al.* Prevention of secondary stroke and resolution of transfusional iron overload in children with sickle cell anemia using hydroxyurea and phlebotomy. *J Pediatr* 2004; **145:** 346–52.
12. Wang WC, *et al.* A two-year pilot trial of hydroxyurea in very young children with sickle-cell anemia. *J Pediatr* 2001; **139:** 790–6.
13. Powars DR. Hydroxyurea in very young children with sickle cell anemia is not a cure-all. *J Pediatr* 2001; **139:** 763–4.
14. Kinney TR, *et al.* Safety of hydroxyurea in children with sickle cell anemia: results of the HUG-KIDS study, a phase I/II trial. *Blood* 1999; **94:** 1550–4.
15. Goldberg MA, *et al.* Treatment of sickle cell anemia with hydroxyurea and erythropoietin. *N Engl J Med* 1990; **323:** 366–72.
16. Rodgers GP, *et al.* Augmentation by erythropoietin of the fetal-hemoglobin response to hydroxyurea in sickle-cell disease. *N Engl J Med* 1993; **328:** 73–80.
17. Hajjar FM, Pearson HA. Pharmacologic treatment of thalassemia intermedia with hydroxyurea. *J Pediatr* 1994; **125:** 490–2.
18. de Paula EV, *et al.* Long-term hydroxyurea therapy in beta-thalassaemia patients. *Eur J Haematol* 2003; **70:** 151–5.
19. Loukopoulos D, *et al*. Hydroxyurea therapy in thalassemia. *Ann N Y Acad Sci* 1998; **30:** 120–8.
20. Rigano P, *et al.* Clinical and hematological responses to hydroxyurea in Sicilian patients with Hb S/β-thalassemia. *Hemoglobin* 2001; **25:** 9–17.
21. Loukopoulos D, *et al.* Reduction of the clinical severity of sickle cell/β-thalassemia with hydroxyurea: the experience of a single center in Greece. *Blood Cells Mol Dis* 2000; **26:** 453–66.
22. Bradai M, *et al.* Hydroxyurea can eliminate transfusion requirements in children with severe β-thalassemia. *Blood* 2003; **102:** 1529–30.
23. Olivieri NF, *et al*. Treatment of thalassaemia major with phenylbutyrate and hydroxyurea. *Lancet* 1997; **350:** 491–2.
24. Hoppe C, *et al.* Hydroxyurea and sodium phenylbutyrate therapy in thalassemia intermedia. *Am J Hematol* 1999; **62:** 221–7.
25. Dover GJ. Hemoglobin switching protocols in thalassemia. *Ann N Y Acad Sci* 1998; **850:** 80–6.

HIV infection and AIDS. Unlike most drugs used to treat HIV, which target viral enzymes, hydroxycarbamide inhibits ribonucleotide reductase, a host cellular enzyme that is less prone to mutation and subsequent development of resistance.[1] The drug acts synergistically with didanosine (p.870). Of 25 HIV-positive patients given didanosine 200 mg twice daily with hydroxycarbamide 15 mg/kg daily in 2 divided doses, all showed a drop in viral load and an increase in CD4+ lymphocyte count.[2] Viraemia was not detectable in 13 of 24 patients evaluated at 6 months and 10 of 20 patients evaluated at 1 year. In 2 of these patients who subsequently received no antiviral treatments for 1 year there was no viral rebound, although some proviral DNA was detected.[3] In another study in 6 patients, didanosine 200 mg twice daily with hydroxycarbamide 250 mg four times daily (suggested to be a better regimen because of the short half-life of the antineoplastic) produced a sharp decrease in viraemia, which was maintained for up to 72 weeks.[4] A rebound occurred in 1 patient on interrupting treatment but viral replication was again suppressed when treatment was restarted.

Combinations with didanosine and other HIV drugs have also been tried.[1] A controlled study[5] of hydroxycarbamide, didanosine, and stavudine indicated significantly enhanced activity when the antivirals were used with the antineoplastic rather than placebo. However, in a long-term follow-up[6] there was a high withdrawal rate amongst patients receiving this combination, due to virological failure and adverse effects such as peripheral neuropathy and fatigue. Another study[7] (ACTG 5025) was terminated due to the high risk of toxicity, including fatal pancreatitis, in patients receiving the hydroxycarbamide regimens. The authors noted that the use of a higher daily dosage of 1200 mg of hydroxycarbamide (rather than the usual 1000 mg daily) and increased exposure to didanosine (itself associated with pancreatitis) may have contributed to toxicity. An analysis of 2613 patients[8] determined that the use of hydroxycarbamide with didanosine, or didanosine and stavudine, resulted in a fourfold increase in the risk for development of pancreatitis, compared to didanosine alone. In a study of patients who had failed protease-inhibitor based regimens,[9] the addition of the antineoplastic to reverse transcriptase inhibitor-based therapy significantly improved virologic response. Despite an increased incidence of adverse events associated with its use, hydroxycarbamide was considered to be a valuable alternative in these patients. A small randomised study[10] of patients with chronic HIV infection given structured treatment interruptions with cycles of HAART, or HAART and hydroxycarbamide, found that use of the latter decreased viral load. There is some suggestion that a lower dose of hydroxycarbamide (300 mg twice daily) may have better antiretroviral activity, and fewer adverse effects, than higher doses.[11] For further discussion of the management of HIV infection and AIDS, see p.856.

1. Gibbs MA, Sorensen SJ. Hydroxyurea in the treatment of HIV-1. *Ann Pharmacother* 2000; **34:** 89–93.
2. Vila J, *et al.* 1-year follow-up of the use of hydroxycarbamide and didanosine in HIV infection. *Lancet* 1996; **848:** 203–4.
3. Vila J, *et al.* Absence of viral rebound after treatment of HIV-infected patients with didanosine and hydroxycarbamide. *Lancet* 1997; **350:** 635–6.
4. Lori F, *et al.* Long-term suppression of HIV-1 by hydroxyurea and didanosine. *JAMA* 1997; **277:** 1437–8.
5. Rutschmann OT, *et al.* A placebo-controlled trial of didanosine plus stavudine, with and without hydroxyurea, for HIV infection. *AIDS* 1998; **12:** F71–7.
6. Rutschmann OT, *et al.* Long-term hydroxyurea in combination with didanosine and stavudine for the treatment of HIV-1 infection. *AIDS* 2000; **14:** 2145–51.
7. Havlir DV, *et al.* Effects of treatment intensification with hydroxyurea in HIV-infected patients with virologic suppression. *AIDS* 2001; **15:** 1379–88.
8. Moore RD, *et al.* Incidence of pancreatitis in HIV-infected patients receiving nucleoside reverse transcriptase inhibitor drugs. *AIDS* 2001; **15:** 617–20.
9. Lafeuillade A, *et al.* The HYDILE trial: efficacy and tolerance of a quadruple combination of reverse transcriptase inhibitors versus the same regimen plus hydroxyurea or hydroxyurea and interleukin-2 in HIV-infected patients failing protease inhibitor-based combinations. *HIV Clin Trials* 2002; **3:** 263–71.
10. García F, *et al.* A cytostatic drug improves control of HIV-1 replication during structured treatment interruptions: a randomized study. *AIDS* 2003; **17:** 43–51.
11. Lisziewicz J, *et al.* Hydroxyurea in the treatment of HIV infection: clinical efficacy and safety concerns. *Drug Safety* 2003; **26:** 605–24.

Malignant neoplasms. Hydroxycarbamide is used in the treatment of chronic myeloid leukaemia (p.653), and may be used in the myeloproliferative disorders polycythaemia vera (p.654) and primary (essential) thrombocythaemia (p.654). Hydroxycarbamide has been tried, often with radiotherapy, in some solid malignancies such as tumours of the cervix (p.663), head and neck (p.666), and ovary (p.670).

Psoriasis. An immunosuppressant (usually methotrexate or ciclosporin) may be useful in patients with severe refractory psoriasis (p.1583). Hydroxycarbamide has also been tried, although experience is limited.[1,2]

1. Layton AM, *et al.* Hydroxyurea in the management of therapy resistant psoriasis. *Br J Dermatol* 1989; **121:** 647–53.
2. Smith CH, *et al*.. Use of hydroxyurea in psoriasis. *Clin Exp Dermatol* 1999; **24:** 2–6.

Preparations

BP 2008: Hydroxycarbamide Capsules;
USP 31: Hydroxyurea Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Dacrodil; Droxiurea†; Hydrea†; ***Austral.:*** Hydrea; ***Austria:*** Litalir; ***Belg.:*** Hydrea; ***Braz.:*** Hydrea; Hydrine†; Oxeron†; Ureax†; ***Canad.:*** Hydrea; ***Chile:*** Hydrea; ***Cz.:*** Litalir; Siklos; ***Denm.:*** Hydrea; ***Fin.:*** Hydrea; ***Fr.:*** Hydrea; Siklos; ***Ger.:*** Litalir; Syrea; ***Gr.:*** Hydrea†; Medroxyurea†; ***Hong Kong:*** Hydrea; ***Hung.:*** Litalir; ***India:*** Cytodrox; Hydab; Neodrea†; Oxyrea; ***Indon.:*** Hydrea; ***Irl.:*** Hydrea; ***Israel:*** Hydrea†; ***Ital.:*** Onco-Carbide; ***Malaysia:*** Hydrea†; ***Mex.:*** Hydrea; ***Neth.:*** Hydrea; ***NZ:*** Hydrea; ***Philipp.:*** Hydab; Krabinex; Litalir; ***Port.:*** Hydrea; Siklos; ***Rus.:*** Gidroksiurea (Гидроксиурея); ***S.Afr.:*** Hydrea; ***Singapore:*** Hydrea; ***Spain:*** Hydrea; ***Swed.:*** Hydrea; ***Switz.:*** Litalir; ***Thai.:*** Hydrea; ***Turk.:*** Hydrea; ***UK:*** Hydrea; ***USA:*** Droxia; Hydrea; Mylocel†.

Ibritumomab Tiuxetan *(BAN, USAN, rINN)*

Ibritumomab tiuxetán; Ibritumomab Tiuxétan; Ibritumomabum Tiuxetanum; IDEC-129; IDEC-Y2B8. Immunoglobulin G1, anti(human CD20 (antigen))(mouse monoclonal IDEC-Y2B8 γ1-chain), disulfide with mouse monoclonal IDEC-Y2B8 κ-chain, dimer tiuxetan conjugate.

Ибритумомаб Тиуксетан

CAS — 206181-63-7.

Adverse Effects and Precautions

For general discussions, see Antineoplastics, p.635 and p.641.

Myelosuppression is common after doses of ibritumomab tiuxetan, and may be prolonged. Fatal intracranial haemorrhage has occurred. Infections and hypersensitivity reactions may also be severe. As ibritumomab tiuxetan is given with rituximab, severe infusion reactions due to the cytokine release syndrome may occur (see under Rituximab, p.767). Severe cutaneous and mucocutaneous reactions, some fatal, have been reported and therapy should be stopped if they occur. Gastrointestinal disturbances are common. Other adverse effects include anorexia, asthenia, fever, cough, dyspnoea, dizziness, headache, insomnia, anxiety, arthralgia, myalgia, and peripheral oedema. Patients should be monitored for signs of extravasation in order to avoid radiation-associated tissue damage. If extravasation occurs, the infusion should be stopped immediately and restarted in another vein.

Complete blood and platelet counts should be monitored weekly, or more frequently if cytopenia is present, until haematological recovery. Ibritumomab tiuxetan should not be given to patients with extensive marrow involvement, impaired bone marrow reserve, or platelet or neutrophil counts below acceptable levels (see also Bone-marrow Depression, p.639). Care should be taken during and after radiolabelling with indium-111 or yttrium-90 to minimise radiation exposure.

Effects on the skin. Severe cutaneous and mucocutaneous reactions have been reported after use of ibritumomab tiuxetan with rituximab, some of them with a fatal outcome.[1,2] Reactions included erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous dermatitis, and exfoliative dermatitis. Onset was reported to vary from days to months. Treatment should be stopped if any patient experiences such a reaction.

1. Kooijmans-Coutinho M [Biogen Idec (USA)]. Important drug warning (issued October 2005). Available at: http://www.fda.gov/medwatch/safety/2005/Zevalin_dearhcp.pdf (accessed 30/07/08)
2. Berlex, Canada. Association of severe mucocutaneous reactions with the ZEVALIN therapeutic regimen (issued 7th December 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/zevalin_nth-aah_e.pdf (accessed 26/04/06)

Uses and Administration

Ibritumomab is a murine monoclonal antibody to CD20 antigen, which is conjugated with tiuxetan to provide a chelation site for radioactive isotopes. Radiolabelled ibritumomab tiuxetan is used in the treatment of relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma (p.656). Patients are pretreated with a low dose of rituximab (p.767). In the USA this is followed by slow intravenous injection of ibritumomab tiuxetan chelated with indium-111 (p.2054) for imaging to confirm that biodistribution of tumour cells is acceptable. A second rituximab treatment is given 7 to 9 days after the first, followed by ibritumomab tiuxetan chelated with yttrium-90 (p.2057) for radio-immunotherapy.

◊ References.

1. Wiseman GA, *et al.* Biodistribution and dosimetry results from a phase III prospectively randomized controlled trial of Zevalin radioimmunotherapy for low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. *Crit Rev Oncol Hematol* 2001; **39:** 181–94.
2. Wagner HN, *et al.* Administration guidelines for radioimmunotherapy of non-Hodgkin's lymphoma with Y-labeled anti-CD20 monoclonal antibody. *J Nucl Med* 2002; **43:** 267–72.
3. Witzig TE, *et al.* Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncol* 2002; **20:** 2453–63.
4. Witzig TE, *et al.* Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. *J Clin Oncol* 2002; **20:** 3262–9.
5. Ansell SM, *et al.* Subsequent chemotherapy regimens are well tolerated after radioimmunotherapy with yttrium-90 ibritumomab tiuxetan for non-Hodgkin's lymphoma. *J Clin Oncol* 2002; **20:** 3885–90.
6. Witzig TE. Yttrium-90-ibritumomab tiuxetan radioimmunotherapy: a new treatment approach for B-cell non-Hodgkin's lymphoma. *Drugs Today* 2004; **40:** 111–19.
7. Hagenbeek A, Lewington V. Report of a European consensus workshop to develop recommendations for the optimal use of Y-ibritumomab tiuxetan (Zevalin) in lymphoma. *Ann Oncol* 2005; **16:** 786–92.
8. Meredith RF. Logistics of therapy with the ibritumomab tiuxetan regimen. *Int J Radiat Oncol Biol Phys* 2006; **66** (suppl): S35–S38.
9. Cheung MC, *et al.* Yttrium 90 ibritumomab tiuxetan in lymphoma. *Leuk Lymphoma* 2006; **47:** 967–77. Correction. *ibid.*; 1719–20.
10. Gisselbrecht C, *et al.* Current status and future perspectives for yttrium-90 (Y)-ibritumomab tiuxetan in stem cell transplantation for non-Hodgkin's lymphoma. *Bone Marrow Transplant* 2007; **40:** 1007–17.

Preparations

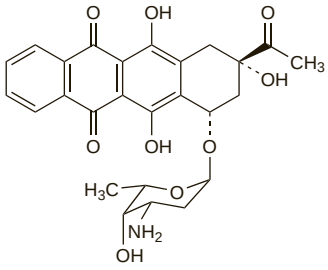
Proprietary Preparations (details are given in Part 3)
Canad.: Zevalin; ***Cz.:*** Zevalin; ***Denm.:*** Zevalin†; ***Fin.:*** Zevalin; ***Fr.:*** Zevalin; ***Ger.:*** Zevalin; ***Hung.:*** Zevalin; ***Irl.:*** Zevalin; ***Ital.:*** Zevalin; ***Neth.:*** Zevalin; ***Norw.:*** Zevalin; ***NZ:*** Zevalin; ***Pol.:*** Zevalin; ***Port.:*** Zevalin; ***Spain:*** Zevalin; ***Swed.:*** Zevalin; ***Switz.:*** Zevalin; ***UK:*** Zevalin; ***USA:*** Zevalin.

Idarubicin Hydrochloride

(BANM, USAN, rINNM)

4-Demethoxydaunorubicin Hydrochloride; Hidrocloruro de idarubicina; Idarubicine, chlorhydrate d'; Idarubicinhydroklorid; Idarubicini hydrochloridum; Idarubisiinihydrokloridi; Idarubisin Hidroklorür; IMI-30; NSC-256439 (idarubicin). (7*S*,9*S*)-9-Acetyl-7-(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyloxy)-7,8,9,10-tetrahydro-6,9,11-trihydroxynaphthacene-5,12-dione hydrochloride.

Идарубицина Гидрохлорид
$C_{26}H_{27}NO_9$,HCl = 534.0.
CAS — 58957-92-9 (idarubicin); 57852-57-0 (idarubicin hydrochloride).
ATC — L01DB06.
ATC Vet — QL01DB06.



(idarubicin)

Pharmacopoeias. In *Jpn* and *US*.
USP 31 (Idarubicin Hydrochloride). A red-orange to red-brown powder. Slightly soluble in water; insoluble in acetone and in solvent ether; soluble in methyl alcohol. A 0.5% solution in water has a pH between 5.0 and 6.5. Store in airtight containers.

Incompatibility. Licensed product information states that precipitation occurs when idarubicin hydrochloride is mixed with heparin, and that it will degrade in alkaline solution.

Adverse Effects, Treatment, and Precautions

As for Doxorubicin, p.712. Raised liver enzymes and bilirubin can occur with idarubicin. Severe enterocolitis with perforation has been reported rarely. A cumulative total dose limit has not yet been defined. UK licensed product information states that total cumulative oral doses up to 400 mg/m^2 have a low probability of cardiotoxicity, and no significant cardiotoxicity was seen in patients treated with mean cumulative intravenous doses of 93 mg/m^2. Cardiomyopathy has been reported in some patients with cumulative intravenous doses of 150 to 290 mg/m^2. It has been suggested that idarubicin may be associated with less cardiotoxicity than doxorubicin. Idarubicin should be given with caution, and in reduced doses, to patients with renal or hepatic impairment.

Effects on the skin and nails. For a report of transverse hyperpigmented bands of the nails in a patient who received idarubicin, see under Doxorubicin, p.713.

Pharmacokinetics

On intravenous dosage idarubicin is rapidly distributed into body tissues and extensively tissue bound, with a volume of distribution which may be in excess of 2000 litres. It is extensively metabolised, both in the liver and extrahepatically; the principal metabolite, idarubicinol (13-dihydroidarubicin) has equal antineoplastic activity. Peak concentrations of idarubicin and idarubicinol in bone marrow and nucleated blood cells are 400 (idarubicin) and 200 (idarubicinol) times greater than those in plasma; cellular concentrations of drug and metabolite decline with apparent terminal half-lives of 15 and 72 hours respectively, whereas plasma half-lives are reported to be 20 to 22 hours and about 45 hours respectively. Idarubicin is excreted in bile, and to a lesser extent in urine, as unchanged drug and metabolites.

Idarubicin is also absorbed orally, but estimates of its oral bioavailability vary from about 20 to 50%.

◊ References.

1. Robert J. Clinical pharmacokinetics of idarubicin. *Clin Pharmacokinet* 1993; **24:** 275–88.

Uses and Administration

Idarubicin is an anthracycline antibiotic with antineoplastic actions similar to those of doxorubicin (p.714). It is used as the hydrochloride, alone or with other drugs, for the induction of remission in patients with acute myeloid leukaemias (p.652). It is also used as a second-line treatment in acute lymphoblastic leukaemia (p.651), and advanced breast cancer (p.661). It has been tried in multiple myeloma (p.658) and non-Hodgkin's lymphoma (p.656).

Idarubicin hydrochloride is given by intravenous injection into a fast-running infusion of sodium chloride 0.9% or glucose 5% over 5 to 15 minutes. The suggested dose in adult acute myeloid leukaemia is 12 mg/m^2 daily for 3 days, with cytarabine. A similar dose, as a single agent, has been given in acute lymphoblastic leukaemia. An alternative dosage schedule in acute myeloid leukaemia is 8 mg/m^2 given daily for 5 days, either alone or in combination therapy. In children with acute lymphoblastic leukaemia a dose of 10 mg/m^2 daily for 3 days as a single agent has been suggested. When the intravenous route cannot be used, idarubicin hydrochloride may be given by mouth. A suggested dose in adult acute myeloid leukaemia as a single agent is 30 mg/m^2 daily for 3 days; 15 to 30 mg/m^2 may be given daily for 3 days when used with other drugs.

In patients with refractory breast cancer idarubicin hydrochloride has been given orally in doses of 45 mg/m^2, as a single dose or divided over 3 consecutive days; the treatment may be repeated every 3 or 4 weeks depending on the haematological recovery.

Blood counts should be performed frequently in patients receiving idarubicin, and monitoring of cardiac, hepatic, and renal function is recommended. Doses should be reduced in patients with hepatic or renal impairment (for further information on the former, see below). In patients who receive a second course of idarubicin dosage should be reduced by 25% if severe mucositis developed with the first course; therapy should be delayed until the patient has recovered from this toxicity.

◊ The actions and uses of idarubicin have been reviewed.[1] A study in leukaemia cells *in vitro* suggested that idarubicin was more active than a conventional anthracycline, daunorubicin, against cells with the multidrug resistance (MDR) phenotype.[2] A collaborative overview of randomised studies for acute myeloid leukaemia found that idarubicin-based therapy achieved better remission rates and overall survival than daunorubicin-based regimens.[3] Its oral bioavailability has been suggested to offer an advantage in the management of malignancies in older patients.[4]

1. Cersosimo RJ. Idarubicin: an anthracycline antineoplastic agent. *Clin Pharm* 1992; **11:** 152–67.
2. Berman E, McBride M. Comparative cellular pharmacology of daunorubicin and idarubicin in human multidrug-resistant leukaemia cells. *Blood* 1992; **79:** 3267–73.
3. AML Collaborative Group. A systematic collaborative overview of randomised trials comparing idarubicin with daunorubicin (or other anthracyclines) as induction therapy for acute myeloid leukaemia. *Br J Haematol* 1998; **103:** 100–9.
4. Crivellari D, *et al.* New oral drugs in older patients: a review of idarubicin in elderly patients. *Crit Rev Oncol Hematol* 2004; **49:** 153–63.

Administration in hepatic impairment. UK licensed product information for idarubicin hydrochloride recommends that a dose reduction be considered in patients with hepatic impairment. Although no specific doses are suggested, it is noted that a 50% reduction in dosage has been used with some other anthracyclines in patients with acute leukaemias whose bilirubin levels were between 12 and 20 micrograms/mL. Furthermore, in studies in breast cancer a 50% dosage reduction of oral idarubicin has sometimes been used in those whose bilirubin rose to 20 to 30 micrograms/mL, with withdrawal if levels rose above this. However, in other studies idarubicin was not used if bilirubin values were above 20 micrograms/mL.

In the USA, similar cautions apply but product information only suggests that idarubicin should be withheld if bilirubin levels exceed 50 micrograms/mL.

Preparations

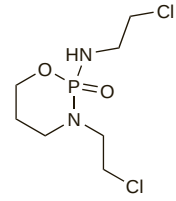
USP 31: Idarubicin Hydrochloride for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Idarrux†; Zavedos; ***Austral.:*** Zavedos; ***Austria:*** Zavedos; ***Belg.:*** Zavedos; ***Braz.:*** Zavedos; ***Canad.:*** Idamycin; ***Chile:*** Zavedos; ***Cz.:*** Zavedos; ***Denm.:*** Zavedos; ***Fin.:*** Zavedos; ***Fr.:*** Zavedos; ***Ger.:*** Zavedos; ***Gr.:*** Zavedos; ***Hong Kong:*** Zavedos; ***Hung.:*** Zavedos; ***Irl.:*** Zavedos; ***Israel:*** Zavedos; ***Ital.:*** Zavedos; ***Malaysia:*** Zavedos; ***Mex.:*** Idamycin; Idaralem; ***Neth.:*** Zavedos; ***Norw.:*** Zavedos; ***NZ:*** Zavedos; ***Philipp.:*** Zavedos; ***Pol.:*** Zavedos; ***Port.:*** Zavedos; ***Rus.:*** Zavedos (Заведос); ***S.Afr.:*** Zavedos; ***Singapore:*** Zavedos; ***Spain:*** Zavedos; ***Swed.:*** Zavedos; ***Switz.:*** Zavedos; ***Thai.:*** Idaralem; Zavedos; ***Turk.:*** Zavedos; ***UK:*** Zavedos; ***USA:*** Idamycin; ***Venez.:*** Zavedos.

Ifosfamide *(BAN, USAN, rINN)*

Ifosfamid; Ifosfamida; Ifosfamidas; Ifosfamidi; Ifosfamidum; Ifoszfamid; Iphosphamide; Isophosphamide; MJF-9325; NSC-109724; Z-4942. 3-(2-Chloroethyl)-2-(2-chloroethylamino)perhydro-1,3,2-oxazaphosphorinane 2-oxide.

Ифосфамид
$C_7H_{15}Cl_2N_2O_2P$ = 261.1.
CAS — 3778-73-2.
ATC — L01AA06.
ATC Vet — QL01AA06.



Pharmacopoeias. In *Eur.* (see p.vii) and *US*.
Ph. Eur. 6.2 (Ifosfamide). A white or almost white, hygroscopic, fine crystalline powder. Soluble in water; freely soluble in dichloromethane. Store in airtight containers.
USP 31 (Ifosfamide). A white, crystalline powder. M.p. about 40°. Freely soluble in water; very soluble in alcohol, in methyl alcohol, in isopropyl alcohol, in dichloromethane, and in ethyl acetate; very slightly soluble in hexanes. A 10% solution in water has a pH of between 4.0 and 7.0. Store in airtight containers at a temperature not exceeding 25°.

Incompatibility. Ifosfamide appears to be compatible when mixed in solution with mesna.[1,2] However, ifosfamide appears to be incompatible with benzyl alcohol used as a preservative in Water for Injections: solutions made up with water preserved in this way became turbid, with the formation of aqueous and oily phases, at concentrations of ifosfamide greater than 60 mg/mL.[3]

1. Shaw IC, Rose JWP. Infusion of ifosphamide plus mesna. *Lancet* 1984; **i:** 1353–4.
2. Rowland CG, *et al.* Infusion of ifosfamide plus mesna. *Lancet* 1984; **ii:** 468.
3. Behme RJ, *et al.* Incompatibility of ifosfamide with benzyl-alcohol-preserved bacteriostatic water for injection. *Am J Hosp Pharm* 1988; **45:** 627–8.

Stability. Ifosfamide undergoes a reversible chemical rearrangement in aqueous solution, which is sensitive to changes in pH.[1] The ratio of these compounds to one another in biological fluids may have a bearing on the toxicity and efficacy of ifosfamide.

1. Küpfer A, *et al.* Intramolecular rearrangement of ifosfamide in aqueous solutions. *Lancet* 1990; **335:** 1461.

Adverse Effects, Treatment, and Precautions

As for Cyclophosphamide, p.702. Toxic effects on the urinary tract may be more severe with ifosfamide and may involve the kidneys as well as the bladder. CNS adverse effects have been reported, especially confusion, drowsiness, depressive psychosis, hallucinations, and rarely, seizures.

Effects on the heart. Severe myocardial depression, with heart failure and ventricular arrhythmias, has been reported in patients given high-dose ifosfamide.[1] Symptoms were reversible with appropriate treatment in most cases although one patient died of cardiogenic shock.

1. Quezado ZMN, *et al.* High-dose ifosfamide is associated with severe, reversible cardiac dysfunction. *Ann Intern Med* 1993; **118:** 31–6.

Effects on the kidneys. In addition to its effects on the bladder ifosfamide may be associated with serious nephrotoxicity. Both proximal and distal tubular damage,[1,2] and to a lesser extent glomerular effects,[2] are seen, and the Fanconi syndrome (with