Preparations

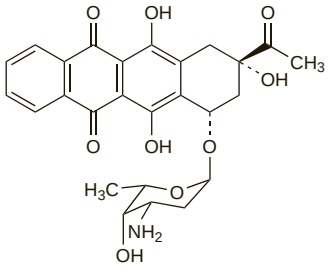
Proprietary Preparations (details are given in Part 3)
Canad.: Zevalin; ***Cz.:*** Zevalin; ***Denm.:*** Zevalin†; ***Fin.:*** Zevalin; ***Fr.:*** Zevalin; ***Ger.:*** Zevalin; ***Hung.:*** Zevalin; ***Irl.:*** Zevalin; ***Ital.:*** Zevalin; ***Neth.:*** Zevalin; ***Norw.:*** Zevalin; ***NZ:*** Zevalin;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

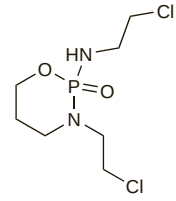
USP 31: Idarubicin Hydrochloride for Injection.

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