Preparations

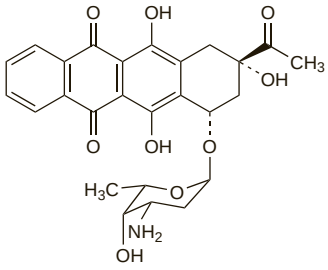
Proprietary Preparations (details are given in Part 3)
Canad.: Zevalin; ***Cz.:*** Zevalin; ***Denm.:*** Zevalin†; ***Fin.:*** Zevalin; ***Fr.:*** Zevalin; ***Ger.:*** Zevalin; ***Hung.:*** Zevalin; ***Irl.:*** Zevalin; ***Ital.:*** Zevalin; ***Neth.:*** Zevalin; ***Norw.:*** Zevalin; ***NZ:*** Zevalin;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

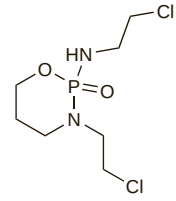
USP 31: Idarubicin Hydrochloride for Injection.

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

development of hypophosphataemic rickets in a number of children),[2-6] and nephrogenic diabetes insipidus[1,6] may result. Progressive chronic renal failure after high-dose ifosfamide has been described.[7] Life-threatening hypokalaemia possibly due to a renal lesion has also occurred.[8] Results in *rats* suggest that generation of toxic metabolites within the kidney itself may be responsible, and that repairable renal damage occurs after the first dose, which is aggravated by repeated toxic insults.[9] This is in agreement with clinical results, since although renal damage has been seen after a single dose, perhaps representing an idiosyncratic reaction,[10,11] most cases have been in children receiving relatively high doses long-term. Renal damage appears to persist after withdrawal of ifosfamide in these patients and may be largely irreversible.[12]

A combination of younger age and high cumulative doses of ifosfamide was found to convey the highest risk of toxicity, but use with cisplatin may also increase the risk.[13] The maximum safe dose of ifosfamide has been debated.[13-15] It has been suggested that cumulative doses of ifosfamide of 100 g/m^2 or more should be avoided in children in an attempt to reduce the incidence of nephrotoxicity,[14] although subsequent reviews have suggested that lower cumulative doses may be toxic, especially in younger children.[13,15]

1. Skinner R, *et al.* Nephrotoxicity after ifosfamide. *Arch Dis Child* 1990; **65:** 732–8.
2. Burk CD, *et al.* Ifosfamide-induced renal tubular dysfunction and rickets in children with Wilms tumor. *J Pediatr* 1990; **117:** 331–5.
3. Skinner R, *et al.* Hypophosphataemic rickets after ifosfamide treatment in children. *BMJ* 1989; **298:** 1560–1.
4. Newbury-Ecob RA, Barbor PRH. Hypophosphataemic rickets after ifosfamide treatment. *BMJ* 1989; **299:** 258.
5. Newbury-Ecob RA, *et al.* Ifosfamide-induced Fanconi syndrome. *Lancet* 1989; **i:** 1328.
6. Skinner R, *et al.* Nephrotoxicity of ifosfamide in children. *Lancet* 1989; **ii:** 159.
7. Krämer A, *et al.* Progressive renal failure in two breast cancer patients after high-dose ifosfamide. *Lancet* 1994; **334:** 1569.
8. Husband DJ, Watkin SW. Fatal hypokalaemia associated with ifosfamide/mesna chemotherapy. *Lancet* 1988; **i:** 1116.
9. Graham MI, *et al.* A proposed mechanism for isophosphamide-induced kidney toxicity. *Hum Toxicol* 1985; **4:** 545–6.
10. Heney D, *et al.* Acute ifosfamide-induced tubular toxicity. *Lancet* 1989; **ii:** 103–4.
11. Devalck C, *et al.* Acute ifosfamide-induced proximal tubular toxic reaction. *J Pediatr* 1991; **118:** 325–6.
12. Heney D, *et al.* Progressive renal toxicity due to ifosfamide. *Arch Dis Child* 1991; **66:** 966–70.
13. Loebstein R, *et al.* Risk factors for long-term outcome of ifosfamide-induced nephrotoxicity in children. *J Clin Pharmacol* 1999; **39:** 454–61.
14. Skinner R, *et al.* Risk factors for ifosfamide nephrotoxicity in children. *Lancet* 1996; **348:** 578–80.
15. Loebstein R, Koren G. Ifosfamide-induced nephrotoxicity in children: critical review of predictive risk factors. *Pediatrics* 1998; **101:** 1067. Full version: http://pediatrics.aappublications.org/cgi/content/full/101/6/e8 (accessed 30/06/04)

Effects on the nervous system. Use of ifosfamide (with mesna for urothelial protection) may be associated with the development of severe encephalopathy, with EEG abnormalities, disorientation, hallucinations, catatonia, and coma; occasionally CNS depression has led to circulatory collapse and death.[1,2] The effect has been suggested to be due to a metabolite, perhaps chloroacetaldehyde,[3] a hypothesis supported by the increased incidence of encephalopathy after oral rather than intravenous doses.[4,5] Others suggest that the dechloroethylated metabolites may contribute, and in particular the *R*-enantiomer of 3-dechloroethyl-ifosfamide which is a metabolite of *S*-ifosfamide.[6] There is some uncertainty about the contributory role of mesna, if any: encephalopathy has not been seen when mesna is given with cyclophosphamide,[7] and has been seen when ifosfamide is given alone,[5] but an exacerbatory role for mesna cannot be ruled out,[8] perhaps via its chelating properties.[1,7]

A nomogram has been proposed to identify patients at greatest risk of toxicity,[9,10] such as those with renal or hepatic impairment,[9] although doubts have been raised as to its general applicability.[11] A retrospective review of 237 patients given ifosfamide, of whom 38 developed encephalopathy, found no evidence that age or ifosfamide dose influenced the development of the condition, and serum creatinine values were in the normal range in the affected group, although they were slightly higher than in those not affected; however, low serum albumin did seem to be associated with greater risk.[12] It has also been suggested that the drug be given by continuous infusion over several days where possible, since this route has by far the lowest incidence of encephalopathy (7%, versus 26% with intravenous bolus and 43% with oral doses).[4] Care may also be required when giving other antineoplastics to patients who have had encephalopathy after ifosfamide, since a case of encephalopathy with bleomycin (not normally associated with neurotoxicity) has been reported in such a patient.[13]

A few reports suggests that methylthioninium chloride can effectively prevent or reverse signs of encephalopathy, and a number of mechanisms have been proposed (see Glutaric Aciduria under Uses of Methylthioninium Chloride, p.1451)

1. Meanwell CA, *et al.* Encephalopathy associated with ifosphamide/mesna therapy. *Lancet* 1985; **i:** 406–7.
2. Cantwell BMJ, Harris AL. Ifosfamide/mesna and encephalopathy. *Lancet* 1985; **i:** 752.
3. Goren MP, *et al.* Dechloroethylation of ifosfamide and neurotoxicity. *Lancet* 1986; **ii:** 1219–20.
4. Cerny T, *et al.* Ifosfamide by continuous infusion to prevent encephalopathy. *Lancet* 1990; **335:** 175.
5. Lewis LD, Meanwell CA. Ifosfamide pharmacokinetics and neurotoxicity. *Lancet* 1990; **335:** 175–6.
6. Wainer IW, *et al.* Ifosfamide stereoselective dichloroethylation [sic] and neurotoxicity. *Lancet* 1994; **343:** 982–3.
7. Osborne RJ, Slevin ML. Ifosfamide, mesna, and encephalopathy. *Lancet* 1985; **i:** 1398–9.
8. Pinkerton R, *et al.* Ifosfamide, mesna, and encephalopathy. *Lancet* 1985; **i:** 1399.
9. Meanwell CA, *et al.* Avoiding ifosfamide/mesna encephalopathy. *Lancet* 1986; **ii:** 406.
10. Perren TJ, *et al.* Encephalopathy with rapid infusion ifosfamide/mesna. *Lancet* 1987; **i:** 390–1.
11. McCallum AK. Ifosfamide/mesna encephalopathy. *Lancet* 1987; **i:** 987. Correction. *ibid.*; 1048.
12. David KA, Picus J. Evaluating risk factors for the development of ifosfamide encephalopathy. *Am J Clin Oncol* 2005; **28:** 277–80.
13. Atherton P, *et al.* Drug-induced encephalopathy after previous ifosfamide treatment. *Lancet* 1988; **ii:** 1084.

Handling and disposal. A study[1] found that ifosfamide 8% solution penetrated all of 4 brands of latex glove and one PVC glove, although the diffusion rate was 4 or more times slower than through cadaver skin. Permeation was greater through the PVC glove than the latex gloves, partly due to its lesser thickness, although permeation was not dependent on thickness alone and varied between gloves of the same brand as well as between brands. They recommended that latex gloves of a suitable brand should be worn when handling ifosfamide, and changed at least every 2 hours. For reference to a method for the destruction of ifosfamide waste, see under Cyclophosphamide, p.703.

1. Corlett SA, *et al.* Permeation of ifosfamide through gloves and cadaver skin. *Pharm J* 1991; **247:** R39.

Interactions

As for Cyclophosphamide, p.703. For a general outline of antineoplastic drug interactions, see p.642. For reference to the effects of ifosfamide on oral anticoagulants, see under Warfarin Sodium, p.1429. For a report of the enhancement of cisplatin-induced ototoxicity and nephrotoxicity, see under Cisplatin, p.700.

Antibacterials. Oral *rifampicin* given twice daily for 6 days, starting 3 days before intravenous ifosfamide (as a 24-hour infusion), increased the clearance of ifosfamide by over 100%; however, exposure to metabolites of ifosfamide was relatively unchanged. The authors considered that rifampicin might decrease the therapeutic efficacy of ifosfamide.[1]

1. Kerbusch T, *et al.* Modulation of the cytochrome P450-mediated metabolism of ifosfamide by ketoconazole and rifampin. *Clin Pharmacol Ther* 2001; **70:** 132–41.

Antifungals. *Ketoconazole* given orally for 4 days, starting 1 day before intravenous ifosfamide (given as a 24-hour infusion), decreased ifosfamide clearance. However, ifosfamide metabolism to active metabolites was decreased, and urinary excretion of ifosfamide was increased. Ketoconazole may decrease the therapeutic efficacy of ifosfamide.[1]

1. Kerbusch T, *et al.* Modulation of the cytochrome P450-mediated metabolism of ifosfamide by ketoconazole and rifampin. *Clin Pharmacol Ther* 2001; **70:** 132–41.

Pharmacokinetics

Ifosfamide is normally given intravenously, although it is well absorbed from the gastrointestinal tract. The pharmacokinetics of ifosfamide are reported to exhibit considerable interindividual variation. It is a prodrug that is extensively metabolised, chiefly by cytochrome P450 isoenzymes such as CYP3A4 and CYP2B6 in the liver, to a variety of active and inactive metabolites; there is some evidence that metabolism is saturated at very high doses. Although the manufacturers state that a mean terminal elimination half-life of about 15 hours has been reported after a single high-dose intravenous bolus, most studies at lower doses appear to have recorded elimination half-lives of about 4 to 8 hours. After repeated doses (fractionated therapy) there is a decrease in the elimination half-life, apparently due to autoinduction of metabolism. Ifosfamide is distributed into the CSF. It is excreted largely in urine, as unchanged drug and metabolites.

◊ General references.

1. Wagner T. Ifosfamide clinical pharmacokinetics. *Clin Pharmacokinet* 1994; **26:** 439–56.
2. Boddy AV, Yule SM. Metabolism and pharmacokinetics of oxazaphosphorines. *Clin Pharmacokinet* 2000; **38:** 291–304.
3. Kerbusch T, *et al.* Clinical pharmacokinetics and pharmacodynamics of ifosfamide and its metabolites. *Clin Pharmacokinet* 2001; **40:** 41–62.

◊ In a study[1] in 20 patients receiving intravenous ifosfamide over 3 or 5 days, the median elimination half-life of ifosfamide was 3.85 hours in patients under 60 years of age compared with 6.03 hours in those over age 60; this difference appeared to be due to an increased volume of distribution in the older age group. The autoinduction of metabolism typically seen with multiple doses of ifosfamide was not affected by age. The increased clearance seen over time during a 5-day cycle of ifosfamide treatment[2] was not sustained over the 21 days between cycles, but was reproducible and of similar magnitude in the subsequent cycle.

In another study[3] the half-life of the *S*-enantiomer of ifosfamide was found to be 5.98 hours after an intravenous bolus of the racemate, compared with 7.12 hours for the *R*-enantiomer.

1. Lind MJ, *et al.* The effect of age on the pharmacokinetics of ifosfamide. *Br J Clin Pharmacol* 1990; **30:** 140–3.
2. Lewis LD. A study of 5 day fractionated ifosfamide pharmacokinetics in consecutive treatment cycles. *Br J Clin Pharmacol* 1996; **42:** 179–86.
3. Corlett SA, *et al.* Pharmacokinetics of ifosfamide and its enantiomers following a single 1h intravenous infusion of the racemate in patients with small cell lung carcinoma. *Br J Clin Pharmacol* 1995; **39:** 452–5.

Uses and Administration

Ifosfamide is an alkylating agent with properties similar to those of cyclophosphamide (p.703), of which it is a congener. It is used in the treatment of solid tumours including those of the cervix, lung, ovary, testis, and thymus, as well as in sarcoma and in the treatment of lymphomas. For further mention of these uses see the cross-references given below.

Ifosfamide is given intravenously, either by injection as a solution diluted to less than 4%, or by infusion. Licensed dosage regimens include a total dose of 8 to 12 g/m^2 divided over 3 to 5 days, with the course repeated at 2 to 4 week intervals; a total dose of 6 g/m^2 divided over 5 days, repeated every 3 weeks; and doses of 5 to 6 g/m^2, to a maximum of 10 g, given as a single 24-hour infusion, repeated at 3 to 4 week intervals. The interval between courses also depends on the blood count (see also Bone-marrow Depression, p.639). Oral ifosfamide has also been studied but is associated with neurotoxicity (see Effects on the Nervous System, above).

Ifosfamide should be given with mesna (see Administration, below), and adequate hydration should be maintained, to avoid urological toxicity; fluid intake should not be less than 2 litres daily.

Administration. Mesna (p.1449) can combine with urotoxic ifosfamide metabolites in the kidney to form stable and non-toxic compounds. It is therefore given prophylactically with ifosfamide. It has a shorter half-life than ifosfamide so repeated doses are needed to provide adequate protection of the bladder. A common schedule uses intravenous mesna at 60% of the ifosfamide dose, divided into 3 doses given with, or 15 minutes before, ifosfamide, then 4 and 8 hours after ifosfamide.[1] Mesna may also be given orally, but higher doses are required.

1. Siu LL, Moore MJ. Use of mesna to prevent ifosfamide-induced urotoxicity. *Support Care Cancer* 1998; **6:** 144–54.

Malignant neoplasms. Ifosfamide may be used as an alternative to cyclophosphamide in lymphomas such as Burkitt's lymphoma (p.657). It is also used in a variety of solid neoplasms, including in palliative regimens for advanced cervical cancer (p.663); in the treatment of lung cancer (p.668); in ovarian cancer (p.670) and second-line and salvage regimens for testicular cancer (p.673); in thymoma (p.674); in adjuvant therapy for bone sarcomas (p.675) and rhabdomyosarcoma (p.676).

Preparations

USP 31: Ifosfamide for Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Asoifos†; Cuantil; Duvaxan†; Fentul; Holoxan†; Ifocris; Ifosmixan; IFX; ***Austral.:*** Holoxan; ***Austria:*** Holoxan; ***Belg.:*** Holoxan; ***Braz.:*** Holoxane; Seromida†; ***Canad.:*** Ifex; ***Chile:*** Holoxan; Ifolem; ***Cz.:*** Holoxan; ***Denm.:*** Holoxan†; ***Fin.:*** Holoxan; ***Fr.:*** Holoxan; ***Ger.:*** Holoxan; IFO-cell; ***Gr.:*** Holoxan; ***Hong Kong:*** Holoxan; ***Hung.:*** Holoxan; ***India:*** Ifos; Ipamide; ***Indon.:*** Holoxan; ***Irl.:*** Mitoxana; ***Israel:*** Ifoxan; ***Ital.:*** Holoxan; ***Malaysia:*** Holoxan†; ***Mex.:*** Alquimid; Ifolem; Ifomida; Ifoxan†; ***Neth.:*** Holoxan; ***Norw.:*** Holoxan; ***NZ:*** Holoxan; ***Philipp.:*** Holoxan; Iphox; ***Pol.:*** Holoxan; Macdafen; ***Port.:*** Holoxan; ***S.Afr.:*** Holoxan; ***Singapore:*** Holoxan; ***Spain:*** Tronoxal; ***Swed.:*** Holoxan; ***Switz.:*** Holoxan; ***Thai.:*** Holoxan; IFO-cell; Ifolem; ***Turk.:*** Holoxan; ***UK:*** Mitoxana†; ***USA:*** Ifex.

Multi-ingredient: ***India:*** Holoxan Uromitexan; Ifex-M; Ipamide with Mesna.

Imatinib Mesilate *(BANM, rINNM)*

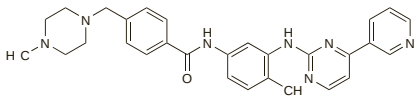
CGP-57-148B; Imatinib, Mésilate d'; Imatinib Mesylate *(USAN)*; Imatinibi Mesilas; Mesilato de imatinib; STI-571. α-(4-Methyl-1-piperazinyl)-3′-{[4-(3-pyridyl)-2-pyrimidinyl]amino}-*p*-tolu-*p*-toluidide methanesulfonate.

Иматиниба Мезилат

$C_{29}H_{31}N_7O,CH_4O_3S$ = 589.7.

CAS — 152459-95-5 (imatinib); 220127-57-1 (imatinib mesilate).

ATC — L01XE01.



(imatinib)

Adverse Effects and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

The most common adverse effects of imatinib mesilate include gastrointestinal disturbances, superficial oedema, myalgia, muscle cramps, rashes, fatigue, and headache. There are reports of erythema multiforme and Stevens-Johnson syndrome. Other adverse effects include dizziness, taste disturbances, paraesthesia, insomnia, eye disorders or visual disturbances, epistaxis, dyspnoea, dry skin, alopecia, night sweats, pyrexia, weakness, and rigors. Hepatotoxicity may occur; fatal cases of hepatic necrosis have been reported. Aseptic necrosis of bone, mainly in the femoral head, has been reported rarely.

Myelosuppression, manifest as neutropenia, thrombocytopenia, or anaemia, occurs more frequently in leukaemic patients, and may be associated with the underlying disease. Gastrointestinal bleeding, however, is more frequent in those patients treated for stromal tumours. Ulceration can occur; gastrointestinal perforation, fatal in some cases, has been reported rarely.

Severe fluid retention can occur, which may result in pleural and pericardial effusion, pulmonary oedema, and ascites. Some fatalities have been reported, and treatment may need to be stopped if there is unexpected, rapid weight gain. Elderly patients and those with a history of cardiac disease may be at increased risk. Isolated cases of left ventricular dysfunction have been reported; patients with cardiac disease or risk factors for cardiac failure should be monitored. There are reports, including fatalities, of cerebral oedema, increased intracranial pressure and papilloedema.

Imatinib mesilate should be taken with food and a large glass of water to minimise gastrointestinal irritation. Complete blood counts and liver function should be monitored regularly.

Effects on the heart. Ten patients receiving imatinib developed severe congestive heart failure without obvious cause; all patients had normal left ventricular function before imatinib was started. Mitochondrial abnormalities were found after myocardial biopsy on 2 of the patients. These findings were confirmed by studies on *mice* and *in vitro*. The authors suggested that patients be closely followed for clinical manifestations of left ventricular dysfunction.[1]

Subsequent evaluation by the manufacturer (*Novartis*) established that the frequency of reported cardiac events was less than 1%. However, they recommended that patients with known cardiac disease or risk factors for cardiac failure be monitored accordingly, that those developing clinical manifestations suggestive of congestive cardiac failure be thoroughly evaluated and treated, and that elderly patients or those with underlying heart disease be evaluated for baseline left ventricular ejection fraction.[2]

1. Kerkelä R, *et al.* Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. *Nat Med* 2006; **12:** 908–16.
2. Novartis, Canada. Health Canada endorsed important safety information on Gleevec (imatinib mesylate): recent safety information regarding reports of significant left ventricular ejection fraction reduction and congestive heart failure with GLEEVEC (imatinib mesylate) (issued 21st September, 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2006/gleevec_2_hpc-cps-eng.php (accessed 01/08/08)

Effects on the kidneys. Imatinib has been associated with the development of acute renal failure, requiring haemodialysis.[1-3]

1. Kitiyakara C, Atichartakarn V. Renal failure associated with a specific inhibitor of BCR-ABL tyrosine kinase, STI 571. *Nephrol Dial Transplant* 2002; **17:** 685–7.
2. Pou M, *et al.* Acute renal failure secondary to imatinib mesylate treatment in chronic myeloid leukemia. *Leuk Lymphoma* 2003; **44:** 1239–41.
3. Foringer JR, *et al.* Acute renal failure secondary to imatinib mesylate treatment in prostate cancer. *Ann Pharmacother* 2005; **39:** 2136–8.

Effects on the lungs. Interstitial pneumonitis has been reported with imatinib;[1-8] presenting symptoms included dry cough and dyspnoea. Doses of imatinib ranged from 100 mg to 600 mg daily. In most cases, the pneumonitis resolved after stopping imatinib and starting corticosteroid therapy. The mechanism was unclear, and may involve a hypersensitivity reaction. In an analysis of 27 cases of interstitial lung disease associated with imatinib therapy,[8] 30% of patients showed a hypersensitivity reaction radiological pattern. Pre-existing lung disease may be a risk factor.

1. Bergeron A, *et al.* Hypersensitivity pneumonitis related to imatinib mesylate. *J Clin Oncol* 2002; **20:** 4271–2.
2. Rosado MF, *et al.* Imatinib mesylate-induced interstitial pneumonitis. *J Clin Oncol* 2003; **21:** 3171–3.
3. Ma CX, *et al.* Imatinib mesylate-induced interstitial pneumonitis. *Mayo Clin Proc* 2003; **78:** 1578–9.
4. Yokoyama T, *et al.* Interstitial pneumonia induced by imatinib mesylate: pathologic study demonstrates alveolar destruction and fibrosis with eosinophilic infiltration. *Leukemia* 2004; **18:** 645–6.
5. Isshiki I, *et al.* Interstitial pneumonitis during imatinib therapy. *Br J Haematol* 2004; **125:** 420.
6. Rajda J, Phatak PD. Reversible drug-induced interstitial pneumonitis following imatinib mesylate therapy. *Am J Hematol* 2005; **79:** 80–1.
7. Lin J-T, *et al.* Fulminant, but reversible interstitial pneumonitis associated with imatinib mesylate. *Leuk Lymphoma* 2006; **47:** 1693–5.
8. Ohnishi K, *et al.* Twenty-seven cases of drug-induced interstitial lung disease associated with imatinib mesylate. *Leukemia* 2006; **20:** 1162–4.

Effects on reproductive potential. Oligospermia[1] and ovarian failure[2] have been reported after treatment with imatinib. Patients should be counselled before therapy about the risk of impaired fertility.

1. Seshadri T, *et al.* Oligospermia in a patient receiving imatinib therapy for the hypereosinophilic syndrome. *N Engl J Med* 2004; **351:** 2134–5.
2. Christopoulos C, *et al.* Primary ovarian insufficiency associated with imatinib therapy. *N Engl J Med* 2008; **358:** 1079–80.

Effects on the skin, hair, and nails. There are reports of acute generalised exanthematous pustulosis in patients receiving imatinib.[1,2] The authors noted that severe skin reactions had been reported in some other patients receiving the drug, and speculated that the effect might be dose-dependent and related to its pharmacological action. In subsequent reports[3-5] of cutaneous adverse effects, this dose-dependency has also been observed, with effects especially at doses of 600 mg daily and above. In a report of a livedoid pattern of rash in 3 patients taking imatinib, the authors noted that adverse skin reactions to imatinib tend to be strongly dose-dependent, are self-limiting, and do not usually affect the mucous membranes.[6] Epidermal necrolysis occurred in a patient who underwent stem cell transplantation after treatment with imatinib.[7] The authors suggested that prolonged inhibition of platelet-derived growth factor by imatinib may have impaired the repair of skin damage caused by the conditioning therapy. In a report of 19 patients exhibiting skin reactions, the authors suggested that the actions of imatinib on platelet-derived growth factor may have caused an increase in dermal interstitial fluid pressure, capable of inducing oedema and the subsequent erythema and desquamation that was observed. Rare reactions included psoriasis, hyaline cell syringoma, and malpighian epithelioma, all of which occurred after at least 1 year of therapy.[8] Follicular mucinosis[9] and panniculitis[10] have also been reported with use of imatinib, as has Stevens-Johnson syndrome.[11,12] Palmoplantar hyperkeratosis and nail dystrophy can occur.[13] Repigmentation of grey hair has also been reported.[14]

Oral corticosteroids have been used to resolve most cases of skin eruptions.[8] In other instances, re-introduction of imatinib at low doses, gradually increased to full dosage, has been successfully tolerated.[8,12,15] In one patient, who developed exfoliative dermatitis with imatinib and had recurrent reactions despite decreased doses, a once-weekly dose of imatinib was associated with a less severe rash that eventually disappeared over a period of 4 months.[16]

1. Brouard M, Saurat J-H. Cutaneous reactions to STI571. *N Engl J Med* 2001; **345:** 618–19.
2. Schwarz M, *et al.* Imatinib-induced acute generalized exanthematous pustulosis (AGEP) in two patients with chronic myeloid leukemia. *Eur J Haematol* 2002; **69:** 254–6.
3. Valeyrie L, *et al.* Adverse cutaneous reactions to imatinib (STI571) in Philadelphia chromosome-positive leukemias: a prospective study of 54 patients. *J Am Acad Dermatol* 2003; **48:** 201–6.
4. Drummond A, *et al.* A spectrum of skin reactions caused by the tyrosine kinase inhibitor imatinib mesylate (STI 571, Glivec). *Br J Haematol* 2003; **120:** 911–13.
5. Ugurel S, *et al.* Dose-dependent severe cutaneous reactions to imatinib. *Br J Cancer* 2003; **88:** 1157–9.
6. Martínez-González MC, *et al.* Livedoid skin reaction probably due to imatinib therapy. *Ann Pharmacother* 2007; **41:** 148–52.
7. Schaich M, *et al.* Severe epidermal necrolysis after treatment with imatinib and consecutive allogeneic hematopoietic stem cell transplantation. *Ann Hematol* 2003; **82:** 303–4.
8. Breccia M, *et al.* Early and tardive skin adverse events in chronic myeloid leukaemia patients treated with imatinib. *Eur J Haematol* 2005; **74:** 121–3.
9. Yanagi T, *et al.* Follicular mucinosis associated with imatinib (STI571). *Br J Dermatol* 2004; **151:** 1276–8.
10. Ugurel S, *et al.* Panniculitis in a patient with chronic myelogenous leukaemia treated with imatinib. *Br J Dermatol* 2003; **149:** 678–9.
11. Hsiao L-T, *et al.* Stevens-Johnson syndrome after treatment with STI571: a case report. *Br J Haematol* 2002; **117:** 620–2.
12. Rule SAJ, *et al.* Managing cutaneous reactions to imatinib therapy. *Blood* 2002; **100:** 3434–5.
13. Deguchi N, *et al.* Imatinib mesylate causes palmoplantar hyperkeratosis and nail dystrophy in three patients with chronic myeloid leukaemia. *Br J Dermatol* 2006; **154:** 1216–18.
14. Etienne G, *et al.* Imatinib mesylate and gray hair. *N Engl J Med* 2002; **347:** 446.
15. Park MA, *et al.* Successful progressive challenge after a cutaneous reaction to imatinib mesylate (Gleevec): a case report and review of the literature. *Allergy Asthma Proc* 2004; **25:** 345–7.
16. Tanvetyanon T, Nand S. Overcoming recurrent cutaneous reactions from imatinib using once-weekly dosing. *Ann Pharmacother* 2003; **37:** 1818–20.

Effects on the spleen. There are isolated reports of splenic rupture in patients receiving imatinib mesilate.[1]

1. Elliott MA, *et al.* Adverse events after imatinib mesylate therapy. *N Engl J Med* 2002; **346:** 712–13.

Gynaecomastia. Gynaecomastia was noted in 7 of 38 men assessed for hormone concentrations while enrolled in studies of imatinib; the authors attributed the disorder to reductions in testosterone concentrations due to imatinib.[1]

1. Gambacorti-Passerini C, *et al.* Gynaecomastia in men with chronic myeloid leukaemia after imatinib. *Lancet* 2003; **361:** 1954–56.

Hypophosphataemia. Hypophosphataemia and associated changes in bone and mineral metabolism were reported in a study of patients receiving imatinib. Patients with normal serum-phosphate concentrations also had similar changes in bone turnover. Hypophosphataemia was apparently related to patient age and imatinib dose; it was also associated with decreased serum concentrations of calcium and vitamin D.[1] In a review of data, the manufacturers (*Novartis*) noted an incidence of 50% of patients in 2 studies; overall 1.5% had grade 4 hypophosphataemia. However, the reported incidence of hypophosphataemia as an adverse effect of imatinib was only 3%. They suggested that phosphate concentrations be monitored in patients taking imatinib until further elucidation of the effect of the drug on bone is available.[2] While some have questioned the association between treatment with imatinib and hypophosphataemia,[3] others have also reported hypophosphataemia during treatment with the drug.[4] The effect, however, appears to be reversible on stopping imatinib.

1. Berman E, *et al.* Altered bone and mineral metabolism in patients receiving imatinib mesylate. *N Engl J Med* 2006; **354:** 2006–13.
2. Owen S, *et al.* Imatinib and altered bone and mineral metabolism. *N Engl J Med* 2006; **355:** 627.
3. Tournis S, Lyritis GP. Imatinib and altered bone and mineral metabolism. *N Engl J Med* 2006; **355:** 627.
4. Joensuu H, Reichardt P. Imatinib and altered bone and mineral metabolism. *N Engl J Med* 2006; **355:** 628. Correction. *ibid.*; 1627.

Pregnancy. Two of 3 pregnancies in 2 patients taking imatinib were successful; the infants were both small for weight, but healthy and without congenital abnormalities. In the third case, a first trimester miscarriage occurred. Both women continued imatinib throughout their pregnancies.[1]

In another report,[2] 10 women became pregnant while being treated with imatinib for chronic myeloid leukaemia. Imatinib therapy was stopped upon discovery of the pregnancy; exposure to imatinib ranged from 4 to 9 weeks. Two patients had a spontaneous abortion shortly after stopping imatinib, and another patient elected to have a therapeutic abortion. Seven other pregnancies went to term, resulting in 8 babies. One infant had hypospadias which was surgically corrected without complications; all other infants were healthy. The partners of 8 male patients also conceived while the men were receiving imatinib, one of them twice. All male patients continued therapy with imatinib. One spontaneous abortion occurred. Of the 8 babies born, 1 was found to have a mild rotation of the small intestine requiring surgery shortly after birth. The authors considered it possible that the brief exposure to imatinib may have slightly increased the risk of spontaneous abortion. While concluding that normal pregnancies are possible during imatinib therapy, the authors of both reports emphasised that possible teratogenic effects cannot be ruled out, and that patients should still be advised to use appropriate and effective contraception.

A similar warning was issued in a review of outcome data from 125 pregnancies involving exposure to imatinib. The authors noted that 63 pregnancies had resulted in the live birth of normal infants; a further 35 women terminated the pregnancy (in 3 cases because fetal abnormalities were found), and 18 ended in spontaneous abortion.[3] However, there were 9 infants with congenital abnormalities, several of which were strikingly similar, a fact that was considered to be of some concern.

1. AlKindi S, *et al.* Imatinib in pregnancy. *Eur J Haematol* 2005; **74:** 535–7.