sion immediately before use. The usual initial dose in adults and children 2 years of age and older is 20 mg/kg once daily, taken on an empty stomach at least 30 minutes before food. Serum ferritin should be monitored monthly and the dose should be adjusted every 3 to 6 months as necessary. The maximum recommended dose is 30 mg/kg daily.

◊ References.

1. VanOrden HE, Hagemann TM. Deferasirox—an oral agent for chronic iron overload. *Ann Pharmacother* 2006; **40:** 1110–17.
2. Stumpf JL. Deferasirox. *Am J Health-Syst Pharm* 2007; **64:** 606–16.
3. Yang LPH, *et al*. Deferasirox: a review of its use in the management of transfusional chronic iron overload. *Drugs* 2007; **67:** 2211–30.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Exjade; ***Austral.:*** Exjade; ***Chile:*** Exjade; ***Cz.:*** Exjade; ***Fr.:*** Exjade; ***Gr.:*** Exjade; ***Hung.:*** Exjade; ***Indon.:*** Exjade; ***Malaysia:*** Exjade; ***NZ:*** Exjade; ***UK:*** Exjade; ***USA:*** Exjade.

Deferiprone *(BAN, rINN)*

CP-20; Deferipron; Deferiprona; Défériprone; Deferiproni; Deferipronum; Dimethylhydroxypyridone; L1. 1,2-Dimethyl-3-hydroxypyrid-4-one; 3-Hydroxy-1,2-dimethyl-4-pyridone.

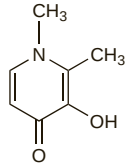
Деферипрон

$C_7H_9NO_2$ = 139.2.

CAS — 30652-11-0.

ATC — V03AC02.

ATC Vet — QV03AC02.



Adverse Effects and Precautions

Deferiprone has been shown to cause neutropenia and should not be used in neutropenic patients; the neutrophil count should be monitored weekly and treatment should be stopped if neutropenia develops. Agranulocytosis has also occurred. Patients should be advised to seek immediate medical attention if symptoms indicative of infection such as fever, sore throat, or flu-like symptoms occur.

Gastrointestinal disorders such as diarrhoea, nausea, vomiting, and abdominal pain are common during deferiprone treatment and may require a temporary reduction in dose. A reddish-brown discoloration of the urine is also common. Other adverse effects that have been reported include arthralgia and increased liver enzymes. Deferiprone may reduce plasma-zinc concentrations and zinc supplements may be required.

Deferiprone is teratogenic in *animals* and should not be used during pregnancy. Women of child-bearing potential should be advised to use contraceptive measures during treatment with deferiprone.

Caution is advised in patients with hepatic or renal impairment.

Effects on the blood. Agranulocytosis, in some cases fatal, has been reported in association with deferiprone use.[1,2]

1. Henter J-I, Karlén J. Fatal agranulocytosis after deferiprone therapy in a child with Diamond-Blackfan anemia. *Blood* 2007; **109:** 5157–9.
2. Anonymous. Deferiprone: agranulocytosis and neurological disorders. *Prescrire Int* 2007; **16:** 72.

Overdosage. Neurological disorders were reported by the manufacturer and the French pharmacovigilance authorities in 2 children aged 7 and 9 who had been treated with deferiprone doses at 2⁄ times the highest recommended dose of 100 mg/kg daily. The children were treated for 1 and 2 years, respectively, and developed nystagmus, gait disorders, ataxia, dystonia, and, in one case, psychomotor retardation. These disorders gradually improved after deferiprone was stopped.[1]

1. Agence française de sécurité sanitaire des produits de santé/Laboratoires Chiesi, France. Risque d'agranulocytoses fatales et de troubles neurologiques lors de l'utilisation de Ferriprox (déféripirone) (issued 1st September, 2006). Available at: http://agmed.sante.gouv.fr/htm/10/filltrpsc/lp060901.pdf (accessed 27/09/07)

Interactions

Deferiprone chelates trivalent metal ions and could interact with aluminium-containing preparations; it should not be given with aluminium-containing antacids. Due to the risk of additive toxicity, use with drugs that may cause neutropenia or agranulocytosis is not recommended.

Pharmacokinetics

Deferiprone is rapidly absorbed from the gastrointestinal tract with peak serum concentrations occurring 45 to 60 minutes after an oral dose; absorption may be slowed in the presence of food and peak serum concentrations may be reduced. Deferiprone is metabolised to an inactive glucuronide metabolite and is excreted primarily in the urine, mainly as the metabolite and the iron-deferiprone complex, with a small amount of unchanged drug. The elimination half-life is about 2 to 3 hours.

Uses and Administration

Deferiprone is an orally active iron chelator used in the treatment of iron overload in patients with thalassaemia for whom desferrioxamine is unsuitable or ineffective. It may be given by mouth in doses of 25 mg/kg three times daily. Doses above 100 mg/kg daily are not recommended. For use in children, see Administration in Children, below.

◊ Reviews.

1. Barman Balfour JA, Foster RH. Deferiprone: a review of its clinical potential in iron overload in β-thalassaemia major and other transfusion-dependent diseases. *Drugs* 1999; **58:** 553–78.
2. Kontoghiorghes GJ, *et al*. Benefits and risks of deferiprone in iron overload in thalassaemia and other conditions: comparison of epidemiological and therapeutic aspects with deferoxamine. *Drug Safety* 2003; **26:** 553–84.
3. Hoffbrand AV. Deferiprone therapy for transfusional iron overload. *Best Pract Res Clin Haematol* 2005; **18:** 299–317.
4. Piga A, *et al*. Deferiprone: new insight. *Ann N Y Acad Sci* 2005; **1054:** 169–74.

Administration in children. UK licensed product information states that there are limited data on the use of deferiprone in children between 6 and 10 years of age, and no data on use in children below 6. Australian licensed product information states that limited data exist for children between the ages of 2 and 10 but that the effects of deferiprone on growth are unknown. Licensed doses in children are calculated by weight on the same basis as adults (see Uses and Administration, above).

Thalassaemia. Patients with thalassaemia receiving regular blood transfusions commonly develop iron overload requiring use of iron chelators. Deferiprone was developed as an oral alternative to desferrioxamine, but its role has been controversial. See Thalassaemia under Uses of Desferrioxamine, p.1442, for further information.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Ferriprox; ***Austral.:*** Ferriprox; ***Belg.:*** Ferriprox; ***Braz.:*** Ferriprox; ***Cz.:*** Ferriprox; ***Denm.:*** Ferriprox; ***Fin.:*** Ferriprox; ***Fr.:*** Ferriprox; ***Ger.:*** Ferriprox; ***Gr.:*** Ferriprox; Kelfer; ***Hong Kong:*** Ferriprox; ***India:*** Kelfer; ***Irl.:*** Ferriprox†; ***Ital.:*** Ferriprox; ***Malaysia:*** Ferriprox; Kelfer; ***Neth.:*** Ferriprox; ***Port.:*** Ferriprox; ***Spain:*** Ferriprox; ***Swed.:*** Ferriprox; ***Switz.:*** Ferriprox; ***Turk.:*** Ferriprox; ***UK:*** Ferriprox.

Desferrioxamine Mesilate *(BANM)*

Deferoxamine Mesilate *(pINNM)*; Ba-33112; Ba-29837 (desferrioxamine hydrochloride); Deferoksamiinimesilaatti; Deferoksamin Mezilat; Deferoksamino mesilatas; Déferoxamine, Mésilate de; Déféroxamine, mésilate de; Deferoxamine Mesylate *(USAN)*; Deferoxamini mesilas; Deferoxaminmesilat; Deferoxaminmesylát; Deferoxamin-mezilát; Desferrioksamin Mesilat; Desferrioxamine Mesylate; Desferrioxamine Methanesulphonate; Mesilato de deferoxamina; NSC-527604 (desferrioxamine). 30-Amino-3,14,25-trihydroxy-3,9,14,20,25-penta-azatriacontane-2,10,13,21,24-pentaone methanesulphonate; *N*′-{5-[(4-{[5-(Acetylhydroxyamino)pentyl]amino}-1,4-dioxobutyl)hydroxyamino]pentyl}-*N*-(5-aminopentyl)-*N*-hydroxy-butanediamide monomethanesulphonate.

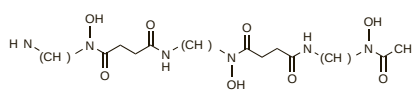
Дефероксамина Мезилат

$C_{25}H_{48}N_6O_8,CH_3SO_3H$ = 656.8.

CAS — 70-51-9 (desferrioxamine); 138-14-7 (desferrioxamine mesilate); 1950-39-6 (desferrioxamine hydrochloride).

ATC — V03AC01.

ATC Vet — QV03AC01.



(desferrioxamine)

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.
Ph. Eur. 6.2 (Deferoxamine Mesilate; Desferrioxamine Mesilate BP 2008). A white or almost white powder. Freely soluble in water; very slightly soluble in alcohol; slightly soluble in methyl alcohol. A freshly prepared 10% solution in water has a pH of 3.7 to 5.5. Store at 2° to 8°. Protect from light.
USP 31 (Deferoxamine Mesylate). A white to off-white powder. Freely soluble in water; slightly soluble in methyl alcohol. pH of a 1% solution in water is between 4.0 and 6.0. Store in airtight containers.

Incompatibility. Licensed product information states that desferrioxamine solutions are incompatible with heparin.

Adverse Effects and Treatment

Rapid intravenous injection of desferrioxamine may cause flushing, urticaria, hypotension, and shock. Local pain may occur with subcutaneous or intramuscular injections and pruritus, erythema, and swelling have occurred after prolonged subcutaneous use. Gastrointestinal disorders, dysuria, fever, allergic skin rashes, tachycardia, cardiac arrhythmias, convulsions, and leg cramps have been reported. Visual disturbances, including retinal changes, and hearing loss may occur and may be reversible if desferrioxamine is withdrawn. Cataract formation has also been reported. Desferrioxamine therapy may retard growth in very young children.

The adverse effects of desferrioxamine generally respond to dosage reduction. In acute overdosage desferrioxamine may be removed by haemodialysis.

◊ Reviews of the adverse effects of desferrioxamine.

1. Bentur Y, *et al.* Deferoxamine (desferrioxamine): new toxicities for an old drug. *Drug Safety* 1991; **6:** 37–46.

Effects on the blood. A patient with end-stage renal disease developed reversible thrombocytopenia on 3 separate occasions after intravenous infusions of desferrioxamine for dialysis osteomalacia.[1] Acute fatal aplastic anaemia occurred in a 16-year-old girl with thalassaemia after high intravenous doses of desferrioxamine (80 mg/kg daily) for 20 days.[2]

1. Walker JA, *et al*. Thrombocytopenia associated with intravenous desferrioxamine. *Am J Kidney Dis* 1985; **6:** 254–6.
2. Sofroniadou K, *et al.* Acute bone marrow aplasia associated with intravenous administration of deferoxamine (desferrioxamine). *Drug Safety* 1990; **5:** 152–4.

Effects on the ears and eyes. Lens opacities, retinal pigmentary changes and other retinal abnormalities, and ocular disturbances including loss of colour vision, night blindness, decreased visual acuity, and field defects, have been reported in patients receiving long-term or high-dose treatment with desferrioxamine.[1-4] The incidence appears to be about 30%, although individual studies have reported widely differing rates; in 2 studies long-term use of desferrioxamine was associated with symptomatic or asymptomatic ocular changes in 4% (2 of 52)[5] and 66% (10 of 15)[6] of patients respectively.

Sensorineural hearing impairment has also been reported,[5,7-12] and in one study[13] was attributed to desferrioxamine in 29% of patients (22 of 75). Tinnitus has been reported in a few patients.[11,14]

The mechanism by which desferrioxamine causes neurotoxicity is unclear. Some studies[8,15] have found an association with dose, suggesting a direct toxic effect of desferrioxamine; other studies[6,16] have suggested that depletion of trace metals, particularly zinc or copper, may be involved. Both ophthalmic and auditory abnormalities can improve when desferrioxamine is withdrawn,[1,3,5-10] although sometimes the effects may be irreversible[17] or recovery may only be partial.[8,9] There has also been a report[18] of improvement following use of zinc supplements.

1. Davies SC, *et al.* Ocular toxicity of high-dose intravenous desferrioxamine. *Lancet* 1983; **ii:** 181–4.
2. Simon P, *et al.* Desferrioxamine, ocular toxicity, and trace metals. *Lancet* 1983; **ii:** 512–13.
3. Borgna-Pignatti C, *et al*. Visual loss in patient on high-dose subcutaneous desferrioxamine. *Lancet* 1984; **i:** 681.
4. Rubinstein M, *et al.* Ocular toxicity of desferrioxamine. *Lancet* 1985; **i:** 817–18.
5. Cohen A, *et al.* Vision and hearing during deferoxamine therapy. *J Pediatr* 1990; **117:** 326–30.
6. De Virgiliis S, *et al.* Depletion of trace elements and acute ocular toxicity induced by desferrioxamine in patients with thalassaemia. *Arch Dis Child* 1988; **63:** 250–5.
7. Guerin A, *et al.* Acute deafness and desferrioxamine. *Lancet* 1985; **ii:** 39.
8. Olivieri NF, *et al.* Visual and auditory neurotoxicity in patients receiving subcutaneous deferoxamine infusions. *N Engl J Med* 1986; **314:** 869–73.
9. Barratt PS, Toogood IRG. Hearing loss attributed to desferrioxamine in patients with beta-thalassaemia major. *Med J Aust* 1987; **147:** 177–9.
10. Wonke B, *et al*. Reversal of desferrioxamine induced auditory neurotoxicity during treatment with Ca-DTPA. *Arch Dis Child* 1989; **64:** 77–82.
11. Porter JB, *et al.* Desferrioxamine ototoxicity: evaluation of risk factors in thalassaemic patients and guidelines for safe dosage. *Br J Haematol* 1989; **73:** 403–9.
12. Argiolu F, *et al*. Hearing impairment during deferoxamine therapy for thalassemia major. *J Pediatr* 1991; **118:** 826.
13. Chiodo AA, *et al*. Desferrioxamine ototoxicity in an adult transfusion-dependent population. *J Otolaryngol* 1997; **26:** 116–22.
14. Marsh MN, *et al.* Tinnitus in a patient with beta-thalassaemia intermedia on long-term treatment with desferrioxamine. *Postgrad Med J* 1981; **57:** 582–4.