

# AUSTRALIAN PRODUCT INFORMATION – FERRIPROX® (DEFERIPRONE)

## 1 NAME OF THE MEDICINE

Deferiprone

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Deferiprone is a white to off-white powder. Deferiprone is sparingly soluble in water, very slightly soluble in acetone and slightly soluble in methanol. It has a melting range of 272°C to 278°C. Deferiprone does not show stereoisomerism.

### **Ferriprox 500 mg film-coated tablet**

Each film-coated tablet contains 500 mg deferiprone as the active ingredient. In addition, each tablet contains the following inactive ingredients: microcrystalline cellulose, magnesium stearate, silicon dioxide, hypromellose, macrogol 3350 and titanium dioxide.

### **Ferriprox 1000 mg film-coated tablet**

Each film-coated tablet contains 1000 mg deferiprone as the active ingredient. In addition, each tablet contains the following inactive ingredients: methylcellulose, crospovidone, magnesium stearate, hypromellose, hypolose, macrogol 8000, and titanium dioxide.

### **Ferriprox 100 mg/mL oral solution**

Each mL of oral solution contains 100 mg deferiprone as the active substance. The 250 mL bottle contains a total dose of 25 g of deferiprone and the 500 mL bottle contains a total dose of 50 g of deferiprone. In addition, the oral solution contains the following inactive ingredients: purified water, hyetellose, glycerol, hydrochloric acid, artificial cherry flavour, peppermint oil, sunset yellow FCF and sucralose.

## 3 PHARMACEUTICAL FORM

### **500 mg film-coated tablet**

Ferriprox tablets are white to off white, capsule-shaped, film-coated, scored and imprinted “APO” bisect “500” on one side, and plain on the other side. The tablets are breakable in half.

### **1000 mg film-coated tablet**

Ferriprox tablets are white to off-white, capsule-shaped, film-coated, scored and imprinted “APO” bisect “1000” on one side, and plain on the other side. The tablets are breakable in half.

### **100 mg/mL oral solution**

Ferriprox oral solution is a clear, reddish orange solution with a peppermint and cherry-flavoured aroma.

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

Ferriprox is indicated for the treatment of iron overload in patients with thalassaemia major who are unable to take desferrioxamine or in whom desferrioxamine therapy has proven ineffective.

## 4.2 DOSE AND METHOD OF ADMINISTRATION

### Dosage

The effect of Ferriprox in decreasing the body iron is influenced by the dose and degree of iron overload. Ferriprox is given as 25 mg/kg to 33 mg/kg body weight, orally, three times a day for a total daily dose of 75 mg/kg to 100 mg/kg body weight. The recommended initial total daily dose of Ferriprox is 75 mg/kg body weight. After starting Ferriprox therapy, it is recommended that serum ferritin concentrations or other indicators of body iron load be monitored every two to three months to assess the long-term effectiveness of the chelation regimen in controlling body iron load. Dose adjustments should be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of body iron burden). Interruption of Ferriprox therapy should be considered if serum ferritin falls below 500 µg/L.

Doses above 100 mg/kg/day are not recommended because of the limited experience with these higher doses of Ferriprox.

Dosage per kilogram body weight should be calculated to the nearest half tablet or to the nearest 2.5 mL. See Dosage Tables below.

### Dosage Tables for 75 mg/kg/day

To obtain a dose of about 75 mg/kg/day, use the dose suggested in the following tables for the body weight of the patient.

#### Dosage table for FERRIPROX 500 mg tablets – 75 mg/kg/day

Body weight (kg)	Total daily dose (mg)	Dose (mg, three times/day)	Number of 500 mg tablets* (three times/day)
20	1500	500	1.0
30	2250	750	1.5
40	3000	1000	2.0
50	3750	1250	2.5
60	4500	1500	3.0
70	5250	1750	3.5
80	6000	2000	4.0
90	6750	2250	4.5

\*rounded to nearest half tablet

#### Dosage table for FERRIPROX 1000 mg tablets – 75 mg/kg/day

Body weight (kg)	Total daily dose (mg)	Number of 1000 mg tablets*		
		Morning	Midday	Evening
20	1500	0.5	0.5	0.5
30	2250	1.0	0.5	1.0
40	3000	1.0	1.0	1.0
50	3750	1.5	1.0	1.5
60	4500	1.5	1.5	1.5
70	5250	2.0	1.5	2.0
80	6000	2.0	2.0	2.0
90	6750	2.5	2.0	2.5

\*rounded to nearest half tablet

**Dosage table for FERRIPROX 100 mg/mL oral solution – 75 mg/kg/day**

<b>Body weight (kg)</b>	<b>Total daily dose (mg)</b>	<b>Dose (mg, three times/day)</b>	<b>mL of oral solution* (three times/day)</b>
20	1500	500	5.0
30	2250	750	7.5
40	3000	1000	10.0
50	3750	1250	12.5
60	4500	1500	15.0
70	5250	1750	17.5
80	6000	2000	20.0
90	6750	2250	22.5

\*rounded to the nearest 2.5 mL

**Dosage tables for 100 mg/kg/day**

To obtain a dose of about 100 mg/kg/day, use the dose suggested in the following tables for the body weight of the patient.

**Dosage table for FERRIPROX 500 mg tablets – 100 mg/kg/day**

<b>Body weight (kg)</b>	<b>Total daily dose (mg)</b>	<b>Dose (mg, three times/day)</b>	<b>Number of 500 mg tablets* (three times/day)</b>
20	2000	667	1.5
30	3000	1000	2
40	4000	1333	2.5
50	5000	1667	3.5
60	6000	2000	4
70	7000	2333	4.5
80	8000	2667	5.5
90	9000	3000	6

\*rounded to nearest half tablet

**Dosage table for FERRIPROX 1000 mg tablets – 100 mg/kg/day**

<b>Body weight (kg)</b>	<b>Total daily dose (mg)</b>	<b>Number of 1000 mg tablets*</b>		
		<b>Morning</b>	<b>Midday</b>	<b>Evening</b>
20	2000	1.0	0.5	0.5
30	3000	1.0	1.0	1.0
40	4000	1.5	1.0	1.5
50	5000	2.0	1.5	1.5
60	6000	2.0	2.0	2.0
70	7000	2.5	2.0	2.5
80	8000	3.0	2.5	2.5
90	9000	3.0	3.0	3.0

\*rounded to nearest half tablet

### Dosage table for FERRIPROX 100 mg/mL oral solution – 100 mg/kg/day

Body weight (kg)	Total daily dose (mg)	Dose (mg, three times/day)	mL of oral solution* (three times/day)
20	2000	667	7.5
30	3000	1000	10.0
40	4000	1333	15.0
50	5000	1667	17.5
60	6000	2000	20.0
70	7000	2333	25.0
80	8000	2667	27.5
90	9000	3000	30.0

\*rounded to the nearest 2.5 mL

Due to the nature of the serious adverse events, which can occur with the use of Ferriprox, special monitoring is required for all patients. Treatment with Ferriprox should not be initiated if the baseline absolute neutrophil count (ANC) is low. Caution must be used when treating patients with renal insufficiency or hepatic dysfunction (see 4.4 - Special Warnings and Precautions for Use).

### Method of administration

For oral administration.

Therapy with Ferriprox should be initiated and maintained by a physician experienced in the treatment of patients with transfusional haemosiderosis.

### Dosage adjustment in renal and hepatic impairment

Currently, there are no available data in patients with renal impairment and limited data on the use of Ferriprox in patients with hepatic impairment. Caution must be used when treating patients with renal insufficiency or hepatic dysfunction (see 4.4 - Special Warnings and Precautions for Use).

### 4.3 CONTRAINDICATIONS

Ferriprox is contraindicated in patients who:

- have demonstrated hypersensitivity to the active substance or any of the excipients
- have a history of recurrent episodes of neutropenia
- have a history of agranulocytosis
- are pregnant or breast-feeding.

### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

#### Neutropenia / agranulocytosis

Ferriprox has been shown to cause neutropenia, including agranulocytosis, which may lead to the development of a serious and potentially life-threatening infection. It is recommended that a patient's neutrophil count be monitored every week.

The most serious adverse event of therapy reported in clinical trials with Ferriprox is agranulocytosis (absolute neutrophil count  $<0.5 \times 10^9/L$ ) with an incidence of 1.9% (0.9 cases per 100 patient-years of treatment). The observed incidence of the less severe form of neutropenia (absolute neutrophil count  $<1.5 \times 10^9/L$  but  $>0.5 \times 10^9/L$ ) is 6.4% (3.6 cases per 100 patient-years). This rate should be considered in context of the underlying elevated incidence of neutropenia in thalassaemia patients, particularly in those with hypersplenism.

Based on clinical trials, it is recommended that the absolute neutrophil count be monitored weekly to enable prompt detection of neutropenia and agranulocytosis. In the event of neutropenia or agranulocytosis, Ferriprox treatment should be stopped (see below for guidelines on re-initiating treatment).

If the patient develops an infection, Ferriprox therapy should be interrupted and the absolute neutrophil count should be monitored more frequently. Patients should be advised to report immediately to their physician any symptoms indicative of infection such as: fever, sore throat or flu-like symptoms.

Suggested management for cases of neutropenia is outlined below. It is recommended that such a management protocol be in place prior to initiating any patient on Ferriprox treatment.

Treatment with Ferriprox should not be initiated if the patient is neutropenic.

### **In the event of neutropenia**

Instruct the patient to immediately discontinue Ferriprox and all other medications with a potential to cause medicinal product-associated neutropenia. The patient should be advised to limit contact with other individuals in order to reduce the risk of potential infection. Obtain a complete blood cell count immediately upon diagnosing the event and then repeat daily. It is recommended that following recovery of the absolute neutrophil count, weekly complete blood cell count continue to be obtained for three consecutive weeks, to ensure that the patient recovers fully. Should any evidence of infection develop concurrent with the neutropenia, the appropriate cultures and diagnostic procedures should be performed and an appropriate antibiotic regimen instituted.

### **In the event of severe neutropenia or agranulocytosis**

Follow the guidelines above and administer appropriate therapy such as granulocyte colony stimulating factor, beginning the same day that the event is identified; administer daily until the absolute neutrophil count recovers. Provide protective isolation and, if clinically indicated, admit patient to hospital.

Limited data are available regarding rechallenge. Therefore, in the event of neutropenia rechallenge is not recommended. In the event of agranulocytosis a rechallenge is contraindicated.

### **HIV positive or other immune compromised patients**

No data are available on the use of Ferriprox in HIV positive or in other immune compromised patients. Given that Ferriprox is associated with neutropenia and agranulocytosis, therapy in immune compromised patients should not be initiated unless potential benefits outweigh potential risks.

### **Allergic reactions**

Ferriprox oral solution contains the colouring agent sunset yellow FCF which may cause allergic reactions.

### **QT prolongation**

No significant inhibition of hERG K<sup>+</sup> channels was seen at deferiprone concentrations up to 3,000 µM, and no effect on QT interval or other cardiovascular and electrocardiographic parameters were noted in iron-loaded and non-iron-loaded monkeys that received deferiprone for up to 12 months. However, the tested concentrations and doses were low, limiting the predictive value of negative findings. One episode of *Torsade de pointes* during therapy with Ferriprox was observed in a patient with a history of QT prolongation. Ferriprox should be administered with caution to patients who may be at increased risk of prolongation of the cardiac QT interval (e.g., those with congestive heart failure, bradycardia, use of a diuretic, cardiac hypertrophy, hypokalemia or hypomagnesemia). Any patient taking Ferriprox who experiences symptoms suggestive of an arrhythmia (such as palpitations, dizziness, lightheadedness, syncope, or seizures) should seek medical attention immediately.

## **Discolouration of urine**

Patients should be informed that a reddish/brown discolouration of the urine is commonly associated with Ferriprox use; the discolouration is due to the excretion of the iron-Ferriprox complex, which is a chromophore.

## **Use in hepatic impairment**

There are limited data on the safety and efficacy of Ferriprox in patients with hepatic impairment. Ferriprox is metabolised by the liver and therefore caution should be exercised in such patients and hepatic function should be monitored.

In thalassaemia patients, there is an association between liver fibrosis and hepatitis C. Special care must be taken to ensure that iron chelation in patients with hepatitis C is optimal. In these patients, careful monitoring of liver histology is recommended.

Ferriprox has been associated with hepatotoxicity (increased ALT) in some patients. If there is a persistent increase in serum ALT, interruption of Ferriprox therapy should be considered.

## **Use in renal impairment**

Currently, there are no available data in patients with renal impairment. Since Ferriprox and its metabolites are excreted by the kidney, there may be an increased risk of complications in patients with impaired renal function. Caution must be used when treating patients with renal impairment.

## **Use in the elderly**

Currently, there are no available data in elderly patients.

## **Paediatric use**

The safety and efficacy of Ferriprox for paediatric use was evaluated in 220 children aged 1 to 15 years with transfusion-dependent anaemias. The data show that Ferriprox was effective in decreasing body iron load as measured by serum ferritin concentrations and it was not associated with new health concerns in this patient population. The effects of Ferriprox on growth are unknown.

## **Effects on laboratory tests**

### **Serum ferritin concentrations**

It is recommended that serum ferritin concentrations be monitored regularly (every two to three months) to assess the long-term effectiveness of the chelation regimen in controlling the body iron load. Interruption of therapy with Ferriprox should be considered if serum ferritin measurements fall below 500 µg/L.

### **Plasma Zn<sup>2+</sup>**

Monitoring of plasma Zn<sup>2+</sup>, and supplementation in case of a deficiency is recommended.

## **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**

Due to the unknown mechanism of Ferriprox-induced neutropenia, patients should not take medicinal products known to be associated with neutropenia or those that can cause agranulocytosis.

Interactions between Ferriprox and other medicinal products have not been reported. However, since this compound binds to some metallic cations, the potential exists for interactions between Ferriprox and trivalent cation-dependent medicinal products such as aluminium-based antacids. Therefore, it is not recommended to concomitantly ingest aluminium-based antacids with Ferriprox.

The safety of concurrent use of Ferriprox and vitamin C has not been formally studied. Based on the reported adverse interaction that can occur between desferrioxamine and vitamin C, caution should be used when administering concurrent Ferriprox and vitamin C.

Studies in vitro and in animals suggest that Ferriprox does not increase the risk of opportunistic *yersinia* infections in iron overload conditions.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

### Effects on fertility

No effect on fertility or early embryonic development, and no effect on reproductive performance were noted in naive (non-iron-loaded) male and female rats that received deferiprone orally at 75 mg/kg twice daily (0.3 times the clinical dose based on body surface area) for 28 days (males) or 2 weeks (females) prior to mating and until termination (males) or through early gestation (females).

Atrophy of the testis was reported at oral doses of greater than or equal to 400 mg/kg/day in non-iron-loaded dogs, corresponding to about 3 times the recommended initial human dose of 75 mg/kg/day, based on body surface area.

### Use in pregnancy

Category D

Reproductive studies in non-iron-loaded rats and rabbits have indicated that Ferriprox is teratogenic and embryotoxic at doses corresponding to human-equivalent doses (on a body surface area basis) considerably below the recommended daily dose in patients.

Women of childbearing potential should be advised to avoid pregnancy due to the potential mutagenic, clastogenic and teratogenic properties identified in pre-clinical studies with Ferriprox. Women should be counselled to take contraceptive measures and should be advised to immediately stop taking Ferriprox should they become pregnant or plan to become pregnant.

### Use in lactation

There is no relevant data on the use of Ferriprox in nursing mothers. No perinatal/post-natal reproductive studies have been conducted in animals. Ferriprox should not be used in nursing mothers.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There is no evidence that Ferriprox affects the ability of patients to drive or use machines.

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse effect information for Ferriprox represents the pooled data collected from 590 subjects with chronic iron overload secondary to transfusion-dependent anemias, primarily subjects with thalassaemia major, who participated in single arm or active-controlled clinical studies.

System Organ Class (MedDRA classification)	VERY COMMON (≥1/10)	COMMON (≥1/100 to 1/10)	UNCOMMON (≥1/1,000 to 1/100)
Blood and Lymphatic System Disorders	None	Agranulocytosis, Neutropenia	Blood Disorder, Hypersplenism, Leukopenia, Thrombocytopenia
Cardiac Disorders	None	None	Arrhythmia, Torsade de Pointes
Ear and Labyrinth Disorders	None	None	Deafness, Ear Pain, Tinnitus, Vertigo

System Organ Class (MedDRA classification)	VERY COMMON (≥1/10)	COMMON (≥1/100 to 1/10)	UNCOMMON (≥1/1,000 to 1/100)
Gastrointestinal Disorders	Nausea, Vomiting	Abdominal Discomfort, Abdominal Pain, Abdominal Pain Upper, Diarrhoea, Dyspepsia	Abdominal Distension, Abdominal Pain Lower, Aphthous Stomatitis, Constipation, Epigastric Discomfort, Eructation, Gastritis, Reflux Oesophagitis, Stomach Discomfort
General Disorders and Administration Site Conditions	None	Oedema Peripheral	Asthenia, Chest Pain, Discomfort, Fatigue, Influenza Like Illness, Malaise, Pyrexia, Thirst
Hepatobiliary Disorders	None	None	Hepatic Pain, Hepatitis, Hepatomegaly, Jaundice, Liver Tenderness
Immune System Disorders	None	None	Hypersensitivity
Infections and Infestations	None	None	Cytomegalovirus Hepatitis, Diabetic Foot Infection, Gastroenteritis, Gastroenteritis Viral, Influenza, Nasopharyngitis, Sepsis, Upper Respiratory Tract Infection, <i>Yersinia</i> Infection
Injury, Poisoning and Procedural Complications	None	None	Epicondylitis, Transfusion Reaction
Investigations	None	Alanine Aminotransferase Increased, Aspartate Aminotransferase Increased, Neutrophil Count Decreased, Weight Increased, White Blood Cell Count Decreased	Blood Bilirubin Increased, Blood Creatinine Increased, Blood Lactate Dehydrogenase Increased, Blood Phosphorus Increased, Blood Zinc Decreased, Electrocardiogram T Wave Inversion, Gamma-Glutamyltransferase Increased, Hepatic Enzyme Increased, Platelet Count Decreased, Platelet Count Increased, Weight Decreased
Metabolism and Nutrition Disorders	None	Anorexia, Increased Appetite	Decreased Appetite, Fluid Retention



System Organ Class (MedDRA classification)	VERY COMMON (≥1/10)	COMMON (≥1/100 to 1/10)	UNCOMMON (≥1/1,000 to 1/100)
Musculoskeletal and Connective Tissue Disorders	Arthralgia	Arthropathy, Back Pain, Joint Swelling, Pain In Extremity	Arthritis, Bone Pain, Joint Crepitation, Joint Effusion, Joint Range Of Motion Decreased, Joint Stiffness, Metatarsalgia, Muscle Spasms, Muscular Weakness, Musculoskeletal Chest Pain, Musculoskeletal Pain, Myalgia, Polyarthritis, Synovial Cyst
Nervous System Disorders	None	Headache	Dizziness, Hypogeusia, Migraine, Somnolence
Renal and Urinary Disorders	Chromaturia (red/brown)	None	Pollakiuria
Reproductive System and Breast Disorders	None	None	Amenorrhoea, Menstruation Irregular
Respiratory, Thoracic and Mediastinal Disorders	None	None	Asthma, Dry Throat, Oropharyngeal Pain
Skin and Subcutaneous Tissue Disorders	None	None	Alopecia, Hyperhidrosis, Pruritus, Rash, Rash Generalised, Rash Pruritic, Skin Hypopigmentation, Urticaria, Xeroderma

Gastrointestinal effects are more frequent at the beginning of therapy with Ferriprox and most resolve within a few weeks without the discontinuation of treatment. In some patients it may be beneficial to reduce the dose of Ferriprox and then scale it back up to 25 mg/kg three times per day.

Arthropathy events ranged from mild pain in one or more joints to severe arthritis with effusion and significant disability. Mild arthropathies are generally transient.

Increased ALT levels have been reported in some patients taking Ferriprox. This increase, which occurred most frequently during the first 3 months of therapy, was generally mild, and resolved either without discontinuation or after decreasing the dosage of Ferriprox in the majority of patients.

Some patients experienced progression of liver fibrosis associated with an increase in iron overload or hepatitis C. Special care must be taken to ensure that iron chelation in patients with hepatitis C is optimal. In these patients, careful monitoring of liver histology is recommended.

Low plasma zinc levels have been associated with Ferriprox, in a minority of patients. The levels normalised with oral zinc supplementation.

### Postmarketing experience

The following adverse experiences have been reported in patients receiving Ferriprox worldwide since its first market authorisation in 1999. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or to establish a causal relationship to drug exposure.

### **Blood and lymphatic system disorders**

Agranulocytosis and mild/moderate neutropenia, febrile neutropenia, thrombocytopenia, thrombocythemia, leukopenia, granulocytopenia, pancytopenia.

### **Cardiac disorders**

Atrial fibrillation, cardiac disorder, cardiac failure congestive cardiac failure, sinus tachycardia.

### **Congenital, familial and genetic disorders**

Congenital anomaly, hypospadias, non acute porphyria.

### **Eye disorders**

Diplopia, papilloedema, eye movement disorder, periorbital oedema, retinal toxicity visual impairment.

### **Gastrointestinal disorders**

Cecitis, enterocolitis, rectal haemorrhage, gastric ulcer, vomiting, nausea, diarrhoea, abdominal pain, stomatitis, pancreatitis, dysphagia, parotid gland enlargement.

### **General disorders and administration site conditions**

Asthenia, chills, difficulty in walking, face oedema, hyperpyrexia, pyrexia, fatigue, oedema peripheral, multi-organ failure.

### **Hepatobiliary disorders**

Hepatic function abnormal, jaundice, hepatomegaly.

### **Immune system disorders**

Anaphylactic shock, hypersensitivity.

### **Infections and infestations**

Cryptococcal cutaneous infection, encephalitis enteroviral, neutropenic sepsis, parapharyngeal abscess, *yersinia* infection, bacterial infection, septic shock, pneumonia, infection, sepsis, parapharyngeal abscess, furuncle, subcutaneous abscess, tonsillitis urinary tract infection.

### **Investigations**

Anti-HBs antibody positive, blood arsenic increased, blood bilirubin increase, haemoglobin decrease, alanine aminotransferase increased, aspartate aminotransferase increased, blood corticotrophin decreased, blood cortisol decreased, hepatic enzymes increased, neutrophil count decreased, urine colour abnormal.

### **Metabolism and nutrition disorders**

Metabolic disorders, dehydration.

### **Musculoskeletal and connective tissue disorders**

Arthralgia, arthritis, bone pain, joint effusion, joint swelling pain in extremity, chondropathy, osteoarthritis, myositis polyarthritis.

### **Neoplasms benign, malignant and unspecified (including cysts and polyps)**

Hepatic neoplasm malignant.

### **Nervous system disorders**

Cerebellar syndrome, cerebral haemorrhage, convulsion, coordination abnormal, dystonia, febrile convulsion, hypotonia, intracranial pressure increased, nystagmus, psychomotor skills impaired, headache, depressed level of consciousness, dizziness, balance disorder.

### **Pregnancy, puerperium and perinatal conditions**

Intra-uterine death.

### **Psychiatric disorders**

Depression, obsessive-compulsive disorder.

### **Renal and urinary disorders**

Renal failure, haemoglobinuria, glycosuria, chromaturia.

### **Reproductive system and breast disorders**

Balanitis.

### **Respiratory, thoracic and mediastinal disorders**

Respiratory acidosis, haemoptysis, dyspnoea, lung disorder, pulmonary embolism, epistaxis, oropharyngolaryngeal pain, pharyngeal erythema.

### **Skin, subcutaneous tissue disorders**

Photosensitivity reaction, pruritus, urticaria, rash erythematous, rash, Henoch-Schonlein purpura, rash maculo-papular.

### **Vascular disorders**

Hypotension, hypertension.

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at <http://www.tga.gov.au/reporting-problems>.

## **4.9 OVERDOSE**

### **Acute toxicity and symptoms**

There have been no reports of acute overdose with Ferriprox.

Neurological disorders (such as cerebellar symptoms, diplopia, lateral nystagmus, psychomotor slowdown, hand movements and axial hypotonia) have been observed in children who had been voluntarily prescribed approximately 3 times the maximum recommended dose for several years. The neurological disorders progressively regressed after Ferriprox discontinuation.

### **Management and treatment**

In case of overdosage, close clinical supervision of the patient is required.

**For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).**

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

#### Mechanism of action

Deferiprone is an orally active synthetic bidentate iron (III) chelator ( $pK_{Fe^{3+}}=19.4$ ) that forms a 3:1 (deferiprone iron) complex. Deferiprone is uncharged at physiological pH and is rapidly absorbed from the gut. Deferiprone has been shown to mobilise iron from primary cultures of cells derived from organs affected clinically by iron overload, including cardiomyocytes, hepatocytes and reticuloendothelial cells.

#### Clinical trials

In a randomised study (LA-01), the efficacy of Ferriprox (25 mg/kg three times per day) was compared with desferrioxamine (50 mg/kg/day, 4 to 7 times/week) in the treatment of iron overload in patients with thalassaemia major for about two years. There were 35 patients in the Ferriprox group and 36 in the desferrioxamine group. At the completion of the second year of the study, no significant change from baseline was observed in serum ferritin concentration or hepatic iron concentration of patients treated with either therapy. The power to detect a 20% difference in serum ferritin or hepatic iron concentration between groups was less than 80% due to the variability of the data and a relatively small sample size.

An uncontrolled multicentre prospective iron chelation study (LA-02) was performed in 187 transfusion-dependent thalassaemia patients over a year. Patients were aged  $\geq 10$  years and had previously been regularly chelated with desferrioxamine. Ferriprox 25 mg/kg orally three times per day was not associated with an increase in body iron stores (as assessed by serum ferritin) after changing from desferrioxamine.

On completion of the study, 84 patients continued Ferriprox treatment in an extension study (LA-06) for a total treatment duration of 4 years. Ferriprox maintained stable body iron stores.

In a randomised, open-label, parallel-group trial (LA-16) in patients with thalassaemia major who had received chelation therapy with desferrioxamine for at least 5 years, 29 patients were switched to Ferriprox and 31 remained on desferrioxamine. Subjects were aged 18 to 35 years. The mean dose of Ferriprox was 92 mg/kg/day and desferrioxamine 43 mg/kg/day (mean 5.7 days per week in the case of desferrioxamine). After 12 months, there were no significant differences between Ferriprox and desferrioxamine in reduction in serum ferritin or liver iron concentration.

### 5.2 PHARMACOKINETIC PROPERTIES

#### Absorption

Deferiprone is rapidly absorbed from the upper part of the gastro-intestinal tract.

Peak serum concentration is reported to occur 45 to 60 minutes following a single dose in fasted patients. This may be extended to 2 hours in fed patients.

Following a dose of 25 mg/kg, lower peak serum concentrations have been detected in patients in the fed state (85  $\mu\text{mol/L}$ ) than in the fasting state (126  $\mu\text{mol/L}$ ), although there was no decrease in the amount of substance absorbed when given with food.

#### Distribution

The protein binding of deferiprone is low ( $<10\%$ ). Following oral administration of deferiprone, the volume of distribution is at least 1.73 L/kg in thalassaemia patients.

#### Metabolism

Deferiprone is cleared from plasma by metabolism, predominantly to a glucuronide metabolite. The rate of clearance has not been determined. The glucuronide metabolite lacks iron binding capacity

because of inactivation of the 3-hydroxy group of deferiprone. Peak concentrations of the glucuronide metabolite occur 2 to 3 hours after administration of deferiprone.

## **Excretion**

In humans, deferiprone is eliminated mainly via the kidneys with reports of 75% to 90% of the ingested dose being recovered in the urine in the first 24 hours, mainly in the form of the glucuronide metabolite and the iron-deferiprone complex. Only 5% of an administered dose of deferiprone is excreted unchanged in the urine. A variable amount of elimination into the faeces has been reported. The elimination half-life in most patients is 2 to 3 hours.

## **5.3 PRECLINICAL SAFETY DATA**

### **Genotoxicity**

The genotoxic potential of deferiprone was evaluated in a set of *in vitro* and *in vivo* tests. Deferiprone was shown to be clastogenic in mouse micronucleus assays, as well as mutagenic and clastogenic *in vitro* in mammalian cells. Deferiprone was non-mutagenic in the bacterial reverse mutation assay.

A comparative study on the assessment of lymphocyte clastogenicity in patients with thalassaemia treated with deferiprone or with desferrioxamine did not show a significant difference in chromosomal aberration frequency between the two therapies.

### **Carcinogenicity**

The carcinogenic potential of deferiprone has not been adequately investigated in long-term animal studies. In view of the genotoxicity results a carcinogenic potential of deferiprone cannot be excluded.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 LIST OF EXCIPIENTS**

Refer to Section 2 – Qualitative and quantitative composition.

### **6.2 INCOMPATIBILITIES**

Refer to Section 4.5 – Interactions with other medicines and other forms of interactions.

### **6.3 SHELF LIFE**

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG).

#### **500 mg film-coated tablet**

The expiry date can be found on the packaging.

#### **1000 mg film-coated tablet**

The expiry date can be found on the packaging. After first opening, use within 50 days.

#### **100 mg/mL oral solution**

The expiry date can be found on the packaging. After first opening, store at 2°C to 8°C (Refrigerate. Do not freeze). Use within 35 days.

### **6.4 SPECIAL PRECAUTIONS FOR STORAGE**

#### **500 mg film-coated tablet**

Store below 25°C.

### 1000 mg film-coated tablet

Store below 30°C. Keep the bottle tightly closed in order to protect from moisture.

### 100 mg/mL oral solution

Store below 30°C. Protect from light.

## 6.5 NATURE AND CONTENTS OF CONTAINER

### 500 mg film-coated tablet

Bottle (HDPE bottle with child resistant cap) of 100 tablets (AUST R 93946).

### 1000 mg film-coated tablet

Bottle (HDPE bottle with child resistant cap) of 50 tablets (AUST R 280204).

### 100 mg/mL oral solution

Bottle (round amber PET bottles with white polypropylene child resistant caps) of 250 mL and one graduated 30 mL plastic dosing cup (AUST R 125665).

Bottle (round amber PET bottles with white polypropylene child resistant caps) of 500 mL and one graduated 30 mL plastic dosing cup (AUST R 125666).

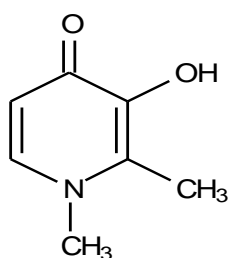
Not all pack sizes may be available.

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

## 6.7 PHYSICOCHEMICAL PROPERTIES

### Chemical structure



### Chemical name

3-hydroxy-1,2-dimethyl-4(1H)-pyridone

### Molecular formula

C<sub>7</sub>H<sub>9</sub>NO<sub>2</sub>

### Molecular weight

139.15

### CAS number

30652-11-0

## **7 MEDICINE SCHEDULE (POISONS STANDARD)**

S4 – Prescription Only Medicine.

## **8 SPONSOR**

Apotex Pty Ltd

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Macquarie Park NSW 2113

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## **9 DATE OF FIRST APPROVAL**

9 April 2003

## **10 DATE OF REVISION**

21 March 2018

### **SUMMARY TABLE OF CHANGES**

<b>Section Changed</b>	<b>Summary of new information</b>
<b>All</b>	Reformatted product information. Minor editorial changes.
<b>2</b>	Updated ingredient names in line with new terminology.