NEW ZEALAND DATA SHEET
FERRIPROX
Deferiprone 500 mg tablet
Deferiprone 1000 mg tablet
Deferiprone 100 mg/mL oral solution

1. PRODUCT NAME

Ferriprox®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Deferiprone 500 mg film-coated tablets
Deferiprone 1000 mg film-coated tablets
Deferiprone 100 mg/mL oral solution

Excipients of known effect
Ferriprox tablets and Ferriprox oral solution are lactose and gluten free.
Ferriprox oral solution contains sucralose and the colorant sunset yellow FCF.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

500 mg film-coated tablets

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

The tablets are breakable in half.

1000 mg film-coated tablets

Ferriprox 1000 mg tablets are white to off white, capsule-shaped, film-coated, scored and imprinted "APO" bisect "1000" on one side, 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 therapy or in whom desferrioxamine therapy has proven ineffective.

4.2 Dose and method of administration

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

Ferriprox is given as 25 mg/kg body weight, orally, three times a day for a total daily dose of 75 mg/kg body weight. The dose was not developed through a formal dose finding study, but rather through literature evaluation and assessment of an effective dose to produce iron excretion equivalent to the transfusional input. Dosage per kilogram body weight should be calculated to the nearest half tablet or to the nearest 2.5 mL. See Dosage Table below.

Dosage table

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

Body Weight (kg)	**Total Daily Dose (mg)**	**Dose (mg, three times/day)**	**500 mg film-coated tablets**	**100 mg/mL oral solution**
			Number of tablets (three times/day)	**mL (three times/day)**
20	1500	500	1.0	5.0
30	2250	750	1.5	7.5
40	3000	1000	2.0	10.0
50	3750	1250	2.5	12.5
60	4500	1500	3.0	15.0
70	5250	1750	3.5	17.5
80	6000	2000	4.0	20.0
90	6750	2250	4.5	22.5

Dosage table for Ferriprox 1000 mg tablets

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

Due to the nature of the serious adverse events, which can occur with the use of deferiprone, special monitoring is required for all patients. Treatment with deferiprone 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 (refer section 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

Deferiprone may be associated with significant toxicity and data available on the efficacy and safety of the drug are limited. Therefore, deferiprone should only be used in patients who cannot tolerate desferrioxamine therapy or in whom desferrioxamine therapy has proven ineffective.

Neutropenia/agranulocytosis

Deferiprone has been shown to cause neutropenia, including agranulocytosis. It is recommended that a patient's absolute neutrophil count be monitored every week.

In clinical trials, this has been effective in identifying cases of neutropenia and agranulocytosis. Neutropenia and agranulocytosis resolved once therapy was withdrawn. If the patient develops an infection, deferiprone therapy should be interrupted and the absolute neutrophil count 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 deferiprone treatment.

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

In the event of neutropenia:
Instruct the patient to immediately discontinue deferiprone 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, white blood cell count, absolute neutrophil count, and a platelet 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, white blood cell count, neutrophil and platelet counts 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 contra-indicated.

Renal or hepatic impairment and liver fibrosis

Renal impairment
Currently, there are no available data in patients with renal impairment. Since deferiprone 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.

Hepatic impairment
There are limited data on the safety and efficacy of deferiprone in patients with hepatic impairment. Deferiprone is metabolized 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.

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

Cardiac function
Studies on cardiac iron concentrations suggest that deferiprone may protect the heart against the toxicity of iron overload.

Patient monitoring
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 deferiprone should be considered if serum ferritin measurements fall below 500 µg/L.

Plasma Zn^{2+}
A monitoring of plasma Zn^{2+}, as well as supplementation in case of a deficiency is recommended.

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

Discoloration of urine
Patients should be informed that a reddish/brown discoloration of the urine is commonly associated with deferiprone use which is reported to be due to the excretion of the iron-deferiprone complex, which is a chromophore.

Neurological disorders
Neurological disorders have been observed in children treated with more than 2.5 times the maximum recommended dose for several months but have also been observed with

standard doses of deferiprone in patients with mild or normal iron load. Prescribers are reminded that the dose should be adjusted to the severity of the iron load and that the use of doses above 100 mg/kg/day is not recommended. Deferiprone use should be discontinued if neurological disorders are observed (see section 4.8).

Use in children

Limited data are available on the use of deferiprone in children between 2-10 years of age. The effects of deferiprone on growth are unknown.

4.5 Interactions with other medicines and other forms of interactions

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

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

The safety of concurrent use of deferiprone 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 deferiprone and vitamin C.

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

4.6 Fertility, pregnancy and lactation

Fertility

No animal studies to evaluate the potential effects of deferiprone on fertility have been conducted.

Pregnancy (Category D)

Reproductive studies in non-iron-loaded rats and rabbits have indicated that deferiprone is teratogenic and embryotoxic at doses giving systemic exposures (on a body surface area basis) considerably below those observed in patients at the recommended dose.

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 deferiprone. Women should be counselled to take contraceptive measures and should be advised to immediately stop taking deferiprone should they become pregnant or plan to become pregnant.

Breast-feeding

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The adverse reactions most commonly reported during therapy with deferiprone in clinical trials were nausea, vomiting, abdominal pain, and arthralgia, which were reported in more than 10% of patients. The most serious adverse reaction reported in clinical trials with deferiprone was agranulocytosis, defined as an absolute neutrophil count of less than 0.5 x 10^9/L, which occurred in approximately 1% to 2% of patients. Less severe episodes of neutropenia were reported in approximately 6% of patients.

List of adverse reactions
The very common (greater than or equal to 10%) and common (1% to <10%) adverse reactions to deferiprone were:

Infections and infestations
Common: *flu syndrome (1%)*

Blood and lymphatic system disorders:
Common: *neutropenia (neutrophils <1.5 x 10^9/L) (6%), agranulocytosis (2%), thrombocytopenia (1%)*

Metabolism and nutrition disorders:
Common: *increased appetite (3%), anorexia (1%)*

Nervous system disorders:
Common: *headache (2%), dizziness (1%), somnolence (1%)*

Gastrointestinal disorders:
Very common: *nausea (15%), vomiting (13%), abdominal pain (11%)*
Common: *dyspepsia (3%), diarrhoea (2%)*

Hepatobiliary disorders
Common: *liver tenderness (1%)*

Skin and subcutaneous tissue disorders:
Common: *pruritus (1%), urticaria (1%)*

Musculoskeletal and connective tissue disorders:
Very Common: *arthralgia (12%)*
Common: *arthrosis (3%), back pain (2%), arthritis (1%), bone pain (1%)*

General disorders and administration site conditions:
Common: *asthenia (1%), pain (3%), peripheral edema (1%)*

Investigations:
Common: *increased ALT values (6%)*

Description of selected adverse reactions
The most serious undesirable effect of therapy reported in clinical trials with deferiprone is agranulocytosis (neutrophils <0.5x10^9/L) with an incidence of 1 to 2 % (0.9 cases per 100 patient-years of treatment). The observed incidence of the less severe form of

neutropenia (neutrophils <1.5x10^9/L) is 6% (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.

Arthropathies have been reported in patients treated with deferiprone. These events ranged from mild pain in one or more joints to severe arthritis. Most patients recover despite continuing therapy.

Gastrointestinal effects include: nausea, vomiting, abdominal pain and increased appetite. These effects are more frequent at the beginning of therapy with deferiprone and most resolve within a few weeks without the discontinuation of treatment. In some patients it may be beneficial to reduce the dose of deferiprone and then scale it back up to 25 mg/kg three times per day.

Increased ALT values have been reported in some patients taking deferiprone. In the majority of these patients this increase was asymptomatic and transient, and their ALT values returned to baseline without discontinuation or decreasing the dose of deferiprone.

Some patients experienced progression of liver fibrosis associated with an increase in iron overload or hepatitis C.

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

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 more than 2.5 times the maximum recommended dose of 100 mg/kg/day for several months. Episodes of hypotonia, instability, inability to walk, and hypertonia with inability of limb movement, have been reported in children in the post-marketing setting with standard doses of deferiprone. The neurological disorders progressively regressed after deferiprone discontinuation (see section 4.4).

Post-marketing experience

No information available.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

Acute toxicity and symptoms

There have been no reports of acute overdose with deferiprone.

Management and treatment

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

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

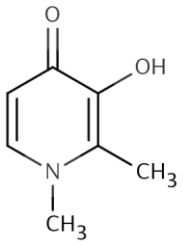
Pharmacotherapeutic group: Iron chelating agent, ATC code: V03AC02

Deferiprone is a white to off-white powder with a melting range of 272°C to 278°C. Deferiprone does not show stereoisomerism.

Deferiprone is sparingly soluble in water, very slightly soluble in acetone and slightly soluble in methanol.

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

Structural Formula



Molecular Formula: $C_7H_9NO_2$

Molecular weight: 139.15

CAS Registry Number: 30652-11-0

Deferiprone is an orally active synthetic bidentate iron chelator that binds to iron in a 3:1 molar ratio.

Clinical studies have demonstrated that deferiprone is effective in promoting iron excretion and can lower serum ferritin levels and tissue iron stores in transfusion-dependent thalassaemia patients. The precise mechanism by which deferiprone is effective in promoting iron excretion and preventing the progression of iron accumulation is unknown. The magnitude of the response is in general directly dependent on the dose of deferiprone, the patients' initial body iron load and their ongoing transfusional requirements.

Clinical trials

Deferiprone has been investigated in 356 patients participating in sponsored clinical trials and a compassionate use programme between 1993 and 2002. Serum ferritin was a common efficacy criterion in the studies

A multicentre prospective iron chelation study (LA-02) was performed on 187 transfusion-dependent thalassaemia patients over a year. The results indicated that Ferriprox at

25 mg/kg three times per day can prevent the progression of body iron load as assessed by serum ferritin, in transfusion-dependent thalassaemia patients previously regularly chelated with desferrioxamine. In this study, a high level of compliance (mean compliance=94%) with the oral iron chelator was observed in this cohort of patients.

On completion of this study, some patients with transfusion-dependent thalassaemia continued treatment and intensive monitoring of their body iron load under another study protocol (LA-06). Eighty-four patients continued to be monitored weekly for four years after their enrolment and had not received any iron chelator other than deferiprone during this period of time. Results from this study demonstrate that under regular monitoring conditions, Ferriprox has a favourable benefit/risk ratio in the treatment of iron overload in patients with transfusion-dependent thalassaemia. No new adverse reactions were observed.

Nausea and/or vomiting were the next most common adverse reactions, reported in 15% and 13% of patients respectively. Neutropenia, defined as a confirmed absolute neutrophil count of between 0.5 and 1.5 x 10^9/L, was observed in 6% of patients. Resolution occurred within 2 weeks to 2 months. Agranulocytosis, defined as a confirmed absolute neutrophil count of less than 0.5 x 10^9/L, was observed in three (0.8%) patients.

The safety and efficacy of Ferriprox (25 mg/kg three times per day) and desferrioxamine (50 mg/kg/day, 4 to 7 times/week) in the treatment of iron overload in patients with thalassaemia major were compared in a randomised study for about two years. At the completion of the second year of the study, no significant change from baseline was observed in the serum ferritin values or in the 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.

A hepatic histology study was commissioned by the Deferiprone International Safety Monitoring Committee to ensure the safety of the patients participating in the clinical trials for the development of deferiprone. The major question addressed was whether chronic treatment with deferiprone was associated with any evidence for hepatotoxicity or worsening of liver fibrosis. Three pathologists performed a blinded assessment of the largest collection of liver biopsies reported to date in patients receiving deferiprone. The histopathological findings confirm the results of several other smaller studies and demonstrate that there is no evidence of progressive fibrosis in patients with thalassaemia while on long-term deferiprone therapy.

5.2 Pharmacokinetics 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 micromol/L) than in the fasting state (126 micromol/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 1.6 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.

Elimination
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

The most common effects of deferiprone in non-clinical studies were haematological effects (most notably bone marrow hypocellularity and decreased white and red blood cell count) and atrophy of lymphoid tissues. These changes were observed at animal systemic exposures to deferiprone (based on AUC or body surface area) similar to, or below those observed in humans at the recommended clinical dose.

Carcinogenicity/mutagenicity
The genotoxic potential of deferiprone was evaluated in a set of *in vitro* and *in vivo* tests (non-iron-loaded models). Deferiprone was non-mutagenic in the bacterial reverse mutation assay, however, it did display genotoxic characteristics in non-iron-loaded *in vitro* and *in vivo* systems. No data on the carcinogenic properties are available. However, in view of the genotoxicity results, a carcinogenic potential of deferiprone cannot be excluded.

A comparative study on the assessment of lymphocyte clastogenicity in patients with thalassaemia treated with deferiprone or with desferrioxamine indicated that deferiprone is not associated with greater frequency of chromosomal aberrations than that observed during therapy with desferrioxamine. This study showed that deferiprone had no greater clastogenicity activity than that of desferrioxamine, in humans.

Atrophy of the testis was reported at oral doses of ≥400 mg/kg/day (corresponding to a systemic exposure, based on body surface area, about 3 times the human exposure at the recommended clinical dose) in non-iron-loaded dogs.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ferriprox 500 mg film-coated tablets contain the following excipients:
- Microcrystalline cellulose
- Magnesium stearate
- Silicon dioxide
- Hypromellose
- Macrogol 3350
- Titanium dioxide

Ferriprox 1000 mg film-coated tablets contain the following excipients:
- Methylcellulose
- Crospovidone
- Magnesium stearate
- Hypromellose
- Hyprolose
- Macrogol 8000
- Titanium dioxide

Ferriprox oral solution contains the following excipients:
- Purified water
- Hyetellose
- Glycerol
- Hydrochloric acid (for pH adjustment)
- Artificial cherry flavour
- Peppermint oil
- Sunset yellow FCF
- Sucralose

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.

6.2 Incompatibilities

Not applicable

6.3 Shelf-Life

Ferriprox 500 mg film-coated tablets: 5 years from the date of manufacture.

Ferriprox 1000 mg film-coated tablets: 4 years from the date of manufacture. After first opening, use within 50 days.

Ferriprox oral solution: 3 years from the date of manufacture. After first opening, use within 35 days

6.4 Special precautions for storage

Ferriprox 500 mg film–coated tablets: Store below 25°C.

Ferriprox 1000 mg film-coated tablets: Store below 30°C. Keep the bottle tightly closed in order to protect from moisture.

Ferriprox oral solution: Store below 30°C. Protect from light. After first opening, store at 2°C to 8°C (Refrigerate. Do not freeze).

6.5 Nature and contents of container

Ferriprox 500 mg film-coated tablets are available in HDPE containers of 100 tablets with child resistant closures.

Ferriprox 1000 mg film coated tablets are available in HDPE containers of 50 tablets with child resistant closures.

Ferriprox oral solution is available in 250 mL and 500 mL round amber polyethylene terephthalate (PET) bottles with white polypropylene child resistant pictorial caps. Each pack contains one bottle and one graduated plastic dosing cup.

Not all strengths and pack sizes may be available

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Chiesi New Zealand Ltd
Bellingham Wallace Ltd
Suite 1, 470 Parnell Road
Parnell
Auckland 1052

Phone number: 09 951 3003
Email: medinfo.au@chiesi.com
Website: https://www.chiesi.com.au/contact-us/

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9. DATE OF FIRST APPROVAL

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10. DATE OF REVISION OF THE TEXT

3 March 2026

Summary table of changes

Section changed	Summary of new information
General	Editorial changes throughout
8	Update to contact details