

KELFER Capsules (Deferiprone)

Composition

KELFER-250 Capsules

Each capsule contains Deferiprone 250 mg

KELFER-500 Capsules

Each capsule contains Deferiprone 500 mg

Dosage Form

Capsules

Pharmacology

► Pharmacodynamics

Deferiprone (L1) is an oral iron chelating agent belonging to the group of hydroxypyridones. Deferiprone forms neutral complexes with iron at physiological pH. It mobilizes iron from the iron storage proteins ferritin and haemosiderin; and from iron saturated transferrin and lactoferrin, but not from haemoglobin and myoglobin. The water soluble complex of iron formed is rapidly excreted in the urine thus reducing pathological iron deposits in organs and tissues.

► Pharmacokinetics

Absorption

Deferiprone is rapidly absorbed from the upper part of the gastrointestinal 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 deferiprone absorbed when it was given with food.

Biotransformation

Deferiprone is metabolised predominantly to a glucuronide conjugate. This metabolite lacks iron-binding capability due to inactivation of the 3-hydroxy group of deferiprone. Peak serum concentrations of the glucuronide occur 2 to 3 hours after administration of deferiprone.

Elimination

In humans, deferiprone is eliminated mainly via the kidneys; 75% to 90% of the ingested dose is reported as being recovered in the urine in the first 24 hours, in the form of free deferiprone, the glucuronide metabolite and the iron-deferiprone complex. A variable amount of elimination via the faeces has been reported. The elimination half-life in most patients is 2 to 3 hours.

Indications

KELFER is indicated in transfusion haemosiderosis, especially in cases of thalassaemia, other haemolytic anaemias, aplastic anaemia and myelodysplastic syndromes, acute iron poisoning, siderosis associated with liver cirrhosis and for the diagnosis of iron-storage diseases.

Dosage And Administration

In adults and children the optimum dose of KELFER to achieve a negative iron balance is 75 mg/kg/day to be administered in 2-4 divided doses. In some patients a lesser dose of 50 mg/kg/day may be adequate while in others the dose may be increased to 100 mg/kg/day.

A total daily dose above 100 mg/kg body weight is not recommended because of the potentially increased risk of adverse reactions.

The effect of deferiprone in decreasing the body iron is directly influenced by the dose and the degree of iron overload. After starting deferiprone 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 the 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 therapy with deferiprone should be considered if serum ferritin measurements fall below 500 µg/l.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

History of recurrent episodes of neutropenia.

History of agranulocytosis.

Pregnancy

Breastfeeding

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

Warnings And Precautions

Neutropenia/Agranulocytosis

Deferiprone has been shown to cause neutropenia, including agranulocytosis. The patient's neutrophil count should be monitored every week.

In clinical trials, weekly monitoring of the neutrophil count has been effective in identifying cases of neutropenia and agranulocytosis. Neutropenia and agranulocytosis resolved once therapy was withdrawn. If the patient develops an infection while on deferiprone, therapy should be interrupted and the 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 and flu-like symptoms.

Suggested management of 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. The risk of agranulocytosis and neutropenia is higher if the baseline absolute neutrophil count (ANC) is less than $1.5 \times 10^9/l$.

In the event of neutropenia:

Instruct the patient to immediately discontinue deferiprone and all other medicinal products with a potential to cause neutropenia. The patient should be advised to limit contact with other individuals in order to reduce the risk of infection. Obtain a complete blood cell (CBC) count, with a white blood cell (WBC) count, corrected for the presence of nucleated red blood cells, a neutrophil count, and a platelet count immediately upon diagnosing the event and then repeat daily. It is recommended that following recovery from neutropenia, weekly CBC, WBC, 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 concurrently with the neutropenia, the appropriate cultures and diagnostic procedures should be performed and an appropriate therapeutic 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 condition resolves. Provide protective isolation and if clinically indicated, admit patient to the hospital.

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

Plasma Zn²⁺ concentration

Monitoring of plasma Zn²⁺ concentration, and 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 can be associated with neutropenia and agranulocytosis, therapy in immune compromised patients should not be initiated unless potential benefits outweigh potential risks.

Renal or hepatic impairment and liver fibrosis

There are no data available on the use of deferiprone in patients with renal or hepatic impairment. Since deferiprone is eliminated mainly via the kidneys, there may be an increased risk of complications in patients with impaired renal function. Similarly, as deferiprone is metabolised in the liver, caution must be exercised in patients with hepatic dysfunction. Renal and hepatic function should be monitored in this patient population during deferiprone therapy. If there is a persistent increase in serum alanine aminotransferase (ALT), interruption of deferiprone therapy should be considered.

In thalassaemia patients there is an association between liver fibrosis and iron overload and/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.

Discoloration of urine

Patients should be informed that their urine may show a reddish/brown discoloration due to the excretion of the iron-deferiprone complex.

Chronic overdose and neurological disorders

Neurological disorders have been observed in children treated with 2.5 to 3 times the recommended dose for several years. Prescribers are reminded that the use of doses above 100 mg/kg/day are not recommended.

▶ Drug Interactions

Due to the unknown mechanism of deferiprone-induced neutropenia, patients must 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 deferiprone binds to 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 and 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 deferoxamine and vitamin C, caution should be used when administering deferiprone and vitamin C concurrently.

► Pregnancy

There are no adequate data from the use of deferiprone in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Women of childbearing potential must be advised to avoid pregnancy due to the clastogenic and teratogenic properties of the medicinal product. These women should be counselled to take contraceptive measures and must be advised to immediately stop taking deferiprone if they become pregnant or plan to become pregnant.

► Lactation

It is not known whether deferiprone is excreted in human milk. No prenatal and postnatal reproductive studies have been conducted in animals. Deferiprone must not be used by breast-feeding mothers. If treatment is unavoidable, breast feeding must be stopped.

► Paediatric Use

There is no clinical experience of KELFER in children below two years of age. Therefore its use is not recommended.

Undesirable Effects

The most common adverse reactions reported during therapy with deferiprone in clinical trials were nausea, vomiting, abdominal pain, and chromaturia, 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 less than $0.5 \times 10^9/l$, which occurred in approximately 1% of patients. Less severe episodes of neutropenia were reported in approximately 5% of patients.

Adverse reaction frequencies: Very common ($\geq 1/10$), Common ($\geq 1/100$ to

SYSTEM ORGAN CLASS	VERY COMMON ($\geq 1/10$)	COMMON ($\geq 1/100$ to
Blood and lymphatic system disorders		Neutropenia Agranulocytosis
Metabolism and nutrition disorders		Increased Appetite
Nervous system disorders		Headache

Gastrointestinal disorders	Nausea Abdominal Pain Vomiting	Diarrhoea
Musculoskeletal and connective tissue disorders		Arthralgia
Renal and urinary disorders	Chromaturia	
General disorders and administration site conditions		Fatigue
Investigations		Increased liver enzymes

The most serious adverse reaction reported in clinical trials with deferiprone is agranulocytosis (neutrophils 9/l), with an incidence of 1.1% (0.6 cases per 100 patient-years of treatment). The observed incidence of the less severe form of neutropenia (neutrophils 9/l) is 4.9% (2.5 cases per 100 patient-years). This rate should be considered in the context of the underlying elevated incidence of neutropenia in thalassaemia patients, particularly in those with hypersplenism (See also Patient Monitoring).

Episodes of diarrhoea, mostly mild and transient, have been reported in patients treated with deferiprone. Gastrointestinal effects are more frequent at the beginning of therapy and resolve in most patients 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 the former dose. Arthropathy events, which ranged from mild pain in one or more joints to severe arthritis with effusion and significant disability, have also been reported in patients treated with deferiprone. Mild arthropathies are generally transient.

Increased levels of serum liver enzymes have been reported in some patients taking deferiprone. In the majority of these patients, the increase was asymptomatic and transient, and returned to baseline without discontinuation or decreasing the dose of deferiprone.

Some patients experienced progression of 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 years. The neurological disorders progressively regressed after deferiprone discontinuation.

Overdosage

No cases of acute overdose have been reported. However, 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 years. The neurological disorders progressively regressed after deferiprone discontinuation. In case of overdose, close clinical supervision of the patient is required.

Packaging Information

KELFER - 250 Capsules Container of 50 capsules

KELFER - 500 Capsules Container of 50 capsules

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KELFER Capsules

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