FERRIPROX™
Deferiprone
Delayed release enteric coated tablets
1000 mg

1. NAME OF THE MEDICINAL PRODUCT

Ferriprox 1,000 mg delayed release enteric coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1,000 mg deferiprone as active substance.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Delayed release enteric coated tablet

White to off-white, capsule-shaped, bevelled edge, biconvex coated tablets.
Engraved "FPX" score "DR" on one side, "APO" score "1000" on the other side.
The tablets are scored and breakable in half.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ferriprox is indicated for the treatment of iron overload in patients 1 year of age and older with thalassaemia major.

4.2 Posology and method of administration

For oral use.

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

Deferiprone is most commonly given at a total daily dose of 75 mg/kg body weight, divided into two doses taken approximately 12 hours apart with food. Dosage per kilogram body weight should be calculated to the nearest half tablet. See Table below.

Doses above 100 mg/kg/day are not recommended because of the potentially increased risk of adverse reactions (see sections 4.4, 4.8, and 4.9).

Due to the serious nature of agranulocytosis that can occur with the use of deferiprone, special monitoring is required for all patients. Caution must be used when the patient's absolute neutrophil count (ANC) is low.

Dose table

To obtain a dose of about 75 mg/kg/day, use the number of tablets suggested in the following table for the body weight of the patient. Sample body weights at 10 kg increments are listed.

Body weight (kg)	Total daily dose (mg)	Number of 1,000 mg delayed release enteric coated tablets*	
		Morning	Evening
20	1500	0.5	1.0
30	2250	1.0	1.5
40	3000	1.5	1.5
50	3750	2.0	2.0
60	4500	2.0	2.5
70	5250	2.5	3.0
80	6000	3.0	3.0
90	6750	3.5	3.5

*number of tablets rounded to nearest half tablet

The effect of Ferriprox in decreasing the body iron is directly influenced by the dose and the degree of iron overload. 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 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.

4.3 Contraindications

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

History of recurrent episodes of neutropenia.

History of agranulocytosis.

Pregnancy or breast-feeding (see section 4.6).

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 (see section 4.5).

4.4 Special warnings and special precautions for use

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.

In the event of neutropenia:
Instruct the patient to immediately discontinue deferiprone and all other medications 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, a rechallenge is contraindicated.

Carcinogenicity/mutagenicity
In view of the genotoxicity results, a carcinogenic potential of deferiprone cannot be excluded (see section 5.3).

Plasma Zn^{2+} concentration
Monitoring of plasma Zn^{2+} 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 end stage renal disease or severe hepatic impairment (see section 5.2). Caution must be exercised in patients with end stage renal disease or severe hepatic dysfunction. Renal and hepatic function should be

monitored in these patient populations 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.

QT prolongation

No significant inhibition of hERG K+ 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.

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.

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.

Chonic overdose and neurological disorders

Neurological disorders have been observed in children treated with 2.5 to 3 times the recommended dose for up to 16 months and have also been observed with standard doses of deferiprone. Prescribers are reminded that the use of doses above 100 mg/kg/day are not recommended (see sections 4.8 and 4.9). Deferiprone use should be discontinued if neurological disorders are observed (see sections 4.8 and 4.9).

4.5 Interaction with other products and other forms of interaction

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 (see section 4.3).

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.

Advise patients to avoid alcohol while taking Ferriprox 1,000 mg delayed release enteric coated tablets. At 40% (v/v) alcohol concentration *in vitro* dissolution studies, there was 88% release of deferiprone from a Ferriprox 1,000 mg delayed release enteric coated tablet within two hours compared to 4% release of deferiprone within 2 hours in the absence of alcohol.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of deferiprone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). 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 advised to take contraceptive measures and must be advised to immediately stop taking deferiprone if they become pregnant or plan to become pregnant (see section 4.3).

Breastfeeding
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 (see section 4.3).

Fertility
No effects on fertility or early embryonic development were noted in animals (see section 5.3).

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The most serious adverse reaction reported in clinical trials with deferiprone is agranulocytosis (neutrophils $<0.5\times10^9$/l), with an incidence between 1% and 2% (see section 4.4). The observed incidence of the less severe form of neutropenia (neutrophils $<1.5\times10^9$/l) is approximately 5%. This rate should be considered in the context of the underlying elevated incidence of neutropenia in thalassaemia patients, particularly in those with hypersplenism.

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 in most patients resolve within a few weeks without 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 (see section 4.4).

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 normalized 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 up to 16 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 sections 4.4 and 4.9).

Adverse reaction frequencies: Very common (≥1/10), Common (≥1/100 to 1/10), Uncommon (≥1/1,000 to 1/100).

System Organ Class	**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
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

System Organ Class	Very Common (≥1/10)	Common (≥1/100 to 1/10)	Uncommon (≥1/1,000 to 1/100)
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, *Yersinia* 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
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

System Organ Class	Very Common (≥1/10)	Common (≥1/100 to 1/10)	Uncommon (≥1/1,000 to 1/100)
			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

4.9 Overdose

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 up to 16 months. The neurological disorders progressively regressed after deferiprone discontinuation. Neurological disorders have also been observed upon treatment with standard doses of deferiprone. Prescribers are reminded that the use of doses above 100 mg/kg/day is not recommended. Deferiprone use should be discontinued if neurological disorders are observed.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Iron chelating agents, ATC code: V03AC02

Mechanism of action
The active substance is deferiprone (3-hydroxy-1,2- dimethylpyridin-4-one), a bidentate ligand which binds to iron in a 3:1 molar ratio.

Pharmacodynamic effects
Clinical studies have demonstrated that Ferriprox is effective in promoting iron excretion and that a dose of 25 mg/kg three times per day can prevent the progression of iron accumulation as assessed by serum ferritin, in patients with transfusion-dependent thalassaemia. However, chelation therapy may not necessarily protect against iron-induced organ damage.

Clinical efficacy and safety
Studies LA16-0102, LA-01 and LA08-9701 compared the efficacy of Ferriprox with that of deferoxamine in controlling serum ferritin in transfusion-dependent thalassaemia patients. Ferriprox and deferoxamine were equivalent in promoting a net stabilization or reduction of body iron load, despite the continuous transfusional iron administration in those patients (no difference in proportion of patients with a negative trend in serum ferritin between the two treatment groups by regression analysis; p >0.05).

A magnetic resonance imaging (MRI) method, T2*, was also used to quantify myocardial iron load. Iron overload causes concentration-dependent MRI T2* signal loss, thus, increased myocardial iron reduces myocardial MRI T2* values. Myocardial MRI T2* values of less than 20 milliseconds represent iron overload in the heart. An increase in MRI T2* on treatment indicates that iron is being removed from the heart. A positive correlation between MRI T2* values and cardiac function (as measured by Left Ventricular Ejection Fraction (LVEF)) has been documented.

Study LA16-0102 compared the efficacy of Ferriprox with that of deferoxamine in decreasing cardiac iron overload and in improving cardiac function (as measured by LVEF) in transfusion-dependent thalassaemia patients. Sixty-one patients with cardiac iron overload, previously treated with deferoxamine, were randomized to continue deferoxamine (average dose 43 mg/kg/day; N=31) or to switch to Ferriprox (average dose 92 mg/kg/day N=29). Over the 12-month duration of the study, Ferriprox was superior to deferoxamine in decreasing cardiac iron load. There was an improvement in cardiac T2* of more than 3 milliseconds in patients treated with Ferriprox compared with a change of about 1 millisecond in patients treated with deferoxamine. At the same time point, LVEF had increased from baseline by 3.07 ± 3.58 absolute units (%) in the Ferriprox group and by 0.32 ± 3.38 absolute units (%) in the deferoxamine group (difference between groups; p=0.003).

Study LA12-9907 compared survival, incidence of cardiac disease, and progression of cardiac disease in 129 patients with thalassaemia major treated for at least 4 years with Ferriprox (N=54) or deferoxamine (N=75). Cardiac endpoints were assessed by echocardiogram, electrocardiogram, the New York Heart Association classification and death due to cardiac disease. There was no significant difference in percentage of patients with cardiac dysfunction at first assessment (13% for Ferriprox vs. 16% for deferoxamine). Of patients with cardiac dysfunction at first assessment, none treated with deferiprone compared with four (33%) treated with deferoxamine had worsening of their cardiac status (p=0.245). Newly diagnosed cardiac dysfunction occurred in 13 (20.6%) deferoxamine-treated patients and in 2 (4.3%) Ferriprox-treated patients who were cardiac disease-free at the first assessment (p=0.013). Overall, fewer Ferriprox-treated patients than deferoxamine-treated patients showed a

worsening of cardiac dysfunction from first assessment to last assessment (4% vs. 20%, p=0.007).

Data from the published literature are consistent with the results from the Apotex studies, demonstrating less heart disease and/or increased survival in Ferriprox-treated patients than in those treated with deferoxamine.

Study LA37-1111 was conducted to evaluate the effect of single therapeutic (33 mg/kg) and supratherapeutic (50 mg/kg) oral doses of deferiprone on the cardiac QT interval duration in healthy subjects. The maximum difference between the LS means of the therapeutic dose and placebo was 3.01 ms (95% one-sided UCL: 5.01 ms), and between the LS means of the supratherapeutic dose and placebo was 5.23 ms (95% one-sided UCL: 7.19 ms). Ferriprox was concluded to produce no significant prolongation of the QT interval.

5.2 Pharmacokinetic properties

Absorption
Ferriprox 1,000 mg delayed release enteric coated tablets are rapidly absorbed from the upper part of the gastrointestinal tract, with the drug appearing in the blood within 5 to 10 minutes of oral administration. Peak serum concentrations occur approximately 2 hours after a single dose in fasted healthy subjects. Administration with food does not impact the pharmacokinetics of the tablets.

After a single 1,000 mg dose of the delayed release enteric coated tablets, the mean maximum concentration (C_{max}) of deferiprone in serum is approximately 6 µg/ml, and the mean total area under the concentration-time curve (AUC) is approximately 28 µg·h/ml.

The volume of distribution of deferiprone is approximately 1 l/kg in healthy subjects. The plasma protein binding of deferiprone is less than 10%.

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.

The peak and extent of exposure to Ferriprox delayed release enteric coated tablets administered twice daily is equivalent to that of Ferriprox 500 mg film-coated tablets taken three times daily over 24 hours at steady state under fed conditions. Accordingly, no adjustment to the total daily dose is necessary when a patient is switched from the 500 mg film-coated tablets to the delayed release enteric coated tablets.

The delayed release properties of an intact 1,000 mg Ferriprox delayed release enteric coated tablet are maintained when the tablet is cut in half.

Elimination
More than 90% of deferiprone is eliminated from plasma within 5 to 6 hours of ingestion. Following oral administration, 75% to 90% is recovered in the urine in the first 24 hours, primarily as the metabolite. The elimination half-life ($t_{1/2}$) of deferiprone is approximately 2 hours.

Renal impairment

An open-label, non-randomized, parallel group clinical study was conducted to evaluate the effect of impaired renal function on the safety, tolerability, and pharmacokinetics of a single 33 mg/kg oral dose of Ferriprox. Subjects were categorized into 4 groups based on estimated glomerular filtration rate (eGFR): healthy volunteers (eGFR ≥ 90 mL/min/1.73m^2), mild renal impairment (eGFR 60-89 mL/min/1.73m^2), moderate renal impairment (eGFR 30–59 mL/min/1.73m^2), and severe renal impairment (eGFR 15–29 mL/min/1.73m^2). Systemic exposure to deferiprone and to its metabolite deferiprone 3-*O*-glucuronide was assessed by the PK parameters C_{max} and AUC.

Regardless of the degree of renal impairment, the majority of the dose of Ferriprox was excreted in the urine over the first 24 hours as deferiprone 3-*O*-glucuronide. No significant effect of renal impairment was seen on systemic exposure to deferiprone. Systemic exposure to the inactive 3-*O*-glucuronide increased with decreasing eGFR. Based on the results of this study, no adjustment of the Ferriprox dosage regimen is required in patients with impaired renal function. The safety and pharmacokinetics of Ferriprox in patients with end stage renal disease is unknown.

Hepatic impairment

An open-label, non-randomized, parallel group clinical study was conducted to evaluate the effect of impaired hepatic function on the safety, tolerability, and pharmacokinetics of a single 33 mg/kg oral dose of Ferriprox. Subjects were categorized into 3 groups based on the Child-Pugh classification score: healthy volunteers, mild hepatic impairment (Class A: 5– 6 points), and moderate hepatic impairment (Class B: 7– 9 points). Systemic exposure to deferiprone and to its metabolite deferiprone 3-*O*-glucuronide was assessed by the PK parameters C_{max} and AUC. Deferiprone AUCs did not differ between treatment groups, but C_{max} was decreased by 20% in mildly or moderately hepatically impaired subjects compared with healthy volunteers. Deferiprone-3-*O*-glucuronide AUC was decreased by 10% and C_{max} by 20% in mildly and moderately impaired subjects compared with healthy volunteers. A serious adverse event of acute liver and renal injury was seen in one subject with moderate hepatic impairment. Based on the results of this study, no adjustment of the Ferriprox dosage regimen is required in patients with mildly or moderately impaired hepatic function.

The influence of severe hepatic impairment on the pharmacokinetics of deferiprone and deferiprone 3-*O*-glucuronide has not been evaluated. The safety and pharmacokinetics of Ferriprox in patients with severe hepatic impairment is unknown.

5.3 Preclinical safety data

Preclinical studies have been conducted in animal species including mice, rats, rabbits, dogs and monkeys.

The most common findings in non-iron-loaded animals at doses of 100 mg/kg/day and above were hematologic effects such as bone marrow hypocellularity, and decreased WBC, RBC and/or platelet counts in peripheral blood.

Atrophy of the thymus, lymphoid tissues, and testis, and hypertrophy of the adrenals, were reported at doses of 100 mg/kg/day or greater in non-iron-loaded animals.

No carcinogenicity studies in animals have been conducted with deferiprone. The genotoxic potential of deferiprone was evaluated in a set of *in vitro* and *in vivo* tests. Deferiprone did not show direct mutagenic properties; however, it did display clastogenic characteristics in *in vitro* assays and *in vivo* in animals.

Deferiprone was teratogenic and embryotoxic in reproductive studies in non-iron-loaded pregnant rats and rabbits at doses at least as low as 25 mg/kg/day. No effects on fertility or early embryonic development were noted in non-iron-loaded male and female rats that received deferiprone orally at doses of up to 75 mg/kg twice daily for 28 days (males) or 2 weeks (females) prior to mating and until termination (males) or through early gestation (females). In females, an effect on the oestrous cycle delayed time to confirmed mating at all doses tested.

No prenatal and postnatal reproductive studies have been conducted in animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Hypromellose acetate succinate
Magnesium oxide
Colloidal silicon dioxide
Magnesium stearate

Coating
Triethyl citrate
Talc
Titanium dioxide
Methacrylic acid and ethyl acrylate copolymer

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date can be found on the packaging

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Aluminium blisters

Pack size of 50 tablets

6.6 Special precautions for disposal

No special requirements

Keep all medicine out of the reach of children

Obat keras

ON MEDICAL PRESCRIPTION ONLY

HARUS DENGAN RESEP DOKTER

Reg. No: XXXXXX

Manufactured by: Apotex Inc., Etobicoke site, Ontario, Canada, for Chiesi Farmaceutici S.p.A, Parma, Italy

Imported by: PT Sydna Farma, Jakarta, Indonesia
Marketed by: PT. Quamed, Jakarta, Indonesia

LEAFLET KEMASAN: INFORMASI UNTUK PENGGUNA

Ferriprox®
Deferiprone
Tablet salut enterik lepas lambat
1000 mg

Baca semua selebaran ini dengan seksama sebelum Anda mulai minum obat ini.
- Simpan selebaran ini. Anda mungkin perlu membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter atau apoteker Anda.
- Obat ini telah diresepkan untuk Anda. Jangan berikan kepada orang lain. Ini dapat membahayakan mereka, bahkan jika gejalanya sama dengan Anda.
- Jika Anda merasakan efek samping yang tidak tercantum dalam selebaran ini, beri tahu dokter atau apoteker Anda.

Dalam selebaran ini:

1. APA ITU FERRIPROX DAN KEGUNAANNYA?

Ferriprox® mengandung zat aktif deferiprone. Ferriprox adalah obat yang menghilangkan zat besi dari tubuh. Ferriprox hanya boleh diresepkan oleh dokter spesialis saja.

Ferriprox diindikasikan untuk pengobatan kelebihan zat besi pada penderita thalassemia mayor usia ≥ 1 tahun.

2. SEBELUM ANDA MENGGUNAKAN FERRIPROX

Jangan menggunakan Ferriprox:
- jika Anda alergi (hipersensitif) terhadap deferiprone atau salah satu bahan Ferriprox lainnya.
- jika Anda memiliki riwayat neutropenia berulang (jumlah sel darah putih (neutrofil) rendah).
- jika Anda memiliki riwayat agranulositosis (jumlah sel darah putih (neutrofil) sangat rendah $<0,5\times10^9$/l)
- jika Anda sedang mengonsumsi obat-obatan yang diketahui menyebabkan neutropenia atau agranulositosis (lihat “Mengkonsumsi obat lain”).
- Jika Anda sedang hamil atau menyusui.

Berhati-hatilah dengan Ferriprox
- Efek samping paling serius yang mungkin terjadi saat mengonsumsi Ferriprox adalah jumlah sel darah putih (neutrofil) yang sangat rendah. Kondisi ini, yang dikenal sebagai neutropenia berat atau agranulositosis, telah terjadi pada 1 hingga 2 dari 100 orang yang menggunakan Ferriprox dalam studi klinis. Karena sel darah putih membantu melawan infeksi, jumlah neutrofil yang rendah dapat menempatkan Anda pada risiko terkena infeksi yang serius dan berpotensi mengancam jiwa. Untuk memantau neutropenia, dokter Anda akan meminta Anda untuk melakukan tes darah (untuk memeriksa jumlah sel darah putih Anda) yang dilakukan secara teratur setiap minggu,

selama Anda dirawat dengan Ferriprox. Sangat penting bagi Anda untuk menepati jadwal pengobatan. Laporkan segera ke dokter Anda setiap gejala infeksi seperti demam, sakit tenggorokan atau gejala seperti flu.
- jika Anda HIV positif atau jika fungsi ginjal atau hati Anda terganggu, dokter Anda mungkin merekomendasikan tes tambahan.

Dokter Anda juga akan meminta Anda datang untuk menjalani tes guna memantau kadar zat besi tubuh. Selain itu dia juga mungkin meminta Anda untuk menjalani biopsi hati.

Mengkonsumsi obat lain
Jangan minum obat yang diketahui menyebabkan neutropenia atau agranulositosis (lihat "Jangan menggunakan Ferriprox").
Mohon beri tahu dokter atau apoteker Anda jika Anda sedang atau baru saja mengkonsumsi obat lain, termasuk obat-obatan yang diperoleh tanpa resep.
Jangan mengkonsumsi antasida berbahan dasar aluminium saat mengonsumsi Ferriprox.
Mohon konsultasi dengan dokter atau apoteker Anda sebelum mengonsumsi vitamin C dengan Ferriprox.

Kehamilan dan menyusui
Jangan minum obat ini jika Anda sedang hamil atau jika Anda sedang merencanakan kehamilan. Obat ini dapat secara serius membahayakan bayi Anda. Anda harus menggunakan kontrasepsi yang efektif saat Anda menggunakan Ferriprox.
Tanyakan kepada dokter Anda metode mana yang terbaik untuk Anda. Jika Anda hamil saat menggunakan Ferriprox, hentikan minum obat segera dan beri tahu dokter Anda.

Jangan menggunakan Ferriprox jika Anda sedang menyusui.

Penggunaan pada anak
Keamanan dan kemanjuran Ferriprox untuk penggunaan pada anak dievaluasi pada 220 anak berusia 1 hingga 15 tahun dengan anemia tergantung transfusi. Data menunjukkan bahwa Ferriprox efektif dalam menurunkan kadar besi tubuh yang diukur dengan konsentrasi feritin serum dan itu tidak terkait dengan masalah kesehatan baru pada populasi pasien ini. Efek Ferriprox pada pertumbuhan tidak diketahui.

Mengemudi dan menggunakan mesin
Tidak berhubungan.

3. CARA PENGGUNAAN FERRIPROX

Selalu gunakan Ferriprox persis seperti yang diresepkan dokter Anda. Anda harus memeriksakan diri ke dokter atau apoteker jika Anda tidak yakin. Jumlah Ferriprox yang Anda gunakan akan tergantung pada berat badan Anda. Total dosis harian yang biasa adalah 75 sampai 100 mg/kg, dibagi menjadi dua dosis. Total dosis harian tidak boleh melebihi 100mg/kg.
Minum dosis pertama Anda di pagi hari. Minum dosis kedua Anda di malam hari, kira-kira 12 jam kemudian. Minum Ferriprox dengan makanan.

Jika Anda menggunakan Ferriprox lebih banyak dari yang seharusnya
Tidak ada laporan overdosis akut dengan Ferriprox. Jika Anda secara tidak sengaja mengkonsumsi lebih dari dosis yang ditentukan, Anda harus menghubungi dokter Anda.

Jika Anda lupa menggunakan Ferriprox
Ferriprox akan paling efektif jika Anda tidak melewatkan dosis sama sekali. Jika Anda melewatkan satu dosis, minumlah sesegera mungkin sewaktu Anda ingat dan meminum dosis berikutnya pada waktu yang dijadwalkan secara teratur. Jika Anda melewatkan lebih dari satu dosis, jangan gunakan dosis ganda untuk menebus dosis individu yang terlupakan, lanjutkan saja dengan jadwal normal Anda Jangan mengubah dosis harian Anda tanpa berbicara dengan dokter Anda terlebih dahulu.

4. EFEK SAMPING YANG MUNGKIN

Seperti semua obat-obatan, Ferriprox dapat memiliki efek samping, meskipun tidak semua orang mendapatkannya.
Efek samping paling serius dari Ferriprox adalah jumlah sel darah putih (neutrofil) yang sangat rendah. Keadaan ini dikenal sebagai neutropenia berat atau agranulositosis, telah terjadi pada 1 hingga 2 dari 100 orang yang telah menggunakan Ferriprox dalam studi klinis. Jumlah sel darah putih yang rendah dapat dikaitkan dengan penyakit serius dan berpotensi infeksi yang mengancam jiwa. Laporkan segera ke dokter setiap gejala infeksi seperti: demam, sakit tenggorokan atau gejala seperti flu.

Efek samping yang sangat umum (dapat mempengaruhi lebih dari 1 dari 10 orang):
- sakit perut
- mual
- muntah
- warna urin kemerahan/coklat

Urine yang berubah warna adalah efek yang sangat umum dan tidak berbahaya.

Efek samping yang umum (dapat mempengaruhi hingga 1 dari 10 orang):
- jumlah sel darah putih rendah (agranulositosis dan neutropenia)
- sakit kepala
- diare
- peningkatan enzim hati
- kelelahan
- menambah nafsu makan

Tidak diketahui (frekuensi tidak dapat diperkirakan dari data yang tersedia):
- reaksi alergi termasuk ruam kulit atau gatal-gatal

Kejadian nyeri sendi dan pembengkakan berkisar dari nyeri ringan pada satu atau lebih sendi hingga kecacatan berat. Di sebagian besar kasus, rasa sakit menghilang selama pasien terus mengkonsumsi Ferriprox secara teratur.

Gangguan neurologis (seperti tremor, gangguan berjalan, penglihatan ganda, kontraksi otot tidak terkendali, masalah dengan koordinasi gerakan) telah dilaporkan pada anak-anak yang telah diresepkan secara sukarela lebih dari 2,5 kali dosis maksimum yang direkomendasikan 100 mg/kg/hari hingga 16 bulan dan juga telah diamati pada anak-anak dengan dosis standar deferiprone. Mereka pulih dari gejala ini setelah penghentian Ferriprox.

Jika Anda melihat ini atau efek samping apa pun yang tidak tercantum dalam selebaran ini, beri tahu dokter, apoteker atau perusahaan distribusi lokal segera.

5. CARA MENYIMPAN FERRIPROX

Jauhkan dari jangkauan dan pandangan anak-anak.
Jangan gunakan Ferriprox setelah tanggal kedaluwarsa yang tertera pada label setelah EXP.
Simpan di bawah 30°C.

6. INFORMASI LEBIH LANJUT

Apa yang terkandung dalam Ferriprox?
Zat aktifnya adalah deferiprone.
Setiap tablet salut enterik lepas lambat Ferriprox 1000 mg mengandung deferiprone 1000 mg. Bahan lainnya adalah: *Tablet core*: hypromellose acetate succinate; light magnesium oxide; silica, colloidal anhydrous; magnesium stearate. *Coating*: triethyl citrate; talc; titanium dioxide; methacrylic acid-ethyl acrylate copolymer (1:1) dispersion 30%.

Seperti apa Ferriprox dan isi kemasan nya?
Ferriprox Tablet salut enterik lepas lambat berwarna putih hingga putih pudar, berbentuk seperti kapsul, tepi miring, tablet berlapis bikonveks dicetak "FPX" membagi dua “DR" di di satu sisi, “APO” membagi dua “1000” pada sisi lain. Tablet diberi tanda dan bisa pecah menjadi dua. Ferriprox dikemas dalam blister 50 tablet

Manufactured by: Apotex Inc., Etobicoke site, Ontario, Canada
For Chiesi Farmaceutici S.p.A., Parma, Italy
Imported by: PT Sydna Farma, Jakarta, Indonesia
Marketed by: PT. Quamed, Jakarta, Indonesia

Selebaran ini terakhir disetujui pada MM/YYYY.

Reg. No.:

Obat keras

HARUS DENGAN RESEP DOKTER

Pelaporan efek samping: Anda juga dapat melaporkan efek samping tersebut ke sistem pelaporan nasional dibawah ini:

Pusat Farmakovigilans/MESO Nasional Badan Pengawasan Obat dan Makanan RI
http://e-meso.pom.go.id/subsite/
Direktorat Pengawasan Distribusi Produk Terapetik dan PKRT Badan POM RI
Jl. Percetakan Negara 23 Jakarta Pusat, 10560
No Telp: (021)-4244691 Ext.1019
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