GPO-L-ONE TABLET 500MG

DOSAGE FORM / STRENGTH
Film coated tablet, each tablet contains Deferiprone 500 mg.

DESCRIPTION
Dark green, oblong biconvex, film-coated tablet, one side bisected with DFP and 500 marked on each section.

PROPERTIES
Deferiprone (L1) is an orally active iron chelator belonging to the group of hydroxypyridones. It binds to iron in a 3:1 molar ratio. The water soluble complex of iron formed is rapidly excreted in the urine thus reducing pathological iron deposits in organs and tissues. Studies have demonstrated that deferiprone is effective in promoting iron excretion and can lower serum ferritin levels and tissue iron stores in patients with transfusion-dependent thalassaemia, however, the precise mechanism of deferiprone in promoting iron excretion and preventing the progress of iron accumulation is unknown.

Pharmacokinetics
Absorption: Deferiprone is rapidly absorbed from the upper part of the gastrointestinal tract. Peak serum concentrations are reached 45 to 60 minutes following administration of a single dose in fasted patients. This may be extended to 2 hours in fed patients. There was no decrease in the amount of drug absorbed when given with food.

Biotransformation: Deferiprone is metabolized predominantly to a glucuronide conjugate. Peak serum concentrations of the glucuronide occur 2 to 3 hours after administration of deferiprone.

Elimination: Deferiprone is eliminated mainly via kidneys (75% to 90% of ingested dose reportedly recoverable from urine during the first 24 hours), in the form of free deferiprone, the glucuronide metabolite and the iron-deferiprone complex. The elimination half-life in most patients is 2 to 3 hours.

INDICATION
GPO-L-One Tablet is indicated for treatment of iron overload in patients with thalassaemia major when deferoxamine therapy is contraindicated or inadequate.

RECOMMENDED DOSAGE
Adult & Children Over 6 Years
GPO-L-One Tablet is given orally, **75 mg/kg body weight daily, in 2 to 4 divided doses**. Dosage per kg body weight should be calculated to the nearest half tablet (see example below for administration in 3 divided doses):

Body weight (kg)	Total Daily Dose (mg)	Total each dose (divided by 3)	Number of tablets daily
20	1500	500	1 x 3 times
30	2250	750	1.5 x 3 times
40	3000	1000	2 x 3 times
50	3750	1250	2.5 x 3 times
60	4500	1500	3 x 3 times
70	5250	1750	3.5 x 3 times
80	6000	2000	4 x 3 times
90	6750	2250	4.5 x 3 times

Dosages can be adjusted up to 100 mg/kg body weight daily, in divided doses. Doses above 100 mg/kg body weight/day are not recommended due to potentially increased risk of side effects.
There is very limited information on deferiprone use in children under 6 years of age.
It may be easier to remember taking deferiprone doses with meals, even if it is not necessary to do so. It has been suggested that nausea may be minimized if deferiprone is taken with food.

CONTRAINDICATION
GPO-L-One Tablet is contraindicated in patients who are:
- hypersensitive to deferiprone or any ingredients in the formulation
- with history of recurrent episodes of neutropenia
- with history of agranulocytosis
- pregnant or breastfeeding

WARNING 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. Agranulocytosis and neutropenia usually resolve upon discontinuation of deferiprone, but fatal cases of agranulocytosis have been reported. If the patient develops an infection while on deferiprone, therapy should be immediately 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 or 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 x 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 re-challenge. Therefore, in the event of neutropenia, re-challenge is not recommended. In the event of agranulocytosis, re-challenge is contraindicated.

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. 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.

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

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

Neurological disorders
Neurological disorders have been observed in children treated with more than 2.5 times the maximum recommended dose for several years but 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. Deferiprone use should be discontinued if neurological disorders are observed.

Combined use with other iron chelators
The use of combination therapy should be considered on a case-by-case basis. The response to therapy should be assessed periodically, and the occurrence of adverse events closely monitored. Fatalities and life-threatening situations (caused by agranulocytosis) have been reported with deferiprone in combination with deferoxamine. Combination therapy with deferoxamine is not recommended when monotherapy with either chelator is adequate or when serum ferritin falls below 500 µg/l. Limited data are available on the combined use of deferiprone and deferasirox, and caution should be applied when considering the use of such combination.

Carcinogenicity/mutagenicity
In view of the genotoxicity results, a carcinogenic potential of deferiprone cannot be excluded.

Plasma Zn^{2+} concentration
Monitoring of plasma Zn^{2+} concentration, and supplementation in case of a deficiency, is recommended.

DRUG INTERACTIONS
Deferiprone chelates trivalent metal ions and could interact with aluminium-containing preparations. Therefore, it is not recommended to take deferiprone together with aluminium-based antacids.
Due to the risk of additive toxicity, the use of deferiprone concomitantly with drugs that may cause neutropenia or agranulocytosis is not recommended.
Concomitant use of deferiprone with vitamin C may increase iron complex excretion and may cause reversible cardiac function impairment. Hence, caution should be exercised when co-prescribing deferiprone and vitamin C.

PREGNANCY AND LACTATION
Pregnancy
There is no adequate information on the use of deferiprone in pregnant women; however, 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 clastogenic and teratogenic properties of deferiprone. 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. Deferiprone should not be used by nursing mothers. If treatment is unavoidable, breastfeeding must be stopped.

SIDE EFFECTS
The most serious side effect reported with deferiprone therapy is agranulocytosis (neutrophils < 0.5 x 10^9/l), with an incidence of 1.1%. The less severe incidence reported is neutropenia (neutrophils < 1.5 x 10^9/l) which is approximately 4.9%. The rate should be considered in the context of the underlying elevated incidence of neutropenia, in thalassaemia patients, particularly in those with hypersplenism.

Episodes of mild and transient diarrhoea have been reported. Gastrointestinal effects such as anorexia, nausea, vomiting, gastric discomfort and altered taste, are more frequent at the beginning of therapy. In most patients, the effects are resolved within a few weeks without discontinuation of treatment.

Other common side effects reported are joint pains or arthropathy events, which involve knees, ankles, elbows, hips and lower back. Patients may also observe pain in the small joints of the hands and feet. The exact mechanism of this arthropathy is not known. If joint pains occur, it may be necessary to stop the drug for a short while or reduce the dose. Once joint pains disappear, the drug may be restarted at lower doses. Concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen or diclofenac may be used to control the pain.

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

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. 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. These disorders regress and resolve with deferipone's discontinuation.

Other side effects reported

Common: Stomach upset, increased appetite, headache, fatigue, flu syndrome, swelling, decline in blood cell counts.

Uncommon: Fever, bacterial infections, malaise, cyst, depletion of minerals, dizziness, sleepiness, decreased muscle activity, deafness, ear pain, sore throat, liver tenderness, jaundice, hepatitis, excess gas, gastritis, skin reactions (rash, itchiness, redness), bone pain, muscle pain, leg cramps, epicondylitis, loss of menstruation, frequent urination.

If patient notices any side effects not mentioned above, he/she should inform the doctor, pharmacist or local distributor immediately.

SYMPTOMS & TREATMENT OF OVERDOSAGE

No acute cases of 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. These disorders regress and resolve with deferipone's discontinuation.

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

STORAGE CONDITION

Do not store above 30°C.
Keep out of the reach of children.
Jauhi daripada kanak-kanak.

Shelf-life: Please refer to outer box label.

PACK SIZE:

100'S in HDPE bottle

MANUFACTURED BY:

The Government Pharmaceutical Organization (GPO)
75/1 Rama 6 Road, Ratchathewi,
Bangkok 10400, Thailand.

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