ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Deferiprone Lipomed 500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg deferiprone.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white, glossy surface, oval film-coated tablet. The tablet is 8.2 mm x 17.2 mm x 6.7 mm and scored. The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Deferiprone Lipomed monotherapy is indicated for the treatment of iron overload in patients with thalassaemia major when current chelation therapy is contraindicated or inadequate.

Deferiprone Lipomed in combination with another chelator (see section 4.4) is indicated in patients with thalassaemia major when monotherapy with any iron chelator is ineffective, or when prevention or treatment of life-threatening consequences of iron overload (mainly cardiac overload) justifies rapid or intensive correction (see section 4.2).

4.2 Posology and method of administration

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

Posology

Deferiprone is usually given as 25 mg/kg body weight, orally, three times a day for a total daily dose of 75 mg/kg body weight. Dose per kilogram body weight should be calculated to the nearest half tablet. See tables below for recommended doses for body weights at 10 kg increments.

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

Dose table for Deferiprone Lipomed 500 mg film-coated tablets

Body weight (kg)	**Total daily dose (mg)**	**Dose (mg, three times/day)**	**Number of tablets (three times/day)**
20	1 500	500	1.0
30	2 250	750	1.5
40	3 000	1 000	2.0
50	3 750	1 250	2.5
60	4 500	1 500	3.0
70	5 250	1 750	3.5
80	6 000	2 000	4.0
90	6 750	2 250	4.5

A total daily dose above 100 mg/kg body weight is not recommended because of the potentially increased risk of adverse reactions (see sections 4.4, 4.8, and 4.9).

Dose adjustment

The effect of Deferiprone Lipomed in decreasing the body iron is directly influenced by the dose and the degree of iron overload. After starting Deferiprone Lipomed 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 falls below 500 µg/l.

Dose adjustments when used with other iron chelators

In patients for whom monotherapy is inadequate, Deferiprone Lipomed may be used with deferoxamine at the standard dose (75 mg/kg/day) but should not exceed 100 mg/kg/day.

In the case of iron-induced heart failure, Deferiprone Lipomed at 75-100 mg/kg/day should be added to deferoxamine therapy. The product information of deferoxamine should be consulted.

Concurrent use of iron chelators is not recommended in patients whose serum ferritin falls below 500 µg/l due to the risk of excessive iron removal (see section 4.4).

Special populations

Renal impairment
Dose adjustment is not required in patients with mild, moderate, or severe renal impairment (see section 5.2). The safety and pharmacokinetics of Deferiprone Lipomed in patients with end stage renal disease are unknown.

Hepatic impairment
Dose adjustment is not required in patients with mildly or moderately impaired hepatic function (see section 5.2). The safety and pharmacokinetics of Deferiprone Lipomed in patients with severe hepatic impairment are unknown.

Paediatric population
There are limited data available on the use of deferiprone in children between 6 and 10 years of age, and no data on deferiprone use in children under 6 years of age.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- History of recurrent episodes of neutropenia.
- History of agranulocytosis.
- Pregnancy (see section 4.6).
- 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 precautions for use

Neutropenia/Agranulocytosis

Deferiprone has been shown to cause neutropenia, including agranulocytosis (see section 4.8 'Description of selected adverse reactions'). The patient's absolute neutrophil count (ANC) should be monitored every week during the first year of therapy. For patients whose deferiprone has not been interrupted during the first year of therapy due to any decrease in the neutrophil count, the frequency of ANC monitoring may be extended to the patient's blood transfusion interval (every 2 – 4 weeks) after one year of deferiprone therapy.

The change from weekly ANC monitoring, to monitoring at the time of transfusion visits after 12 months of deferiprone therapy should be considered on an individual patient basis, according to the physician's assessment of the patient's understanding of the risk minimization measures required during therapy (see section 4.4 below).

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 an ANC obtained without delay. The neutrophil count should then be monitored more frequently.

Patients should be aware to contact their physician if they experience any symptoms indicative of infection (such as fever, sore throat and flu-like symptoms). Immediately interrupt deferiprone if the patient experiences infection.

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 ANC is less than 1.5×10^9/l.

For neutropenia events (ANC < 1.5×10^9/l and > 0.5×10^9/l)

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.

For agranulocytosis (ANC < 0.5×10^9/l)

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.

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 immunocompromised patients

No data are available on the use of deferiprone in HIV positive or 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.

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.

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 is not recommended. Deferiprone use should be discontinued if neurological disorders are observed (see sections 4.8 and 4.9).

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.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet and that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal 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).

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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in men and women

Due to the genotoxic potential of deferiprone (see section 5.3), women of childbearing potential are recommended to use effective contraceptive measures and avoid becoming pregnant while being treated with Deferiprone Lipomed and for 6 months following the completion of treatment.

Men are recommended to use effective contraceptive measures and to not father a child while receiving Deferiprone Lipomed and for 3 months following completion of treatment.

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.

Pregnant women must be advised to immediately stop taking deferiprone (see section 4.3).

Breast-feeding

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

This medicinal product has no or negligible influence on the ability to drive and use machinery.

4.8 Undesirable effects

Summary of the safety profile

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 0.5×10^9/l, which occurred in approximately 1% of patients. Less severe episodes of neutropenia were reported in approximately 5% of patients.

Tabulated list of adverse reactions

The adverse reactions are listed below by system organ class (SOC) and by frequency, with the following frequency grouping: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

System organ class	**Very common**	**Common**	**Frequency not known**
Blood and lymphatic system disorders		Agranulocytosis Neutropenia	
Immune system disorders			Hypersensitivity reactions
Metabolism and nutrition disorders		Increased appetite	
Nervous system disorders		Headache	
Gastrointestinal disorders	Vomiting Nausea Abdominal pain	Diarrhoea	
Skin and subcutaneous tissue disorders			Rash Urticaria
Musculoskeletal and connective tissue disorders		Arthralgia	
Renal and urinary disorders	Chromaturia		
General disorders and administration site conditions		Fatigue	
Investigations		Increased liver enzymes	

Description of selected adverse reactions

The most serious adverse reaction reported in clinical trials with deferiprone is agranulocytosis (neutrophils <0.5 x 10^9/l), with an incidence of 1.1% (0.6 cases per 100 patient-years of treatment) (see section 4.4). Data from pooled clinical trials in patients with systemic iron overload show that 63% of the episodes of agranulocytosis occurred within the first six months of treatment, 74% within the first year and 26% after one year of therapy. The median time to onset of the first episode of agranulocytosis was 190 days (ranged 22 days- 17.6 years) and median duration was 10 days in clinical trials. A fatal outcome was observed in 8.3% of the reported episodes of agranulocytosis from clinical trials and post-marketing experience.

The observed incidence of the less severe form of neutropenia (neutrophils <1.5 x 10^9/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.

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 (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 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. 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).

The safety profile of combination therapy (deferiprone and deferoxamine) observed in clinical trials, post-marketing experience or published literature was consistent with that characterised for monotherapy.

Data from the pooled safety database from clinical trials (1 343 patient-years exposure to deferiprone monotherapy and 244 patient-years exposure to deferiprone and deferoxamine) showed statistically significant ($p<0.05$) differences in the incidence of adverse reactions based on System Organ Class for “Cardiac disorders”, “Musculoskeletal and connective tissue disorders” and “Renal and urinary disorders”. The incidences of “Musculoskeletal and connective tissue disorders” and “Renal and urinary disorders” were lower during combination therapy than monotherapy, whereas the incidence of “Cardiac disorders” was higher during combination therapy than monotherapy. The higher rate of “Cardiac disorders” reported during combination therapy than monotherapy was possibly due to the higher incidence of pre-existing cardiac disorders in patients who received combination therapy. Careful monitoring of cardiac events in patients on combination therapy is warranted (see section 4.4).

Paediatric population

The incidences of adverse reactions experienced by 18 children and 97 adults treated with combination therapy were not significantly different between the two age groups except in the incidence of arthropathy (11.1% in children vs. none in adults, $p=0.02$). Evaluation of rate of reactions per 100 patient-years of exposure showed that only the rate of diarrhoea was significantly higher in children (11.1) than in adults (2.0, $p=0.01$).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 several years. The neurological disorders progressively regressed after deferiprone discontinuation.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: All other therapeutic products, 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 iron in a 3:1 molar ratio.

Pharmacodynamic effects

Clinical trials have demonstrated that deferiprone 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. Data from the published literature on iron balance studies in patients with thalassaemia major show that the use of deferiprone concurrently with deferoxamine (co-administration of both chelators during the same day, either simultaneously or sequentially, e.g., deferiprone during the day and deferoxamine during the night), promotes greater iron excretion than either medicinal product alone. Doses of deferiprone in those studies ranged from 50 to 100 mg/kg/day and doses of deferoxamine from 40 to 60 mg/kg/day. 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 deferiprone with that of deferoxamine in controlling serum ferritin in transfusion-dependent thalassaemia patients. Deferiprone 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 ms 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 deferiprone 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 deferiprone (average dose 92 mg/kg/day; N=29). Over the 12-month duration of the study, deferiprone was superior to deferoxamine in decreasing cardiac iron load. There was an improvement in cardiac T2* of more than 3 ms in patients treated with deferiprone compared with a change of about 1 ms in patients treated with deferoxamine. At the same time point, LVEF had increased from baseline by 3.07 ± 3.58 absolute units (%) in the deferiprone 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 deferiprone (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 deferiprone 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%) deferiprone-treated patients who were cardiac disease-free at the first assessment (p=0.013). Overall, fewer deferiprone-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 studies, demonstrating less heart disease and/or increased survival in deferiprone-treated patients than in those treated with deferoxamine.

A randomized, placebo-controlled, double-blind trial evaluated the effect of concurrent therapy with deferiprone and deferoxamine in patients with thalassaemia major, who previously received the standard chelation monotherapy with subcutaneous deferoxamine and had mild to moderate cardiac iron loading (myocardial T2* from 8 to 20 ms). Following randomization, 32 patients received deferoxamine (34.9 mg/kg/day for 5 days/week) and deferiprone (75 mg/kg/day) and 33 patients received deferoxamine monotherapy (43.4 mg/kg/day for 5 days/week). After one year of study therapy, patients on concurrent chelation therapy had experienced a significantly greater reduction in serum ferritin (1 574 µg/l to 598 µg/l with concurrent therapy vs. 1 379 µg/l to 1 146 µg/l with deferoxamine monotherapy, p<0.001), significantly greater reduction in myocardial iron overload, as assessed by an increase in MRI T2* (11.7 ms to 17.7 ms with concurrent therapy vs. 12.4 ms to 15.7 ms with deferoxamine monotherapy, p=0.02) and significantly greater reduction in liver iron concentration, also assessed by an increase in MRI T2* (4.9 ms to 10.7 ms with concurrent therapy vs. 4.2 ms to 5.0 ms with deferoxamine monotherapy, p<0.001).

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 least square (LS) means of the therapeutic dose and placebo was 3.01 ms (95% one-sided upper confidence limit (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). Deferiprone was concluded to produce no significant prolongation of the QT interval.

5.2 Pharmacokinetic properties

Absorption

Deferiprone is rapidly absorbed from the upper part of the gastrointestinal tract. Peak serum concentration occurs 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 µmol/l) than in the fasting state (126 µmol/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.

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 deferiprone. Subjects were categorized into 4 groups based on estimated glomerular filtration rate (eGFR): healthy volunteers (eGFR $\geq$ 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 pharmacokinetic (PK) parameters maximum concentration (C_{max}) and area under the curve (AUC).

Regardless of the degree of renal impairment, the majority of the dose of deferiprone 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 deferiprone dose regimen is required in patients with impaired renal function. The safety and pharmacokinetics of deferiprone 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 deferiprone. 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 deferiprone dose 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 deferiprone in patients with severe hepatic impairment is unknown.

5.3 Preclinical safety data

Non-clinical 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, red blood cell (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 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
Croscarmellose sodium
Silica, colloidal anhydrous
Microcrystalline cellulose
Magnesium stearate

Coating

Hypromellose
Macrogol 6 000
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Aluminium/PVC-PVDC blisters in cartons of 100 film-coated tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Lipomed GmbH
Hegenheimer Strasse 2
79576 Weil am Rhein
Germany
Phone number: +49 7621 1693 472
Fax number: +49 7621 1693 474
Electronic mail: lipomed@lipomed.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1310/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 September 2018
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release
Lipomed GmbH
Hegenheimer Strasse 2
79576 Weil am Rhein
GERMANY

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where Deferiprone Lipomed is marketed, all patients/carers who are expected to use Deferiprone Lipomed are provided with the patient card as a part of the outer packaging.

The patient card shall contain the following key messages (full text is included in Annex IIIA of the marketing authorisation):

- To increase patient awareness of the importance of regular monitoring of the neutrophil count during treatment with Deferiprone Lipomed
- To increase patient awareness of the significance of any symptoms of infection while taking Deferiprone Lipomed
- To warn women of childbearing age to not become pregnant because deferiprone may seriously harm the unborn baby

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Deferiprone Lipomed 500 mg film-coated tablets
deferiprone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 500 mg deferiprone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Lipomed GmbH
Hegenheimer Strasse 2
79576 Weil am Rhein
Germany
Tel: +49 7621 1693 472
Fax: +49 7621 1693 474
lipomed@lipomed.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1310/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Deferiprone Lipomed 500 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Deferiprone Lipomed 500 mg film-coated tablets
deferiprone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lipomed GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PATIENT CARD

((Front Cover)) **PATIENT CARD** **Important Safety Reminders for Patients Taking Deferiprone Lipomed** Prescribing doctor:_____ Phone no:_____	((Back Cover)) **Pregnancy, fertility, lactation** Do not take Deferiprone Lipomed if you are pregnant, trying to become pregnant, or are breastfeeding. Deferiprone Lipomed may seriously harm the baby. If you are pregnant, or breast-feeding during treatment with Deferiprone Lipomed, tell your doctor and get medical advice immediately. Women of childbearing potential are recommended to use effective contraception during the treatment with Deferiprone Lipomed, and for 6 months after the last dose. Men are recommended to use effective contraception during treatment and for 3 months after the last dose. Ask your doctor which method is best for you.
((Inside 1)) **Monitoring your white blood cell count with Deferiprone Lipomed** There is a small chance that you may develop agranulocytosis (very low white blood cell count) while taking Deferiprone Lipomed, which may lead to a serious infection. Even though agranulocytosis only affects 1 to 2 out of 100 users, it is important to monitor your blood on a regular basis.	((Inside 2)) **Make sure you do the following:** 1. Have your blood monitored on a weekly basis for the first one year of treatment with deferiprone and as regularly as your doctor recommends thereafter. 2. If you get any symptoms of infection such as fever, sore throat or flu-like symptoms, immediately seek medical attention. Your white blood cell count must be checked within 24 hours in order to detect potential agranulocytosis.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Deferiprone Lipomed 500 mg film-coated tablets
deferiprone

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.
- Provided in the folding box, you will find a patient card. You should complete and read the card carefully and carry it with you. Provide this card to your doctor if you develop infection symptoms such as a fever, sore throat or flu-like symptoms.

What is in this leaflet

1. What Deferiprone Lipomed is and what it is used for

Deferiprone Lipomed contains the active substance deferiprone. Deferiprone Lipomed is an iron chelator, a type of medicine that removes excess iron from the body.

Deferiprone Lipomed is used to treat iron overload caused by frequent blood transfusions in patients with thalassaemia major when current chelation therapy is contraindicated or inadequate.

2. What you need to know before you take Deferiprone Lipomed

Do not take Deferiprone Lipomed
- if you are allergic to deferiprone or any of the other ingredients of this medicine (listed in section 6);
- if you have a history of repeated episodes of neutropenia (low white blood cell (neutrophil) count);
- if you have a history of agranulocytosis (very low white blood cell (neutrophil) count);
- if you are currently taking medicines known to cause neutropenia or agranulocytosis (see “Other medicines and Deferiprone Lipomed”);
- if you are pregnant or breast-feeding.

Warnings and precautions
The most serious side effect that may occur while taking Deferiprone Lipomed is a very low white blood cell (neutrophil) count. This condition, known as severe neutropenia or agranulocytosis, has occurred in 1 to 2 out of 100 people who have taken deferiprone in clinical trials. Because white blood cells help to fight infection, a low neutrophil count may place you at risk of developing a serious and potentially life-threatening infection. To monitor for neutropenia, your doctor will ask you to have a blood test (to check your white blood cell count) performed regularly, as frequently as every week, while you are being treated with Deferiprone Lipomed. It is very important for you to keep all of these appointments. Please refer to the patient card provided in the folding box. If you get any symptoms of infection such as fever, sore throat or flu-like symptoms, immediately seek medical attention. Your white blood cell count must be checked within 24 hours in order to detect potential agranulocytosis.

If you are HIV positive or if your liver or kidney function is severely impaired, your doctor may recommend additional tests.

Your doctor will also ask you to come in for tests to monitor body iron load. In addition, he or she might ask you to undergo liver biopsies.

Talk to your doctor or pharmacist before taking Deferiprone Lipomed.

Other medicines and Deferiprone Lipomed
Do not take medicines known to cause neutropenia or agranulocytosis (see “Do not take Deferiprone Lipomed”). Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines, including medicines obtained without a prescription.

Do not take aluminium-based antacids at the same time as taking Deferiprone Lipomed.

Please consult with your doctor or pharmacist before taking vitamin C with Deferiprone Lipomed.

Pregnancy and breast-feeding
Deferiprone Lipomed may cause harm to unborn babies when used by pregnant women. Deferiprone Lipomed must not be used during pregnancy unless clearly necessary. If you are pregnant or you become pregnant during treatment with Deferiprone Lipomed, get medical advice immediately.

Both female and male patients are recommended to take special precautions in their sexual activity if there is any possibility for pregnancy to occur. Women of childbearing potential are recommended to use effective contraception during treatment with Deferiprone Lipomed and for 6 months after the last dose. Men are recommended to use effective contraception during treatment and for 3 months after the last dose. This should be discussed with your doctor.
Do not use Deferiprone Lipomed if you are breast-feeding. Please refer to the patient card provided in the folding box.

Driving and using machines
This medicine has no or negligible influence on the ability to drive and use machinery.

Deferiprone Lipomed contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet and that is to say essentially ‘sodium-free’.

3. How to take Deferiprone Lipomed

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. The amount of Deferiprone Lipomed that you take will depend on your weight. The usual dose is 25 mg/kg, 3 times per day, for a total daily dose of 75 mg/kg. The total daily dose should not exceed 100 mg/kg. Take your first dose in the morning. Take your second dose midday. Take your third dose in the evening. Deferiprone Lipomed can be taken with or without food; however, you may find it easier to remember to take Deferiprone Lipomed if you take it with your meals.

If you take more Deferiprone Lipomed than you should
There are no reports of acute overdose with deferiprone. If you have accidentally taken more than the prescribed dose, you should contact your doctor.

If you forget to take Deferiprone Lipomed
Deferiprone Lipomed will be most effective if you do not miss any doses. If you do miss one dose take it as soon as you remember and take your next dose at its regularly scheduled time. If you miss more than one dose do not take a double dose to make up for forgotten individual doses, just continue with your normal schedule. Do not change your daily dose without first talking to your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most serious side effect of Deferiprone Lipomed is a very low white blood cell (neutrophil) count. This condition, known as severe neutropenia or agranulocytosis, has occurred in 1 to 2 out of 100 people who have taken deferiprone in clinical trials. A low white blood cell count can be associated with a serious and potentially life-threatening infection. Report immediately to your doctor any symptoms of infection such as: fever, sore throat or flu-like symptoms.

Very common side effects (may affect more than 1 in 10 people):
- abdominal pain
- nausea
- vomiting
- reddish/brown discolouration of urine

If you experience nausea or vomiting, it may help to take your Deferiprone Lipomed with some food. Discoloured urine is a very common effect and is not harmful.

Common side effects (may affect up to 1 in 10 people):
- low white blood cell count (agranulocytosis and neutropenia)
- headache
- diarrhoea
- increase in liver enzymes
- fatigue
- increase in appetite

Not known (frequency cannot be estimated from the available data):
- allergic reactions including skin rash or hives

Events of joint pain and swelling ranged from mild pain in one or more joints to severe disability. In most cases, the pain disappeared while patients continued taking deferiprone.

Additional side effects in children
In post-marketing experience with deferiprone, neurological disorders (such as tremors, walking disorders, double vision, involuntary muscle contractions, problems with movement coordination) have been reported in children who had been voluntarily prescribed more than double the maximum recommended dose of 100 mg/kg/day for several years and have also been observed in children with standard doses of deferiprone. They recovered from these symptoms after discontinuation of deferiprone.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Deferiprone Lipomed

Keep this medicine out of the sight and reach of children.

Do not store above 25°C.

Do not use this medicine after the expiry date which is stated on the carton and on the blister after EXP. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Deferiprone Lipomed contains
The active substance is deferiprone. Each film-coated tablet contains 500 mg deferiprone.

The other ingredients are:

Tablet core: hypromellose, croscarmellose sodium (see section 2 “Deferiprone Lipomed contains sodium”), silica, colloidal anhydrous, microcrystalline cellulose, magnesium stearate

Coating: hypromellose, macrogol 6 000, titanium dioxide

What Deferiprone Lipomed looks like and contents of the pack
Deferiprone Lipomed 500 mg film-coated tablets are white to off-white, glossy surface, oval film-coated tablets. The tablets are scored and breakable in half. Deferiprone Lipomed is packaged in blisters. One pack contains 100 film-coated tablets.

Marketing Authorisation Holder and Manufacturer
Lipomed GmbH
Hegenheimer Strasse 2
79576 Weil am Rhein
Germany
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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.