Summary of Product Characteristics

1. Name of the medicinal product

NOVATOR 500 (Deferiprone Capsules 500

2. Qualitative and quantitative composition

Each Capsule contains 500 mg deferiprone.

3. Pharmaceutical form

Hard Gelatin Capsules

Maroon / yellow colored size '0' hard gelatin capsules containing a white to almost whitepowder.

4. Clinical Particulars:

4.1 Therapeutic indications:

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

NOVATOR in combination with another chelator 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.

4.2 Posology and method of administration:

This drug should be used under physician's prescription only.For oral use.
Deferiprone therapy should be initiated and maintained by a physician experienced in the treatment of patients with thalassemia.

Posology
Deferiprone is usually given as 25 mg/kg body Weight, orally, three times a dayfor a total daily dose of 75 mg/kg body Weight.

* Note: Physicians should choose suitable capsule strength as NOVATOR 500 cannot be divided.

Doses above 100 mg/kg/day are not recommended because of the potentially

increased risk of adverse reactions; chronic administration of more than 2.5 times the maximum recommended dose has been associated with neurological disorders.

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.

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 patients' absolute neutrophil count (ANC) is low, as well as when treating patients with renal insufficiency or hepatic dysfunction.

Dose adjustment
The effect of Deferiprone in decreasing the body iron is directly influenced by te dose and the degree of iron overload. After starting Deferiprone therapy, it is recommended that serum ferritin concentrations, or other indicators of body iron load, be monitored every two to three months to assess the long-term effectiveness of the chelation regimen in controlling the body iron load. Dose adjustments should be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of body iron burden). Interruption of therapy with deferiprone should be considered if serum ferritin falls below 500 µg/L.

Dose adjustments when used with other iron chelators

In patients for whom monotherapy is inadequate, Deferiprone 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 at 75-100 mg/kg/day should be added to deferoxamine therapy. The product information of deferoxamine should be consulted.

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

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.

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 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 in patients with severe hepatic impairment are unknown.

Method of administration
For oral use.

4.3 Contraindications:

- Hypersensitivity to the active substance or to any of the excipients.
- History of recurrent episodes of neutropenia.
- History of agranulocytosis.
- Pregnancy
- Breast-feeding
- Due to the unknown mechanism of deferiprone-induced neutropenia, patients must not take medicinal products known to be associated with neutropenia orthose that can cause agranulocytosis.

4.4 Special warnings and precautions for use:

Novator 500 contains: Methyl Paraben, Propyl Paraben, Sunset Yellow and Ponceau 4R which may cause allergic reactions (possibly delayed)
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.

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 $1.5x10^9$/l.

In the event of neutropenia:

Instruct the patient to immediately discontinue deferiprone and all other medicinal products with a potential to cause neutropenia. The patient should be advised to limit contact with other individuals in order to reduce the risk of infection. Obtain a complete blood cell (CBC) count, with a white blood cell (WBC) count, corrected for the presence of nucleated red blood cells, a neutrophil count, and a platelet count immediately upon diagnosing the event and then repeat daily. It is recommended that following recovery from neutropenia, weekly CBC, WBC, neutrophil and platelet counts continue to be obtained for three consecutive weeks, to ensure that the patient recovers fully. Should any evidence of infection develop concurrently with the neutropenia, the appropriate cultures and diagnostic procedures should be performed and an appropriate therapeutic regimen instituted.

In the event of severe neutropenia or agranulocytosis:

Follow the guidelines above and administer appropriate therapy such as granulocyte colony stimulating factor, beginning the same day that the event is identified; administer daily until the condition resolves. Provide protective isolation and if clinically indicated, admit patient to the hospital.

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

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 renal or hepatic impairment. Since deferiprone is eliminated mainly via the kidneys, there may be an increased risk of complications in patients with impaired renal function. Similarly, as deferiprone is metabolised in the liver, caution must be exercised in patients with hepatic dysfunction. Renal and hepatic function should be monitored in this patient population during deferiprone therapy. If there is a persistent increase in serum alanine aminotransferase (ALT), interruption of deferiprone therapy should be considered.

In thalassaemia patients there is an association between liver fibrosis and iron overload and/or hepatitis C. Special care must be taken to ensure that iron chelation in patients with hepatitis C is optimal. In these patients, careful monitoring of liver histology is recommended.

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

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 (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 NOVATOR and deferasirox, and caution should be applied when considering the use of such combination.

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.

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 Pregnancy and lactation:

Pregnancy
There are no adequate data from the use of deferiprone in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

Women of childbearing potential must be advised to avoid pregnancy due to the clastogenic and teratogenic properties of the medicinal product. These women should be advised to take contraceptive measures and must be advised to immediately stop taking deferiprone if they become pregnant or plan to become pregnant.

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.

Fertility
No effects on fertility or early embryonic development were noted in animals.

4.7 Effects on ability to drive and use machines:

No studies on the effects on the ability to drive and use machines havebeen performed.

4.8 Undesirable effects:

Summary of the safety profile

The most common adverse reactions reported during therapy with deferiprone inclinical 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 x 10^9/l, which occurred in approximately 1% of patients. Less severe episodes of neutropenia were reported inapproximately 5% of patients.

Tabulated list of adverse reactions

Adverse reaction frequencies: Very common (≥1/10), Common (≥1/100 to <1/10), not known (cannot be estimated from the available data)

SYSTEM ORGAN CLASS	**VERY COMMON (≥1/10)**	**COMMON (≥1/100 to <1/10)**	**FREQUENCY NOT KNOWN**
Blood and lymphatic system disorders		Neutropenia Agranulocytosis	
Immune system disorders			Hypersensitivity reactions
Metabolism and nutrition disorders		Increased Appetite	
Nervous system disorders		Headache	
Gastrointestinal disorders	Nausea Abdominal Pain Vomiting	Diarrhoea	
Skin and subcutaneous tissuedisorders			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 $<0.5x10^9/l$), with an incidence of 1.1% (0.6 cases per 100 patient-years of treatment) (see section 4.4). The observed incidence of the less severe form of neutropenia (neutrophils $<1.5x10^9/l$) 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 characterized for monotherapy.

Data from the pooled safety database from clinical trials (1343 patient-years exposure

to NOVATOR monotherapy and 244 patient-years exposure to NOVATOR 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).

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 (11.05)
than in adults (2.01, $p=0.01$).

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.

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 NOVATOR 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 NOVATOR concurrently with deferoxamine (coadministration of both chelators during the same day, either simultaneously or sequentially, e.g., NOVATOR during the day and deferoxamine during the night), promotes greater iron excretion than either drug alone. Doses of NOVATOR 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.

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 theingested 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.

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, 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 diddisplay 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-loadedmale 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:

Colloidal Anhydrous Silica BP
Maize Starch BP
Purified Talc BP
Magnesium Stearate BP
Croscarmellose Sodium BP

Empty Hard Gelatin Capsule Size "0"Color:
Maroon/Yellow IH
Gelatin BP
Methyl Paraben BP
propyl Paraben BP
Silicon Dioxide BP
Sodium Lauryl Sulphate BP
Glycerine BP
Purified Water BP
Titanium Dioxide BP
Sunset Yellow IH
Patent Blue IH
Carmosine IH
Quinoline Yellow IH
Ponceau 4R IH

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

3 years

6.4 Special precautions for storage:

Store in cool dry place below 30^0C. Protect from light.

6.5 Nature and contents of container:

Alu-Alu blister of 10 capsules.
i) such 3 blisters are packed in carton along with pack insert.
ii) Such 5 blisters are packed in carton along with pack insert.

6.6 Special precautions for disposal:

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

7. Marketing authorisation holder:

Name: ATRA Pharmaceuticals Limited
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Maharashtra State, India
Telephone no.: +91 240 6649311/22
Fax no.: -
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8. Marketing authorisation number(s)

TAN 22 HM 0125

9. Date of first authorisation/renewal of the authorization

Date of first authorization: November 26, 2021
Date of latest renewal: N/A

10. Date of revision of the text

April, 2022

Distribution category: Prescription Only Medicine (POM)