LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Deferiprone DOC
(deferiprone)

SE/H/1687/01-02/DC

This module reflects the scientific discussion for the approval of Deferiprone DOC. The procedure was finalised on 2017-12-14. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Deferiprone DOC, film-coated tablet, 500 mg and 1000 mg, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, DOC Generici Srl, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and IT as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Ferriprox, film-coated tablet, 500 mg authorised in EU since 1999-08-25, with Apotex Europe B.V. as marketing authorisation holder.
The reference product used in the bioequivalence study is Ferriprox, film-coated tablet, 1000 mg from Germany with Apotex Europe B.V. as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing deferiprone, 1000 mg, film-coated tablet with Ferriprox, 1000 mg, film-coated tablet under fasting conditions. The study was conducted at Veeda Clinical Research Pvt. Ltd., Ahmedabad, India between 13th to 19th November 2014. Blood samples were collected pre-dose and up to 24 hours post-dose. The study design is considered acceptable. Plasma concentrations of deferiprone were determined with an adequately validated LC-MS/MS method.

The results are presented in Table 1.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for deferiprone, n=36.

Treatment	AUC_{0-t} µg*h/ml	C_{max} µg/ml	t_{max} h
Test	**38.13 ± 10.40**	**17.45 ± 7.34**	**0.50 0.33-4.00**
Reference	**37.11 ± 9.80**	**16.73 ± 6.47**	**0.50 0.33-2.00**
***Ratio (90% CI)**	**102.58 (99.71-105.53)**	**101.62 (89.63-115.22)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%. Bioequivalence between Deferiprone DOC 1000 mg film-coated tablets and Ferriprox 1000 mg film-coated tablets was shown.

Absence of studies with the lower strength 500 mg is acceptable, since all criteria for biowaiver of additional strength(s) were fulfilled. Studying the highest strength is adequate as the pharmacokinetics of deferiprone is linear in the dose range 25 mg/kg to 50 mg/kg.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Deferiprone DOC.

Safety specification

Summary table of safety concerns as proposed by applicant

Summary of safety concerns	
Important identified risks	• Agranulocytosis • Neutropenia • Use in pregnancy • Arthropathy (including arthralgia) • Increased liver function test values • Skin disorders • Allergic reactions
Important potential risks	• Carcinogenicity
Missing information	• Lactation toxicity • Off-label use • Long-term safety data • Risk in immunocompromised patients

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and additional pharmacovigilance activities in line with the reference product are proposed by the applicant, this includes patient alert cards in every package. This is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested but also additional risk minimisation activities are proposed by the applicant. This includes patient alert cards in every package. This is endorsed and a condition for market authorisation. Please see section VI 1.3 for details.

Summary of Safety Concerns and Planned Risk Minimisation Activities as proposed in RMP

Important identified risks

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Agranulocytosis	Reference to this safety concern is made in SmPC sections: 4.3 Contraindications 4.4 Special warnings and precautions for use 4.5 Interaction with other medicinal products and other forms of interaction 4.8 Undesirable effects	Patient/carer reminder card in each package

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	- Prescription Only Medicine	
Neutropenia	Reference to this safety concern is made in SmPC sections: 4.3 Contraindications 4.4 Special warnings and precautions for use 4.5 Interaction with other medicinal products and other forms of interaction 4.8 Undesirable effects - Prescription Only Medicine	Patient/carer reminder card in each package
Use in pregnancy	Reference to this safety concern is made in SmPC sections: 4.3 Contraindications 4.6 Fertility, pregnancy and lactation - Prescription Only Medicine	Patient/carer reminder card in each package
Arthropathy (including arthralgia)	Reference to this safety concern is made in SmPC sections: 4.8 Undesirable effects - Prescription Only Medicine	Not applicable
Increased liver function test values	Reference to this safety concern is made in SmPC sections: 4.4 Special warnings and precautions for use 4.8 Undesirable effects -Prescription Only Medicine	Not applicable
Skin disorders	Reference to this safety concern is made in SmPC sections: 4.8 Undesirable effects -Prescription Only Medicine	Not applicable
Allergic reactions	Reference to this safety concern is made in SmPC sections: 4.3 Contraindications 4.8 Undesirable effects	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	-Prescription Only Medicine	

Important potential risks

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Carcinogenicity	Reference to this safety concern is made in SmPC sections: 4.4 Special warnings and precautions for use 5.3 Preclinical safety data -Prescription Only Medicine	Not applicable

Missing information

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Lactation toxicity	Reference to this safety concern is made in SmPC sections: 4.3 Contraindications 4.6 Fertility, pregnancy and lactation - Prescription Only Medicine	Patient/carer reminder card in each package
Off-label use	Reference to this safety concern is made in SmPC sections: 4.1 Therapeutic indications 4.2 Posology and method of administration -Prescription Only Medicine	Not applicable
Long-term safety data	Reference to this safety concern is made in SmPC sections: 4.4 Special warnings and precautions for use - Prescription Only Medicine	Not applicable
Risk in immunocompromised patients	Reference to this safety concern is made in SmPC sections: 4.4 Special warnings and	Not applicable

Summary of the RMP

The RMP is in line with the reference product and approvable. It is a condition for market authorisation that the applicant includes a patient alert card in each package. Please see section VI 1.3 for details.

The 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 RMS;
- 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Deferiprone DOC, is found adequate. There are no objections to approval of Deferiprone DOC, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable.
The application is therefore recommended for approval.

Please see section VIII.3 for specific condition for market authorisation.
The MAH should provide a patient/carer reminder card in each pack, the text should be in accordance with the card for the original.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**

The MAH should provide a patient/carer reminder card in each pack, the text should be in accordance with the card for the original:

The information that is included in the package of the reference product, please see below.

FOR WOMEN OF CHILD BEARING AGE
Do not take Deferiprone if you are pregnant or if you are trying to become pregnant. If taken during pregnancy, Deferiprone may seriously harm the unborn baby.
You must use effective contraception while you are taking Deferiprone . Ask your doctor which method is best for you. If you become pregnant while taking Deferiprone , stop taking the medicine immediately and tell your doctor. Do not take Deferiprone if you are breast-feeding.

MONITORING YOUR WHITE BLOOD CELL COUNT WITH Deferiprone
There is a small risk that you may develop agranulocytosis (very low white blood cell count) while taking Deferiprone , 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.

Make sure you do the following:
1. Have your blood monitored on a weekly basis.
2. Contact your doctor immediately if you develop a fever, sore throat or flu like symptoms

VII. APPROVAL

The Decentralised procedure for Deferiprone DOC, 500 mg and 1000 mg, film-coated tablet, was positively finalised on 2017-12-14.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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