EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 July 2018
EMA/535221/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Deferiprone Lipomed

International non-proprietary name: deferiprone

Procedure No. EMEA/H/C/004710/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE:	Adverse Event
ANOVA:	Analysis of Variance
ASMF:	Active Substance Master File
ATC:	Anatomical therapeutic chemical classification system
AUC:	Area under the Curve
BE:	Bioequivalence
BLOQ:	Below Limit of Quantitation
BMI:	Mody-Mass Index
CFU:	Colony-forming unit
CHMP:	Committee for Medicinal Products for Human Use
CPMP	Committee for Proprietary Medicinal Products
CV:	Captured volume or Coefficient of Variation
EC	European Commission
EU:	European Union
FAS:	Full Analysis Set
GC:	Gas chromatography
GCP:	Good Clinical Practice
HCl:	Hydrochloric acid
HPLC:	High Performance Liquid Chromatography
ICH:	International Conference on Harmonisation
IMP:	Investigated Medicinal Product
IPC:	In-process controls
IR:	Infra-Red Spectroscopy
LC-MS/MS:	Liquid Chromatography Coupled with Tandem Mass Spectrometry
LDPE:	Low-density polyethylene
LLOQ:	Lower Limit of Quantitation
MAH:	Marketing Authorisation Holder
MedDRA:	Medical Dictionary for Regulatory Activities
MS:	Mass Spectrometry
NaOH:	Sodium hydroxide
NLT:	Not Less Than
NMR:	Nuclear Magnetic Resonance
NMT	Not More Than
p.a.	Post administrationem
Ph.Eur:	European Pharmacopoeia
PPS:	Per Protocol Set
PT:	Preferred Term
PTSS:	Pre-treatment Sign and Symptom
PVC:	Polyvinyl chloride
PVDC:	Polyvinylidene chloride
QC:	Quality Control
QWP	Quality Working Party (of the EMA)
RH:	Relative humidity
SAP:	Statistical Analysis Plan
SD:	Standard Deviation
SOC:	System Organ Class
SOP:	Standard Operating Procedure
TAMC:	Total Aerobic Microbial Count
TYMC:	Total Combined Yeasts/Moulds Count
ULOQ:	Upper Limit of Quantitation
UV:	Ultraviolet
XRPD:	X-ray Powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Lipomed GmbH submitted on 2 June 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Deferiprone Lipomed, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 December 2016.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

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 justifies rapid or intensive correction (see section 4.2).

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Ferriprox instead of non-clinical and clinical data unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

Product name, strength, pharmaceutical form: Ferriprox, 500 mg film-coated tablets

- Marketing authorisation holder: Apotex Europe B.V.
- Date of authorisation: 25-08-1999
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/99/108/001

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Ferriprox, 500 mg film-coated tablets
- Marketing authorisation holder: Apotex Europe B.V.
- Date of authorisation: 25-08-1999
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/99/108/001

Medicinal product which is or has been authorised in accordance with Union provisions in force and to

which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Ferriprox, 500 mg film-coated tablets
- Marketing authorisation holder: Apotex Europe B.V.
- Date of authorisation: 25-08-1999
- Marketing authorisation granted by:
  - Marketing authorisation number: EU/1/99/108/001
- Bioavailability study number: 2015-005301-36

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	2 June 2017
The procedure started on	13 July 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	21 September 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	13 October 2017
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	9 November 2017
The applicant submitted the responses to the CHMP consolidated List of Questions on	16 March 2018
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	2 May 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	17 May 2018
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	31 May 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 June 2018

The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	13 July 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Deferiprone Lipomed on	26 July 2018

2. Scientific discussion

2.1. Introduction

The present application is made under Article 10(1) generic application, i.e. Deferiprone 500 mg film-coated tablets of Lipomed is a generic version of the already approved reference product Ferriprox 500 mg film-coated tablets of Apotex Europe B.V.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 500 mg of deferiprone as active substance.

Other ingredients are:

Tablet core: hypromellose, croscarmellose sodium, silica, colloidal anhydrous, microcrystalline cellulose, magnesium stearate.

Coating: hypromellose, macrogol 6000, titanium dioxide.

The product is available in aluminium/PVC-PVDC blisters in cartons of 100 film-coated tablets as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of deferiprone is 3-hydroxy-1,2-dimethyl-4(1*H*)-pyridone corresponding to the molecular formula $C_7H_9NO_2$. It has a relative molecular mass of 139.15 g/mol and structure as show in Figure 1.

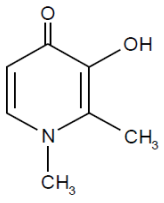

Figure 1: active substance structure

The chemical structure of deferiprone was elucidated by a combination of elemental analysis and spectroscopic methods including mass spectrometry (MS), ultraviolet spectroscopy (UV), infrared spectroscopy (IR) and nuclear magnetic resonance spectroscopy investigations (^{1}H-NMR, ^{13}C-NMR).

Deferiprone is a white crystalline powder, slightly sweet (caramel) odour. It is slightly soluble in cold water, soluble in hot water. It is a neither hygroscopic, nor chiral, compound. The active substance is micronised before being used in the manufacture of the finished product.

No information on polymorphic forms has been described in the literature. Analysis was performed on batches of deferiprone before and after micronisation. No difference or change in the polymorphic form could be observed either for batches after long term storage or after the micronisation process.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the application dossier and in the restricted part of an ASMF and it was considered satisfactory.

The synthetic route of the active substance used is known from literature. Deferiprone is synthesized in one main step using commercially available well defined starting materials with acceptable specifications. The commercial batch sizes of pure deferiprone have been defined. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged, stored and shipped in LDPE bags which comply with the EC directive 2002/72/EC and EC 10/2011 as amended. The bags are placed inside a cardboard drum.

Specification

The active substance specification includes tests for appearance, identity (IR, UV), melting point (Ph. Eur.), impurities (HPLC, GC), water content (Ph. Eur.), sulfated ash (Ph. Eur.), assay (titration), residual solvents (GC), particle size distribution (Ph. Eur.) and microbiological purity (Ph. Eur.).

Appropriate justification of the specification and limits was made according to the requirements of the general monograph of Ph.Eur. and relevant EU quality guidelines. Impurities present are controlled in line with ICH Q3A guideline.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for identity and impurities testing has been presented.

Batch analysis data for a sufficient number of batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 6 batches of active substance stored in the intended commercial package for up to 60 months under long term conditions (25 ºC / 60% RH), intermediate conditions (30 ºC / 65% RH) and accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested in the stability studies: appearance, assay, purity, impurities. All tested parameters were within the specifications.

Photostability testing following the ICH guideline Q1B was performed on one batch. Results of related substance (impurity) testing by HPLC on forced degradation samples under stress conditions were also provided on one batch. During the forced degradation studies, almost no appreciable changes were observed for thermal stress and photolytic degradation, although there was a brownish colouration of

deferiprone. Deferiprone showed some degradation by acidic hydrolysis and to a lesser extent by basic hydrolysis.

The stability results indicate that the active substance is sufficiently stable. The stability results justify the proposed retest periods of 5 years in the proposed container with no special storage conditions.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is presented as oval white to almost white film-coated tablets containing 500 mg of deferiprone as active substance.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report.

The finished product is packed in blisters consisting of transparent, thermo-formable rigid PVC film, PVDC coated and aluminium foil with heat-sealing lacquer packed in a cardboard box. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Deferiprone is an oral iron chelating agent (ATC code: V03AC02). The intention of the pharmaceutical development of the medicinal product was to create an immediate release solid dosage form with the active substance deferiprone at a strength of 500 mg per tablet which is bioequivalent to the reference medicinal product, Ferriprox 500 mg film-coated tablets.

Deferiprone Lipomed and Ferriprox have the same qualitative composition in terms of excipients, apart from inclusion of croscarmellose sodium in the Deferiprone Lipomed formulation as an additional excipient. Comparative impurity profile data for Deferiprone Lipomed and Ferriprox has been provided. The proposed commercial formulation of Deferiprone Lipomed is identical to that used in the bioequivalence study, apart from a slight reduction in the target amount of film-coating to make sure that that there are no differences between the actual formulation used for the bioequivalence study and the future commercial formulation.

The physicochemical property which is most relevant with regard to the *in vivo* performance of the finished product, is the particle size of the active substance. Appropriate acceptance limits have been established for the particle size distribution based on the experience gained during development and the batches used for the bioequivalence study.

During development, *in vitro* dissolution testing was performed in various media across the physiological pH range. An appropriate dissolution method was chosen for routine quality control (QC) testing of finished product. The discriminatory power of this dissolution method has been demonstrated.

A bioequivalence study was performed which demonstrated *in vivo* bioequivalence between the test product, Deferiprone Lipomed, and the reference product, Ferriprox. The clinical assessment of this bioequivalence study is discussed in section 2.4 of this report.

Manufacture of the product and process controls

The manufacturing process consists of the following steps: preparation of granulation liquid, granulation of the active substance, preparation of compression mixture, compression, preparation of film-coating solution, preparation of film-coating suspension, film-coating, blistering, secondary packaging.

Appropriate in-process controls are applied throughout the process**.** The process is considered to be a standard manufacturing process. Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product specifications include appropriate tests for this kind of dosage form: visual appearance, dimensions, average mass, uniformity of mass (Ph. Eur.), identity of active substance (HPLC, UV), identity of colourant (Ph. Eur.), assay (HPLC), uniformity of dosage units (Ph. Eur.), impurities (HPLC), loss on drying (Ph. Eur.), dissolution (Ph. Eur.) and microbiological purity (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three commercial scale batches of finished product stored for 12 months (2 batches) and 24 months (one batch) under long term conditions (25 ºC / 60% RH), intermediate conditions (30 ºC / 65% RH) and for up to 6 months (2 batches) and 12 months (one batch) under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested as per the shelf life specifications. The analytical procedures used are stability indicating. However, not all parameters were tested for each storage time point.

Supportive stability data from seven development batches stored up to 60 months under long term conditions (25 ºC / 60% RH), 12 months under intermediate conditions (30 ºC / 65% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. However, as some crucial specification parameters have not been tested in the stability specification of these historic batches, the data obtained from these studies can be treated as supportive only.

There were no out of specification results or trends observed for appearance, assay, impurities, hardness or dissolution results at any storage conditions. The test parameter loss on drying was out of specification in all three commercial batches after 6 months storage at accelerated conditions (40 ºC / 75% RH) and was out of specification in two batches after 12 months storage at intermediate conditions (30 ºC / 65% RH). It was concluded that this increase in loss on drying results is linked to the relative humidity (RH) of the storage conditions. The loss on drying result remained within specification at long term conditions (25 ºC / 60% RH) up to 12 months in all three primary stability batches (and at 24 months for one of the batches). The observed out of specification results on loss on drying do not likely pose any risk to product quality as there is no impact on any other specification parameters (i.e. dissolution or impurities) at the levels detected .Nevertheless, in the absence of any long term data relating to this parameter from the supportive studies, the approved final shelf-life and storage conditions are based on the available 12 months long term data from the three recent commercial batches.

Stability data for one batch of Deferiprone Lipomed 500 mg film-coated tablets stored as bulk (film-coated tablets prior to blistering) covering 6 months of storage at 25°C/60% RH and 40°C/75% RH

are provided. The acceptable holding time for the bulk tablets prior to packaging is 6 months if stored in flat bags made of high density polyethylene at room temperature.

Based on available stability data, the proposed shelf-life of 12 months when stored below 25°C in the proposed blisters as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. Bioequivalence to the reference product, Ferriprox 500 mg film-coated tablets, has been demonstrated. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Deferiprone Lipomed manufactured by Lipomed is considered unlikely to result in any significant increase in the combined sales volumes for all Deferiprone containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Discussion on non-clinical aspects

The Applicant has presented a non-clinical discussion, including a description of impurities expected and their acceptability thresholds which is acceptable. The non-clinical data is reflected in the appropriate

sections of the SmPC. In line with the requirements for generic products, no new non-clinical data was submitted and none is expected.

2.3.4. Conclusion on the non-clinical aspects

The non-clinical aspects are considered acceptable and support the approval of Deferiprone Lipomed 500 mg film-coated tablets.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablets containing deferiprone. To support the marketing authorisation application the applicant conducted 1 bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for the assessment.

GCP

The bioequivalence study was performed in accordance with GCP as claimed by the applicant. No other clinical trial reports have been submitted in support of this marketing authorisation application.

Exemption

This is a generic application for only one strength, hence a biowaiver is not applicable.

Clinical studies

To support the application, the applicant has submitted 1 bioequivalence study.

Table 1: Tabular overview of clinical studies

Type of study	Study identifier	Objective of the study	Study design and type of control	Test products, dosage regimen; route of administration	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status
BE	1221def09ct	The aims of this clinical trial were: - assessment of bioequivalence of test vs. reference after single dose administration under fasting conditions, - evaluation	Single centre, open-label, randomised, balanced, 2-period, 2-sequence, single dose cross-over trial with administration under fasting conditions	One tablet formulation, single dose, oral administration	35 enrolled, 25 randomised, 25 full analysis set, 23 per protocol set	Healthy subjects	A single oral dose of either the test or reference product was administered in one period.	Comple-ted

		of safety and tolerability of test and reference						

2.4.2. Pharmacokinetics

Study 1221 def09ct

Methods

The Applicant has submitted a comparative bioequivalence study protocol number 1221def09ct dated 09/06/2016 which was approved together with the informed consent forms by The Ethics Committee of the Landesärztekammer Thüringen (2016/06/16).

The study centre was SocraTec R&D GmbH, Clinical Pharmacology Unit, Mainzerhofplatz 14, 99084 Erfurt, Germany. Pharmacokinetic evaluation: SocraMetrics GmbH c/o SocraTec R&D GmbH, Im Setzling 35, 61440 Oberursel, Germany; Bioanalytics: ACC GmbH Analytical Clinical Concepts, Schöntalweg 9, 63849 Leidersbach, Germany; Monitoring: SocraTec R&D GmbH, Im Setzling 35, 61440 Oberursel, Germany.

Study design

This was a single centre, open-label, randomised (order of treatments), balanced, 2-period, 2-sequence, single dose crossover trial with administration under fasting conditions to establish comparative bioequivalence of Deferiprone Lipomed 500 mg film-coated tablets and Ferriprox 500 mg film-coated tablets in 25 healthy, adult, male human subjects under fasting conditions (one subject No. 024 was randomised, but dropped out in period I before receiving at least one dosage of the study medication). The objectives of the study were: a) to assess bioequivalence of test vs. reference products after single dose administration under fasting conditions, determined by use of $AUC_{0\text{-tlast}}$ and C_{max} obtained for deferiprone from plasma concentrations; b) to evaluate safety and tolerability of test and reference products considering adverse events observed in the study. One tablet of each product (test and reference) were administered. According to data from literature the elimination half-life of deferiprone had been determined as 2 to 3 hours. Thus, a wash out period of at least three treatment-free days between administrations was sufficient for complete elimination of the active ingredient of the previous administered investigational product from the body.

Test and reference products

The reference product Ferriprox is approved in the European Union. Samples originated from normal production batches. Prior to start of the clinical trial the Reference product was checked with respect to the relevant parameters of pharmaceutical quality.

Population(s) studied

Twenty-five (25) healthy male subjects, Caucasian, aged ≥ 18 years, were randomised. The mean age was 33 years, ranging from 21 to 54 years.

Total number of subjects (planned and analysed): 24 intended to be randomised, 35 enrolled, 25 randomised, 25 full analysis set, 23 per protocol set [(1) subject No. 024 was randomised, but dropped out in period I before receiving at least one dosage of the study medication; (2) for subject No. 015, blood samples No. 3 and 4 (20 min. and 30 min p.a.) could not be withdrawn in period I due to difficulties in

blood sampling]. Since the missing samples were expected to affect the primary parameter C_{max}, this deviation was classified as major and the subject was excluded from PPS and thus from bioequivalence assessment. Intra-individual variability given in the literature determined the CV_{ANOVA} for AUC_{0-inf} with 10 % and C_{max} with 19 %. Thus, following a sample size estimation considering an α = 5 %, 1-α = 80 %, a product ratio of μT/μR of 0.95 to 1.05 as well as acceptance criteria of 80 % - 125 % for AUC_{0-t} and C_{max}, 20 subjects should have been sufficient. Thus, for safety reasons, a sample size of 24 subjects has been chosen for this study. Enrolled subjects formed two population sets. Full analysis set (FAS) defined as all subjects randomised. Per protocol set (PPS) defined as all subjects randomised, who finished the clinical trial as defined in the clinical trial protocol without major protocol deviations.

The decision to exclude subject No. 015 was documented on 13 September 2016 (date of the last signature) prior to sending the bioanalytical samples to the bioanalytical department as well as to their receipt on 14 September 2016 and thus prior to start of bioanalytical measurements.

The primary evaluation in the per protocol set (N=23) excluding subject no. 015 clearly demonstrated bioequivalence between the Test product (Deferiprone Lipomed 500 mg) and the Reference product (Ferriprox) under single dose fasting conditions in the 23 eligible subjects as presented in the following table:

Parametric point estimates and 90% confidence intervals determined for the pharmacokinetic parameters of deferiprone; comparison of Test vs. Reference; excluding subject no. 015

			90% confidence interval		
Parameter	**N**	**Point estimate [%]**	**Lower limit [%]**	**Upper limit [%]**	**CV_{ANOVA} [%]**
$AUC_{0-tlast}$	23	99.72	97.04	102.46	5.36
$AUC_{0-\infty}$	23	99.33	96.65	102.09	5.40
C_{max}	23	97.61	87.52	108.86	21.73

An additional statistical analysis identical to the primary evaluation was conducted including subject no. 015 (for individual values reference is made to the appendix of the clinical trial report). The results of this additional statistical evaluation including subject no. 015 are presented in the following table:

Parametric point estimates and 90% confidence intervals determined for the pharmacokinetic parameters of deferiprone; comparison of Test vs. Reference; including subject no. 015

			90% confidence interval		
Parameter	**N**	**Point estimate [%]**	**Lower limit [%]**	**Upper limit [%]**	**CV_{ANOVA} [%]**
$AUC_{0-tlast}$	24	100.10	97.46	102.82	5.41
$AUC_{0-\infty}$	24	99.67	97.04	102.38	5.41
C_{max}	24	97.37	87.74	108.05	21.24

In summary, inclusion of subject no. 015 in the statistical evaluation does not change the assessment of bioequivalence between the Test product (Deferiprone Lipomed 500 mg) and the Reference product (Ferriprox) under single dose fasting conditions and clearly indicates that the impact of the exclusion of subject no. 015 from the primary evaluation is nearly negligible.

Main inclusion criteria

Male subjects must fulfilled all the following criteria:

1. sex: male

2. ethnic origin: Caucasian

3. age: 18 years or older

4. body-mass index1 (BMI): ≥ 18.5 kg/m² and ≤ 30.0 kg/m²

5. good state of health

6. non-smoker or ex-smoker for at least 1 month

7. written informed consent, after having been informed about benefits and potential risks of the clinical trial, as well as details of the insurance taken out to cover the subjects participating in the clinical trial

Analytical methods

Deferiprone in plasma samples was analysed by use of a validated method.

Storage period of study samples

Blood samples for concentration measurements of deferiprone were collected in 7.5 ml tubes (Lithium heparinized tubes) from a vein using an indwelling cannula with switch valve or by direct venipuncture.

After blood collection lithium heparinized tubes were cooled immediately in an ice bath until centrifugation. The samples were centrifuged within 30 min (centrifugation conditions: 2000 x g, 10 min, 4°C) in order to separate formed elements. The supernatant plasma was divided into two parts and was transferred to two clean tubes and subsequently frozen at a temperature below -20°C. Time span between blood sampling and freezing of the samples should not have exceeded 60 min. Plasma was stored in frozen state at or below -20°C until time of analysis.

Bioanalytical report

The bioanalytical report was submitted. Analyses were performed by ACC GmbH Analytical Clinical Concepts. The quantification of deferiprone in plasma was performed using a validated method.

Dosing started on 01.09.2016 and the bioanalysis was performed between 19.09.2016 to 29.09.2016 (two shipments – 1) 14.09.2016; 2) 21.09.2016). Long term stability was determined for 43 days at below-20^{0}C. This time span was sufficient as time between withdrawal of first PK sample and last analytical measurement did not exceed 15 days. 816 (for 24 subjects) samples were expected according to the protocol however 814 blood samples were received. There were 1.6 % haemolysed samples in the study (≤ 1 % haemolysis). There were no lipaemic samples in the study.

According to the Analytical Study Protocol the study samples were to be stored at or below -20 °C at ACC GmbH. However, in the time span between receipt and measurement of the study samples the temperature increased above -20 °C for about 60 min with the highest temperature being -15.2 °C. As stability of deferiprone in plasma was proven for 6 hours at room temperature and for three thaw/freeze cycles during method validation, the above mentioned increase of the storage temperature did not affect the concentration of deferiprone in the study samples and has therefore no influence on the obtained study results.

In this study the total number of study samples measured was 814. In total 0.2 % of the samples were repeated.

Incurred Sample Reanalysis

In this study, the scheduled total number of subject samples was 816. Incurred sample reanalysis was performed on 88 samples (10.8 %). As a criterion of acceptance two thirds of the repeat samples should agree within ± 20 %. In total, 94.3 % of the repeat samples agreed within ± 20 %. Therefore, the acceptance criteria were fulfilled and incurred sample reanalysis was in accordance with the European guideline.

Pharmacokinetic variables

Pharmacokinetic parameters were derived by means of non-compartmental analysis and were listed and evaluated descriptively (number of subjects (N), arithmetic mean, standard deviation (SD), geometric mean, geometric coefficient of variation (CV), median, minimum and maximum) separated by treatment.

Primary parameters: C_{max}, $AUC_{0\text{-}tlast}$

Secondary parameters: $AUC_{0\text{-}\infty}$, $AUC_{expol\%,}$ Clast, t_{max}, t1/2, t_{last}, Lz (= λ), t_{lag} of deferiprone.

Bioequivalence criteria: Analysis of Variance (ANOVA) was performed and used as basis for the calculation of 90 % confidence intervals; point estimates and confidence intervals for AUC- and C_{max}-values and the comparison of Test vs. Reference were calculated by parametric analysis. AUC0-tlast and C_{max} were considered as primary decision criteria for bioequivalence assessment. For parametric 90 % confidence intervals, acceptance limits of 80.00 % - 125.00 % for $AUC_{0\text{-}tlast}$ and C_{max} were applied.

Statistical methods

The statistical analyses were performed as a valid case analysis including all subjects of the per-protocol set (no subgroup analysis was planned). Descriptive statistics (N, arithmetic means, SD, geometric means, geometric CV, medians, minimum, and maximum) were presented for all pharmacokinetic parameters. The statistical analyses were carried out on the basis of a multiplicative model for all AUC- and C_{max}-values. Analyses of variances were performed as pairwise comparison of Test vs. Reference for $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$ and C_{max}-values including the factors formulation, period, sequence and subject (sequence). Intra-subject variability was estimated and period, subject and sequence effects were determined. Affiliated statistical analyses were conducted with α = 0.05. Parametric point and interval estimates of Test/Reference ratio were calculated for AUC and C_{max}–values. Relative bioavailability of Test vs. Reference was assessed by the ratios of geometric means (point estimates). Ninety (90) % confidence intervals served as interval estimates and were determined by parametric analysis (two one-sided t-tests). Testing for bioequivalence was performed considering the primary target variables ($AUC_{0\text{-}tlast}$ and C_{max}). Decision in favor of bioequivalence was accepted when the parametric 90 % confidence intervals did not exceed the limits of 80.00 and 125.00% for the ratio of primary target variables. The decision procedure based on 90 % confidence intervals corresponded to two one-sided tests with an error probability α= 0.05.

Also submitted study had data quality assurance procedures established. Methods of detecting outliers, corrections of data and missing data handling were established in protocol. This included all activities undertaken during and after the clinical trial to verify and control quality. It embraced internal quality control by the staff itself and by independent second persons as well as monitoring and separate auditing activities. All activities were performed according to written procedures of the MAH and the facilities involved.

Results

Maximum exposure, represented by geometric mean C_{max}-values, was quite similar for both products with 7020.22 ng/ml for Test and 7153.44 ng/ml for Reference. The ranges of observed C_{max}-values were similar for both products with 3336.60 ng/ml to 11168.50 ng/ml for Test and 3739.60 ng/ml to 11322.40 ng/ml for Reference.

Extent of bioavailability, represented by geometric mean AUC0-tlast-values, was (13263.53 h*ng/ml) for Test and (13294.49 h*ng/ml) for Reference. The ranges were 8098.20 to 19812.03 h*ng/ml for Test and 7901.32 to 21760.13 h*ng/ml for Reference. The mean time points of maximum exposure, represented by median values of t_{max}, were comparable for both treatments (0.67 h for Test and 0.60 h for Reference). The latest t_{max} observed was at 1.67 h after Test and at 1.35 h after Reference. Mean apparent terminal elimination half-life ($t_{1/2}$) has been calculated with 1.71 h for Test and 1.74 h for Reference and was comparable.

Table 2: Mean pharmacokinetic parameters of deferiprone after oral single dose administration of Deferiprone 500 Lipomed (Test) or Ferriprox (Reference) under fasting conditions to 23 subjects (500 mg deferiprone per treatment)

Pharmacokinetic parameter	Test		Reference	
	<arithmetic> <geometric> mean	<SD> <CV%>	<arithmetic> <geometric> mean	<SD> <CV%>
$AUC_{(0\text{-}tlast)}$	13679.53 13263.53	3409.74 26.16	13809.76 13294.49	3805.94 29.19
$AUC_{(0\text{-}\infty)}$	14258.45	3594.78	14464.62	4081.01
C_{max}	7364.50	2268.42	7419.12	1978.81
T_{max}*	0.67	0.39	0.60	0.29

$AUC_{(0\text{-}tlast)}$ area under the concentration vs. time curve from dosing to the last measurable concentration
$AUC_{0\text{-}\infty}$ area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
T_{max} time for maximum concentration (* median, range)

Table 3 Parametric point estimates and 90 % confidence intervals determined for the primary pharmacokinetic parameters of deferiprone; comparison of Test vs. Reference

			90% confidence interval		
Parameter	N	Point estimate [%]	Lower limit [%]	Upper limit [%]	CV_{ANOVA} [%]
$AUC_{0\text{-}tlast}$	23	99.72	97.04	102.46	5.36
C_{max}	23	97.61	87.52	108.86	21.73

For the primary pharmacokinetic parameter $AUC_{0\text{-}tlast}$ a point estimate of 99.72 % with an affiliated confidence interval of 97.04 – 102.46 % was calculated. For C_{max}, which was also defined as primary criterion, a point estimate of 97.61 % with an affiliated confidence interval of 87.52 – 108.86 % was calculated. Thus, both confidence intervals were within the pre-set acceptance limits of 80.00 – 125.00 %, and bioequivalence of Test and Reference was demonstrated with regard to $AUC_{0\text{-}tlast}$ and C_{max} of the compound deferiprone. CV_{ANOVA} was lower for $AUC_{0\text{-}tlast}$ compared to C_{max} with values of 5.36 % and 21.73 %, respectively.

Safety data

Twenty-four subjects received at least 1 tablet of Test or Reference. One subject No. 024 was randomised, but was excluded from the study before receiving at least one dosage of the study medication. In the remaining subjects drug exposure was in accordance with the protocol. Twenty-four subjects received 1 tablet of Test and Reference each. Therefore, drug exposure was 1 x 500 mg of deferiprone in each period. Hence, total dose of each subject was 2 x 500 mg resulting in 1000 mg deferiprone in total.

After study drug intake, 5 subjects showed 7 AEs (according to their MedDRA coded preferred term (PT) grouped by system organ class (SOC), intensity and relationship to IMPs); 5 after Test treatment and 2 after Reference treatment. The most frequent AE, which was reported after study drug intake was headache (4 cases). All other AEs occurred only once. In total, 5 out of 7 AEs were classified as study drug related. Two of the AEs were classified with no causal relationship to the investigational products. All AEs reported after study drug intake resolved completely. No subject dropped out due to AEs.

Based on the results obtained in the bioequivalence study (EudraCT-No.: 2015-005301-36), the Deferiprone 500 Lipomed (Test) and Ferriprox (Reference) in healthy human adult subjects, could be judged as bioequivalent.

Conclusions

Based on the presented bioequivalence study Deferiprone Lipomed is considered bioequivalent with Ferriprox.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

Deferiprone monotherapy is indicated for the treatment of iron overload in patients with thalassaemia major when current chelation therapy is contraindicated or inadequate. Deferiprone is furthermore indicated in combination with another chelator 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 justifies rapid or intensive correction.

To support the application, the Applicant has submitted one bioequivalence study (BE). The BE has been performed using the originator; the test product (Deferiprone Lipomed 500 mg film-coated tablets) and the reference product (Ferriprox 500 mg film coated tablets). The reference product Ferriprox is approved in the European Union (MA Holder: Apotex Europe B.V., MA number: EU/1/99/108/001). The study has been performed under fasting conditions. According to the reference product SmPC recommendation (Ferriprox, SmPC), the drug should be taken on an empty stomach.

According to literature data obtained earlier, mean maximum serum concentrations of approximately 32.4 (± 13.2) µg/ml were expected after a dose of 1500 mg deferiprone in Thai healthy volunteers. The analytical method planned for this clinical trial was intended to allow a LLOQ of 0.20 µg/ml for deferiprone. Therefore, deferiprone at dose 500 mg was chosen to achieve sufficient plasma levels to characterize the pharmacokinetic profile.

The methodology related to sample size calculation and statistical evaluation of bioequivalence of two products was clearly presented and properly discussed. Parameters chosen for sample size calculations were appropriate and in line with the requirements of the guidelines. $AUC_{0\text{-}tlast}$ and C_{max} were considered as primary decision criteria for bioequivalence assessment. Statistical analyses in presented study were designed and conducted according to assumptions and recommendations for bioequivalence studies. The SAP often referred to the Guideline on the Investigation of Bioequivalence. The methodology related to ANOVA modelling and two one-sided test (TOST) was clearly presented and properly discussed. Moreover, submitted dossier was implemented with widely described data management procedures and data assurance procedures. Presented protocol included list of software to be used to results analyses.

The subjects were randomly assigned to one of the 2 possible treatment sequences according to Latin square. Blood samples were taken at the following time points: pre-dose samples: within 1.5 h prior to dosing; post-dose samples: 10 min, 20 min, 30 min, 40 min, 50 min, 1 h, 1 h 20 min, 1 h 40 min, 2 h, 2 h 30 min, 3 h, 4 h, 5 h, 6 h, 7 h and 8 h p.a. The sampling periods are acceptable with sample time points around t_{max} for deferiprone and with an adequate wash-out period (at least 3 treatment free days) at greater than five times the $t_{1/2}$ (2-3 hours for deferiprone). The sampling frequency enabled an adequate

estimation of C_{max}. The sampling schedule covered the plasma concentration time curve long enough to provide a reliable estimate of the extent of exposure.

Certificates of analysis for both the test and reference products have been provided. Assay values of 99.5% (497.5 mg) and 100.24% (501.2 mg) for the test and reference are reported respectively. The assayed content of the batch used as test product did not differ more than 5% from that of the batch used as reference product. The batch size and manufacturing date of the test product have been declared and are acceptable.

Data from literature showed gender-related differences with higher AUC and lower clearance-values in females. Inter-individual variability of C_{max} seemed to be higher in females.

Furthermore, as females often suffer from menstruation related iron deficiency anaemia which might worsen after intake of study medication and due to the clastogenic and teratogenic properties of the deferiprone, females were not intended to participate for safety reasons, too. Thus, only male subjects participated in the study. Twenty-five healthy male subjects, Caucasian, aged ≥ 18 years, were randomised. The mean age was 33 years, ranging from 21 to 54 years. Total number of subjects (planned and analysed): 24 intended to be randomised, 35 enrolled, 25 randomised, 1 drop out, 25 full analysis set, 23 per protocol set.

The inclusion and exclusion criteria are acceptable and performed according to the protocol. All subjects are observed and treated according to the same rules. The data from all treated subjects was treated equally. The population studied is appropriate and the main inclusion and exclusion criteria are in line with the requirements of the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01). It appeared that 20 subjects would be sufficient to demonstrate the bioequivalence of Deferiprone and Ferriprox. However, bearing in mind that intra-individual variability of AUC and C_{max} was established in the study with Asian people, a bigger sample size has been was chosen (n=24). That approach is accepted. 23 subjects completed the study.

The analytical method for the determination of deferiprone in human plasma seems to be described adequately; the validations were performed according to the requirements of the EMA "Guideline on bioanalytical method validation" (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**)". Acceptance criteria are in a plausible range. The analytical methods used are acceptable and appropriate. The calibration curves are appropriate and the stability testing supports the conditions the samples were exposed to during collection and testing. The Applicant has also provided relevant supportive data together with certificates of analysis for the analyte standard and internal standards used in the analytical method validation. The relevant SOPs have been provided and deemed valid. The validation report (Validation of determination of deferiprone in plasma samples of subjects) was provided, which contains the requested full recovery results.

Pharmacokinetic parameters were derived by means of non-compartmental analysis and were listed and evaluated descriptively (number of subjects (N), arithmetic mean, standard deviation (SD), geometric mean, geometric coefficient of variation (CV), median, minimum and maximum) separated by treatment. Primary parameters: C_{max}, $AUC_{0\text{-}tlast}$. Secondary parameters: $AUC_{0\text{-}\infty}$, $AUC_{expol\%}$, C_{last}, t_{max}, $t_{1/2}$, t_{last}, Lz (= λ), t_{lag} of deferiprone. These parameters were estimated to evaluate bioavailability.

Bioequivalence criteria: Analysis of Variance (ANOVA) was performed and used as basis for the calculation of 90 % confidence intervals; point estimates and confidence intervals for AUC- and C_{max}-values and the comparison of Test vs. Reference were calculated by parametric analysis. $AUC_{0\text{-}tlast}$ and C_{max} were considered as primary decision criteria for bioequivalence assessment. For parametric 90 % confidence intervals, acceptance limits of 80.00 % - 125.00 % for $AUC_{0\text{-}tlast}$ and C_{max} were applied. The pharmacokinetic variables are adequate. Acceptance range for bioequivalence is 80.00%-125.00% for

90% confidence intervals of the geometric least square means ratio for C_{max} and $AUC_{0\text{-}tlast}$ of deferiprone. This is a conventional approach. The appropriate variables were measured and statistical methodology is accepted. The sampling schedule provides adequate estimation of C_{max}. Statistical data and a graphical representation to cover the plasma concentration time curve long enough to provide an estimate of the extent of absorption, has been provided.

It was observed that maximum exposure, represented by geometric mean C_{max}-values, was similar for both products with 7020.22 ng/ml for Test and 7153.44 ng/ml for Reference. The ranges of observed C_{max}-values were similar for both products with 3336.60 ng/ml to 11168.50 ng/ml for Test and 3739.60 ng/ml to 11322.40 ng/ml for Reference.

Extent of bioavailability, represented by geometric mean $AUC_{0\text{-}tlast}$-values, was (13263.53 h*ng/ml) for Test and (13294.49 h*ng/ml) for Reference, the ranges were 8098.20 to 19812.03 h*ng/ml for Test and 7901.32 to 21760.13 h*ng/ml for Reference. The mean time points of maximum exposure, represented by median values of t_{max}, were comparable for both treatments (0.67 h p.a. for Test and 0.60 h p.a. for Reference). The latest t_{max} observed was at 1.67 h after test and at 1.35 h after reference. Mean apparent terminal elimination half-life ($t_{1/2}$) has been calculated with 1.71 h for test and 1.74 h for reference and was comparable.

For the primary pharmacokinetic parameter $AUC_{0\text{-}tlast}$ a point estimate of 99.72 % with an affiliated confidence interval of 97.04 – 102.46 % was calculated. For C_{max}, which was also defined as primary criterion, a point estimate of 97.61 % with an affiliated confidence interval of 87.52 – 108.86 % was calculated. Thus, both confidence intervals were within the pre-set acceptance limits of 80.00 – 125.00 %, and bioequivalence of Test and Reference was demonstrated with regard to $AUC_{0\text{-}tlast}$ and C_{max} of the compound deferiprone. CV_{ANOVA} was lower for $AUC_{0\text{-}tlast}$ compared to C_{max} with values of 5.36 % and 21.73 %, respectively.

A total of 25 subjects were evaluated for safety. One subject was randomized, but dropped out in period I before receiving at least one dosage of the study medication. A total of 24 subjects were exposed to the IMPs. Both products were found to be safe and well tolerated. There were no serious adverse events (AEs) reported in this study. The adverse event was not life threatening or required the subjects to be hospitalized.

After study drug intake, 5 subjects showed 7 AEs -5 after Test treatment and 2 after Reference treatment. The most frequent AE, which was reported after study drug intake was headache (4 cases). In total, 5 out of 7 AEs were classified as study drug related. Two of the AEs were classified with no causal relationship to the investigational products. All AEs reported after study drug intake resolved completely.

The incidence of AEs reported for the bioequivalence study was moderate. After study drug intake, 5 subjects showed 7 AEs; 5 after Test treatment and 2 after Reference treatment. All AEs reported after study drug intake resolved completely. No subject dropped out due to AEs. There were no serious AEs reported. The most frequent AE, which was reported after study drug intake was headache (4 cases). All other AEs occurred only once: vision blurred, diarrhoea, nausea. Two cases of headache occurred in Test-treated subjects and two cases of headache occurred in Reference-treated subjects. All cases were of mild intensity. With regard to the occurrence of headache, there is no difference between Test treatment and Reference treatment.

One case of vision blurred of mild intensity occurred in a Test-treated subject while no case of vision blurred occurred in a Reference-treated subject. This case of vision blurred was classified as not related to study medication. Due to this classification of relationship and given the very low number of one case only, it is not considered that this could represent an actual difference between Test treatment and Reference treatment.

One case of diarrhoea of mild intensity occurred in a Test-treated subject while no case of diarrhoea occurred in a Reference-treated subject. Given the very low number of one case only, it is not considered that this could represent an actual difference between Test treatment and Reference treatment. One case of nausea of mild intensity occurred in a Test-treated subject while no case of nausea occurred in a Reference-treated subject. Given the very low number of one case only, it is not considered that this could represent an actual difference between Test treatment and Reference treatment.

In general, the tolerability of both Test and Reference medication was completely in accordance with the known safety and tolerability profile of the drug substance.

2.4.6. Conclusions on clinical aspects

The presented study was designed and conducted according to recommendations of the EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). The sample size was calculated to provide adequate power of bioequivalence analysis and the statistical methodology was justified and consistent with the principles of guidelines on the investigation of bioequivalence. Based on the results obtained in the bioequivalence study (EudraCT-No.: 2015-005301-36) in healthy male subjects, Deferiprone Lipomed (Test) and Ferriprox (Reference) could be judged as bioequivalent.

2.5. Risk management plan

Safety concerns

The summary of safety concerns has been adapted to the current version for the reference product.

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 sufficient to identify and characterise the risks of this generic product as most studies conducted by the MAH of the reference product are already finalized or will be soon finalized (2019/2020 USA/Canada).

Routine pharmacovigilance remains sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

In line with the reference product the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

Direct Healthcare Professional Communication (DHPC) has already been addressed to the healthcare professional by MAH of the reference product in 2006. As no increase of reporting rate of cases of agranulocytosis and neutropenia have been identified in the last PSUR of the reference product and the risks are well identified, no DHPC is necessary for generics.

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important identified risks		
Agranulocytosis	Routine risk minimisation measures: Routine risk communication in SmPC sections 4.3 and 4.4 / PL section 2 Recommendation for specific clinical measures in SmPC section 4.4 Prescription only Additional risk minimisation measures: Wallet-sized patient/carer reminder card provided in the folding box (Annex IIIA)	Routine Pharmacovigilance
Neutropenia	Routine risk minimisation measures: Routine risk communication in SmPC sections 4.3 and 4.4 / PL section 2 Recommendation for specific clinical measures in SmPC section 4.4 Prescription only Additional risk minimisation measures: Wallet-sized patient/carer reminder card provided in the folding box (Annex IIIA)	Routine Pharmacovigilance
Use in pregnancy	Routine risk minimisation measures: Routine risk communication in SmPC sections 4.3, 4.6, 5.3 / PL section 2 Prescription only Additional risk minimisation measures: Wallet-sized patient/carer reminder card provided in the folding box (Annex IIIA)	Routine Pharmacovigilance
Arthropathy (including arthralgia)	Routine risk minimisation measures: Routine risk communication in SmPC sections 4.8 / PL section 4 Prescription only Additional risk minimisation measures:	Routine Pharmacovigilance

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	None	
Increased liver function test values	Routine risk minimisation measures: Routine risk communication in SmPC section 4.8 / PL section 4 Recommendations for specific clinical measures in SmPC section 4.4 / PL section 2 Prescription only Additional risk minimisation measures: None	Routine Pharmacovigilance
Skin disorders	Routine risk minimisation measures: Routine risk communication in SmPC section 4.8 / PL section 4 Prescription only Additional risk minimisation measures: None	Routine Pharmacovigilance
Allergic reactions	Routine risk minimisation measures: Routine risk communication in SmPC section 4.8 / PL section 4 Prescription only Additional risk minimisation measures: None	Routine Pharmacovigilance
Important potential risks		
Carcinogenicity	Routine risk minimisation measures: Routine risk communication in SmPC section 4.4 Prescription only Additional risk minimisation measures: None	Routine Pharmacovigilance
Missing information		
Lactation toxicity	Routine risk minimisation measures: Routine risk communication in SmPC sections 4.3 and 4.6 / PL section 2 Prescription only Additional risk minimisation measures: None	Routine Pharmacovigilance
Off-label use	Routine risk minimisation measures: Routine risk communication in SmPC sections 4.2 and 4.3 / PL sections 2 and 3 Prescription only Additional risk minimisation measures: None	Routine Pharmacovigilance
Long-term safety	Routine risk minimisation measures:	Routine Pharmacovigilance

Safety concern	Risk minimisation measures	Pharmacovigilance activities
data	Prescription only Additional risk minimisation measures: None	
Risk in immunocompromised patients	Routine risk minimisation measures: Routine risk communication in SmPC section 4.4 / PL section 2 Recommendations for specific clinical measures in SmPC section 4.4 / PL section 2 Prescription only Additional risk minimisation measures: None	Routine Pharmacovigilance

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.2 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports 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.

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Ferriprox. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of deferiprone film coated tablets. The reference product Ferriprox 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 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 justifies rapid or intensive correction. No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and

considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with a single centre, open-label, randomised (order of treatments), balanced, 2-period, 2-sequence, single dose crossover trial with administration under fasting conditions to establish comparative bioequivalence of Deferiprone Lipomed 500 mg film-coated tablets and Ferriprox 500 mg film coated tablets. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Deferiprone Lipomed met the protocol-defined criteria for bioequivalence when compared with Ferriprox. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Deferiprone Lipomed is favourable in the following indication:

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 justifies rapid or intensive correction (see section 4.2).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports 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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

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 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/Carer reminder card as a part of the outer packaging.

The Patient/Carer reminder 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

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.