Public Assessment Report

Decentralised Procedure

Deferasirox Alkem 125 mg Dispersible Tablets
Deferasirox Alkem 250 mg Dispersible Tablets
Deferasirox Alkem 500 mg Dispersible Tablets
(deferasirox)

Procedure No: UK/H/6770/001-003/DC
UK Licence Number/s: PL 35646/0071-0073

Alkem Pharma GmbH
Lay Summary

Deferasirox Alkem 125, 250 & 500 mg Dispersible Tablets
(deferasirox)

This is a summary of the Public Assessment Report (PAR) for Deferasirox Alkem 125, 250 & 500 mg Dispersible Tablets (PL 35646/0071-0073; UK/H/6770/001-003/DC). It explains how Deferasirox Alkem 125, 250 & 500 mg Dispersible Tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products. These products will be collectively referred to as Deferasirox Dispersible Tablets throughout the lay summary, for ease of reading.

For practical information about using Deferasirox Dispersible Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Deferasirox Dispersible Tablets and what are they used for?
Deferasirox Dispersible Tablets are ‘generic medicines’. This means that Deferasirox Dispersible Tablets are similar to ‘reference medicines’ already authorised in the European Union (EU) called Exjade 125 mg, 250 mg & 500 mg dispersible tablets (EU/1/06/356/001-010).

Deferasirox Alkem Dispersible Tablets are used to treat chronic iron overload caused by frequent blood transfusions in patients with a type of anaemia called beta thalassaemia major, aged 6 years and older.

Deferasirox Alkem Dispersible Tablets are also used to treat chronic iron overload when deferoxamine therapy (another medicine) is contraindicated or inadequate in:

- children aged 2 to 5 years with beta thalassaemia major with iron overload caused by frequent blood transfusions,
- adults and children aged 2 years and above with beta thalassaemia major with iron overload caused by infrequent blood transfusions,
- adults and children aged 2 years and above with other types of anaemias.

Deferasirox Alkem Dispersible Tablets are also used when deferoxamine therapy is contraindicated or inadequate to treat patients aged 10 years or older who have iron overload associated with their thalassaemia syndromes, but who are not transfusion dependent.

How do Deferasirox Dispersible Tablets work?
Deferasirox Alkem Dispersible Tablets contain an active substance called deferasirox. It is an iron chelator meaning that it binds to iron. Deferasirox Dispersible Tablets are used to remove excess iron from the body (also called iron overload), it does this by trapping excess iron which is then excreted mainly in the stools.

How are Deferasirox Dispersible Tablets used?
The pharmaceutical form of this medicine is a dispersible tablet and the route of administration is oral (by mouth).

The dose of Deferasirox Dispersible Tablets is related to body weight for all patients. The patient’s doctor will calculate the dose needed and tell their patient how many tablets to take each day.

- The usual daily dose for Deferasirox Dispersible Tablets at the start of the treatment for patients receiving regular blood transfusions is 20 mg per kilogram body weight. A higher or lower starting dose may be recommended by the patient’s doctor based on their individual treatment needs.
- The usual daily dose for Deferasirox Dispersible Tablets at the start of the treatment for patients not receiving regular blood transfusions is 10 mg per kilogram body weight.
• Depending on how the patient responds to treatment, the patient’s doctor may later adjust the treatment to a higher or lower dose.

• The maximum recommended daily dose for Deferasirox Dispersible Tablets is:
  - 40 mg per kilogram body weight for patients receiving regular blood transfusions,
  - 20 mg per kilogram body weight for adult patients not receiving regular blood transfusions
  - 10 mg per kilogram body weight for children and adolescents not receiving regular blood transfusions.

Deferasirox is also available as “film-coated” tablets and granules. If the patient is switching from the film-coated tablets or granules to these dispersible tablets, an adjustment of the dose will be required.

For further information on how Deferasirox Dispersible Tablets are used, refer to the package leaflet and Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

**What benefits of Deferasirox Dispersible Tablets have been shown in studies?**
Because Deferasirox Dispersible Tablets are generic medicines, studies have been limited to tests to determine that they are bioequivalent to the reference medicines, Exjade 125 mg, 250 mg & 500 mg dispersible tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Deferasirox Dispersible Tablets?**
Because Deferasirox Dispersible Tablets are generic medicines and are bioequivalent to the reference medicines, Exjade 125 mg, 250 mg & 500 mg dispersible tablets, their benefits and possible side effects are taken as being the same as the reference medicines.

For the full list of restrictions, see the package leaflet.
For the full list of all side effects reported with Deferasirox Dispersible Tablets, see section 4 of the package leaflet available on the MHRA website.

**Why were Deferasirox Dispersible Tablets approved?**
It was concluded that, in accordance with EU requirements, Deferasirox Dispersible Tablets have been shown to have comparable quality and to be bioequivalent to Exjade 125 mg, 250 mg & 500 mg dispersible tablets. Therefore, the MHRA decided that, as for Exjade 125 mg, 250 mg & 500 mg dispersible tablets, the benefits are greater than the risks and recommended that the products can be approved for use.

**What measures are being taken to ensure the safe and effective use of Deferasirox Dispersible Tablets?**
A risk management plan (RMP) has been developed to ensure that Deferasirox Dispersible Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPCs) and the package leaflet for Deferasirox Dispersible Tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

**Other information about Deferasirox Dispersible Tablets**
Germany and the UK agreed to grant Marketing Authorisations for Deferasirox Dispersible Tablets on 11 December 2018. Marketing Authorisations were granted in the UK on 10 January 2019.

The full PAR for Deferasirox Dispersible Tablets follows this summary.

This summary was last updated in March 2019.
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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Deferasirox Alkem 125, 250 & 500 mg Dispersible Tablets (PL 35646/0071-0073; UK/H/6770/001-003/DC), are approvable. Deferasirox Alkem 125, 250 & 500 mg Dispersible Tablets are prescription only medicines (POM) indicated for:

- The treatment of chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older.
- Deferasirox Alkem Dispersible Tablets are also indicated for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups:
  - in paediatric patients with beta thalassaemia major with iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) aged 2 to 5 years,
  - in adult and paediatric patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells) aged 2 years and older,
  - in adult and paediatric patients with other anaemias aged 2 years and older.

Deferasirox Alkem Dispersible Tablets are also indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older.

The active substance deferasirox is an orally active chelator that is highly selective for iron (III). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Deferasirox promotes excretion of iron, primarily in the faeces. Deferasirox has low affinity for zinc and copper, and does not cause constant low serum levels of these metals.

The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. The reference products are Exjade 125 mg, 250 mg & 500 mg dispersible tablets (EU/1/06/356/001-010) authorised to Novartis Europharm Limited, registered since 31 August 2006. The orphan market exclusivity period for Exjade 125 mg, 250 mg & 500 mg dispersible tablets expired on 1st September 2016, and their use as reference products is accepted.

A single bioequivalence study conducted under fasting conditions was submitted to support these applications. The bioequivalence study is stated to have been conducted in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that these applications were based on products being generic medicinal products of an originator product that has been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considered that these applications could be approved at the end of procedure on 11 December 2018. After a subsequent national phase, Marketing Authorisations (PL 35646/0071-0073) were granted in the UK on 10 January 2019.
II QUALITY ASPECTS

II.1 Introduction
Each tablet contains 125, 250, or 500 mg of deferasirox as the active ingredient. The other ingredients are microcrystalline cellulose, crospovidone type A, hydroxypropyl cellulose (low-substituted) colloidal silicon dioxide, hypromellose, sodium lauryl sulfate, disodium hydrogen phosphate, hydrogenated castor oil, and magnesium stearate.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

Deferasirox Dispersible Tablets are packaged in a high-density polyethylene (HDPE) bottle pack in a pack size of 30 dispersible tablets. The bottle also includes a canister with silica gel, which is not for human consumption.

Deferasirox Dispersible Tablets are also packaged in a polyvinyl chloride (PVC)-Aclar/aluminium (Alu) blister pack and PVC-polyethylene (PE)-polyvinylidene chloride (PVdC)/Alu blister pack containing 10, 14, 28, 84, or 252 dispersible tablets.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance
INN: Deferasirox
Chemical name: 4-[3,5-bis(2-hydroxyphenyl)-1H[1,2,4]triazol-1-yl]benzoic acid

Structure:

![Structure of Deferasirox]

Molecular formula: \( \text{C}_{21}\text{H}_{15}\text{N}_{3}\text{O}_{4} \)
Molecular weight: 373.36
Appearance: Off white to pale yellow colour powder.
Solubility: Soluble in dimethyl formamide, slightly soluble in methanol, insoluble in water, very slightly soluble in methylene chloride, practically insoluble toluene

Deferasirox is the subject of an active substance master file (ASMF).

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.
An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards used.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product

Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious dispersible tablets containing 125, 250 or 500 mg of deferasirox per dispersible tablet, that are generic versions of the reference products Exjade 125 mg, 250 mg & 500 mg dispersible tablets (EU/1/06/356/001-010).

A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro dissolution profiles have been provided for the proposed and reference products.

No materials of animal origin covered by the TSE guideline are contained or used in the manufacturing process of the medicinal product.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the products
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished products. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications
The finished product release and shelf life specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications have been provided. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of the finished products in the packaging proposed for marketing. The data from these studies support a shelf life of 2 years. This medicinal product does not require any special storage conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of these applications from a pharmaceutical viewpoint.
III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of deferasirox are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Related substances and residual solvents are in line with ICH Q3A for drug substance impurities and ICH Q3C for residual solvents.

A satisfactory risk assessment for elemental impurities in line with ICH Q3D has been provided.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Deferasirox Alkem 125, 250 & 500 mg Dispersible Tablets are intended for generic substitution, this will not lead to an increased environmental exposure. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of these applications from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology of deferasirox is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of deferasirox.

Based on the data provided, Deferasirox Alkem 500 mg Dispersible Tablets can be considered bioequivalent to Exjade® (Deferasirox) 500 mg dispersible tablets, (Novartis Europharm Limited).

IV.2 Pharmacokinetics
In support of these applications, the applicant submitted the following bioequivalence study:

An open label, balanced, pivotal, laboratory blind, randomized, two period, two treatment, two sequence, single dose, two way crossover, bioequivalence study of the applicant’s test product Deferasirox tablets, for oral suspension 500 mg (Deferasirox Alkem 500 mg Dispersible Tablets), versus the reference product Exjade® (Deferasirox) 500 mg dispersible tablets, (Novartis Europharm Limited) in 34 healthy adult male human subjects under fasting condition.

Following an overnight fast of at least 10 hours, subjects were administered a single oral dose (1 x 500mg dispersible tablet) of the test or reference product.
Blood samples were collected for plasma levels before dosing and up to and including 72 hours after each administration. The washout period between the treatment phases was 7 days.
Summary of pharmacokinetic results:

<table>
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<th>Parameter</th>
<th>Ratio % (T/R)</th>
<th>Lower Limit %</th>
<th>Upper Limit %</th>
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<td>Cmax (ng/ml)</td>
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<td>AUC (0-1) (ng/ml).hr</td>
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</table>

Study conclusion
The 90% confidence intervals of the test/reference ratio for AUC0-t and Cmax values for deferasirox lie within the acceptable limits of 80.00% to 125.00%, in line with the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr*). Thus, the data support the claim that the applicant’s test product Deferasirox tablets, for oral suspension 500 mg is bioequivalent to the reference product Exjade® (Deferasirox) 500 mg dispersible tablets, (Novartis Europharm Limited).

As the 125 and 250 mg strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence study with the 500mg tablet strength can be extrapolated to the 125 and 250 mg strengths.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for applications of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted, and none were required for applications of this type.

IV.5 Clinical safety
Apart from the data from the bioequivalence study, no new safety data were submitted and none are required. No new or unexpected safety concerns were identified in the study.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
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 Deferasirox Dispersible 125, 250 & 500 mg Tablets.

The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns (labelling in the SmPC and the PIL). This is agreed.

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 MHRA;
- 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 an RMP coincide, they can be submitted at the same time, but via different procedures.
IV.7  Discussion on the clinical aspects
The grant of marketing authorisations is recommended for these applications from a clinical viewpoint.

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 products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with deferasirox is considered to have demonstrated the therapeutic value of the compound. The products are bioequivalent to the marketed reference products and their risks and benefits are considered similar. The benefit-risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for this medicine is presented below:
DCPAR Deferasirox Alkem 125, 250 & 500 mg Dispersible Tablets

**Warning/Other information**

**Oral use**

Read the package leaflet before use.

Take this medicine on an empty stomach.

Disperse tablets in water, orange juice or apple juice before swallowing.

Do not swallow whole or chew.

**POM**

Medical product subject to medical prescription.

Keep out of the sight and reach of children.

PL 39846/0071

Barcode

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Each dispersible tablet contains 125 mg of deferasirox.

10 Tablets

125 mg

Deferasirox Alkem Dispersible Tablets
Deferasirox Alkem 125, 250 & 500 mg Dispersible Tablets

Warning/Other Information

Oral use

Read the package leaflet before use.

Take this medicine on an empty stomach.

Dispense tablets in water, orange juice or apple juice before swallowing.

Do not swallow whole or chew.

POM

Medicinal product subject to medical prescription.

Keep out of the sight and reach of children.

PL 254480071

Each dispersible tablet contains 125 mg of deferasirox.

84 Tablets

Deferasirox Alkem Dispersible Tablets

125 mg

8 Tablets

Deferasirox Alkem Dispersible Tablets

125 mg
DCPAR Deferasirox Alkem 125, 250 & 500 mg Dispersible Tablets

UK/H/6770/001-003/DC
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Batch: 0036

Deferasirox Alkem Dispersible Tablets 250 mg deferasirox
Alkem Pharma GmbH
Deferasirox Alkem
#250 mg
Dispersible Tablets

Warning/Other Information

Coad use
Read the package leaflet before use
Take this medicine on an empty stomach.
Disperse tablets in water, orange juice or apple juice before swallowing.
Do not swallow whole or chew.

POM

Medicinal product subject to medical prescription.
Keep out of the sight and reach of children.
PL 35446/0072

Barcode

Space for Dispensing label

Each dispersible tablet contains 250 mg of deferasirox.

10 Tablets
Deferasirox Alkem Dispersible Tablets

250 mg
Annex 1

Table of content of the PAR update for MRP and DCP
Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

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<th>Date of end of procedure</th>
<th>Approval/ non-approval</th>
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