LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Deferasirox Sandoz
(deferasirox)

SE/H/2606/01-03/DC

This module reflects the scientific discussion for the approval of Deferasirox Sandoz. The Public Assessment Report was written in June 2022 by the previous RMS AT after initial procedure AT/H/1077/001-003/DC and is attached at the end of this document. RMS transfer from AT to SE was completed 7 June 2024. For information on changes after this date please refer to the module 'Update'.

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LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary Justificati for refuse

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Bundesamt für Sicherheit im Gesundheitswesen

CMDh/223/2005

Public Assessment Report

I. SCIENTIFIC DISCUSSION

Deferasirox Sandoz 80 mg - Filmtabletten, Deferasirox Sandoz 360 mg - Filmtabletten, Deferasirox Sandoz 90 mg - Filmtabletten

DEFERASIROX

II. AT/H/1077/001-003/DC

Date: 09.06.2022

This module reflects the scientific discussion for the approval of Deferasirox Sandoz 80 mg - Filmtabletten, Deferasirox Sandoz 360 mg - Filmtabletten, Deferasirox Sandoz 90 mg - Filmtabletten

. The procedure was finalised on 16.03.2021. For information on changes after this date please refer to the module 'Update'.

II.1 I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation Deferasirox Sandoz 90 mg – film-coated tablets Deferasirox Sandoz 180 mg - film-coated tablets, Deferasirox Sandoz 360 mg - film-coated tablets, from Sandoz GmbH

The product is 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.

-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.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10 (1) of Directive 2001/83/EC.

Mechanism of action
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.

Pharmacodynamic effects
In an iron-balance metabolic study in iron-overloaded adult thalassaemic patients, deferasirox at daily doses of 10, 20 and 40 mg/kg (dispersible tablet formulation) induced the mean net excretion of 0.119, 0.329 and 0.445 mg Fe/kg body weight/day, respectively.

II.2 II. QUALITY ASPECTS

II.2.1 II.1 Introduction

Deferasirox Sandoz is a film-coated tablet which is presented in a PVC/PVDC//Aluminium blister and a PA/AL/PVC//Aluminium blister.

Drug Substance

The active substance in Deferasirox Sandoz is Deferasirox. The specification of the active substance meets the current scientific requirements. The adequate quality of the active substance has been shown by submitting the appropriate control data. The stability of the active substance has been tested under ICH conditions. The results of the stability studies support the established retest-period.

II.2.2 II.2 Medicinal Product

Deferasirox Sandoz contains the following excipients:

Tablet core:
Cellulose, microcrystalline
Crospovidone
Magnesium stearate
Povidone
Poloxamer
Silica, colloidal anhydrous

Film-coating: opadry blue:

Hypromellose
Titanium dioxide (E171)
Macrogol
Talc
Indigo carmine aluminium lake (E132)

The development of the product has been sufficiently made and deemed appropriate. The usage of all the excipients has been described.
The release specification includes the check of all parameters relevant to this pharmaceutical form. Appropriate data concerning the control of the finished product support the compliance with the release specifications.

The packaging of the medicinal product complies with the current legal requirements.
Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SmPC, with a shelf life of 3 years. This medicinal product does not require any special storage conditions.

The pharmaceutical quality of Deferasirox Sandoz has been adequately shown.

II.2.3 II.3 Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of active substance and medicinal product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics.

II.3 III. NON-CLINICAL ASPECTS

II.3.1 III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of deferasirox are well known. As deferasirox is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview is dated October 2019. Report refers 91 publications up to year 2019.

II.3.2 III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Deferasirox Sandoz is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

II.3.3 III.3 Discussion on the non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

II.4 IV. CLINICAL ASPECTS

II.4.1 IV.1 Introduction

No clinical studies or bioequivalence studies have been performed with the applied products.

An identity statement of the MAH of the reference medicinal product has been provided in Module 1.2 of the dossier, confirming that is foreseen to manufacture the generic products with the same qualitative and quantitative composition, at the same manufacturing site, using the same manufacturing procedure and the same sources of active substance as the currently manufactured reference products.
Hence, no bioequivalence study is required.

The clinical overview is dated October 2019. Report refers 133 publications up to year 2019.

II.4.2 IV.2 Risk Management Plan and Summary of the Pharmacovigilance System Master File

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
Deferasirox Sandoz 80 mg - Filmtabletten, Deferasirox Sandoz 360 mg - Filmtabletten, Deferasirox Sandoz 90 mg - Filmtabletten

-Summary table of safety concerns as approved in RMP

Important identified risks	-Renal disorders (increased serum creatinine, acute renal failure (ARF), renal tubular disorders [acquired Fanconi's syndrome]) -Increased liver transaminases/Hepatic failure -Gastrointestinal hemorrhage and ulcers; esophagitis -Hearing loss -Lens opacities, retinal changes and optic neuritis -Severe cutaneous adverse reactions (SCARs) (including Stevens- Johnson syndrome [SJS], Toxic epidermal necrolysis [TEN] and Drug reaction with eosinophilia and systemic symptoms [DRESS])
Important potential risks	-Compliance with posology and biological monitoring -Medication errors
Missing information	-Long term safety in pediatric NTDT patients aged 10 to 17 years -Safety of new formulation (film-coated tablets)

-Summary of pharmacovigilance plan

Routine pharmacovigilance activities are suggested and no additional pharmacovigilance activities are proposed by the applicant, which is accepted.

-Summary of risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Renal disorders (increased serum creatinine, ARF, renal tubular disorders [acquired Fanconi's syndrome])	**Routine risk minimization measures:** SmPC sections 4.2, 4.3, 4.4 and 4.8 PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Follow-up using following targeted checklist: "Serum creatinine increase checklist" and "Renal impairment or failure checklist" **Additional pharmacovigilance activities:** None
Increased liver transaminases/Hepatic failure	**Routine risk minimization measures:** SmPC sections 4.2 , 4.4 and 4.8 PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Follow-up using a targeted checklist "Liver injury checklist", and expedited reporting in accordance with statutory requirements and SmPC and Package leaflet. **Additional pharmacovigilance activities**: None
Gastrointestinal hemorrhage and ulcers; esophagitis	**Routine risk minimization measures:** SmPC sections 4.4, 4.5 and 4.8 PL section 4 Legal status: Prescription only **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Follow-up using targeted checklist "Gastrointestinal ulcers & bleed checklist" **Additional pharmacovigilance activities:** None
Hearing loss	**Routine risk minimization measures:** SmPC sections 4.4 and 4.8 PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Follow-up using targeted checklist "Hearing loss checklist" and expedited reporting in accordance with statutory requirements and SmPC and Package leaflet. **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Lens opacities, retinal changes and optic neuritis	**Routine risk minimization measures:** SmPC sections 4.4, 4.8 and 5.3 PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Follow-up using targeted checklist "Lens opacities/cataracts checklist" and expedited reporting in accordance with statutory requirements and SmPC and Package leaflet. **Additional pharmacovigilance activities:** None
SCARs including SJS, TEN and DRESS	**Routine risk minimization measures:** SmPC sections 4.4 and 4.8 PL sections 2 and 4S Legal status: Prescription only **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Follow-up using targeted checklist "Severe skin reaction checklist" **Additional pharmacovigilance activities:** None
Compliance with posology and biological monitoring	**Routine risk minimization measures:** SmPC sections 4.2 and 4.4 Legal status: Prescription only **Additional risk minimization measures:** Education materials: - Guide for HCPs - Prescriber checklist - Patient guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Medication errors	**Routine risk minimization measures:** SmPC section 4.2 Legal status: Prescription only **Additional risk minimization measures:** Education materials: - Guide for HCPs - Prescriber checklist - Patient guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Long term safety in pediatric NTDT patients aged 10 to 17 years	**Routine risk minimization measures:** SmPC sections 4.2 and 4.4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Legal status: Prescription only **Additional risk minimization measures:** None	**Additional pharmacovigilance activities:** None
Safety of new formulation (film-coated tablets)	**Routine risk minimization measures:** None Legal status: Prescription only **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

- If applicable: Table of Ongoing and Planned Additional Pharmacovigilance Studies / Activities in the Pharmacovigilance Plan as approved in RMP

Not applicable

Summary of the Pharmacovigilance System Master File
The applicant submitted the summary of the pharmacovigilance system in the scope of this procedure. The summary includes the following elements:

- Proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance
- The Member States in which the qualified person resides and carries out his/her tasks
- The contact details of the qualified person
- A statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC
- The pharmacovigilance system master file (PSMF) is located in Germany

IV.3 Discussion on the clinical aspects

The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

II.5 V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Exjade, EMEA/H/C/000670 and to the following procedures, AT/H/0350/DC, DE/H/1354-1356 and NL/H/1170-1172. The bridging report submitted by the applicant has been found acceptable.

II.6 VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The pharmaceutical quality of Deferasirox Sandoz l has been adequately shown, and no new non-clinical or clinical concerns have been identified.
The benefit/risk relation is considered positive.

Bundesamt für Sicherheit im Gesundheitswesen

Public Assessment Report

III. UPDATE

Deferasirox Sandoz 180 mg - Filmtabletten, Deferasirox Sandoz 360 mg - Filmtabletten, Deferasirox Sandoz 90 mg - Filmtabletten

DEFERASIROX

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Procedure number*	Scope	Product Information affected
AT/H/1077/001-002-003/IA/001	Addition of batch release site, not including batch control/testing-Sandoz S.R.L	no
AT/H/1081/001-002003/IA/001	Addition of batch release site, not including batch control/testing-Sandoz S.R.L	no
AT/H/1077/001-002003/IB/002/G	1. 2. Addition of DS-manufacturer SK Biotek 3. 4. Addition alternative quality control testing sites SK Biotek Co., Ltd., South Ko 5. 6. Change in manufacturing process of the active substance 7. 8. Change in Batch size 9. Deletion of in-process tests 10. Deletion of supplier of a starting material 11. Addition of manufacturer starting material Salicylic acid 12. Addition of manufacturer starting material Salicylamide 13. Addition of manufacturer starting material 4-Hydrazinobenzoic acid 14. Addition of alternative quality control testing sites SGS Institut Fresenius Gmb 15. Minor changes to an approved test procedure: : 4-Hydrazinobenzoic acid- Change I Minor changes to the raw material (reagents and solvents):Deletion of a non-sign Minor changes to the raw material (reagents and solvents)::-Deletion of an alt Minor changes to the raw material (reagents and solvents)::-acid soluble arsenic Minor changes to the raw material (reagents and solvents)::-identification by GC	no
AT/H/1081/IB/002/G	1. 2. Addition of DS-manufacturer SK Biotek 3. 4. Addition alternative quality control testing sites SK Biotek Co., Ltd., South Ko 5. 6. Change in manufacturing process of the active substance 7. 8. Change in Batch size 9. Deletion of in-process tests 10. Deletion of supplier of a starting material 11. Addition of manufacturer starting material Salicylic acid 12. Addition of manufacturer starting material Salicylamide 13. Addition of manufacturer starting material 4-Hydrazinobenzoic acid 14. Addition of alternative quality control testing sites SGS Institut Fresenius Gmb 15. Minor changes to an approved test procedure: : 4-Hydrazinobenzoic acid- Change I Minor changes to the raw material (reagents and solvents):Deletion of a non-sign Minor changes to the raw material (reagents and solvents)::-Deletion of an alt Minor changes to the raw material (reagents and solvents)::-acid soluble arsenic Minor changes to the raw material (reagents and solvents)::-identification by GC	no
AT/H/1077/IB/003/G	1. 2. Addition of manufacturer: Sandoz S.R.L., Targu Mures, Romania 3. 4. Deletion of secondary packaging site Wase Werkplaats 5. 6. Change in Batch size 7. Change in manufacturing process Change in in-process test or limits Change in manufacturing process Change in specification parameters and/or limits	no

AT/H/1081/IB/003/G	1. 2. Addition of manufacturer: Sandoz S.R.L., Targu Mures, Romania 3. 4. Deletion of secondary packaging site Wase Werkplaats 5. 6. Change in Batch size 7. Change in manufacturing process Change in in-process test or limits Change in manufacturing process Change in specification parameters and/or limits	no
AT/H/1081/IB/004/G	1. Change in name of the DS-manufacturer from Novartis International Pharmaceutical 2. Addition of DS-manufacturer SK Biotek Co. Ltd., Daejon Korea, South 3. Addition of test procedure of an active substance heavy metals by ICP-MS is adde	no
AT/H/1077/IB/005/G	1. Change in name of the DS-manufacturer from Novartis International Pharmaceutical 2. 3. Addition of DS-manufacturer SK Biotek Co. Ltd., Daejon Korea, South 4. Addition of test procedure of an active substance heavy metals by ICP-MS is adde	no
AT/H/1081/001-002003/IA/005	Change in name of the DS-manufacturer Novartis Integrated Services Limited - Int	no
AT/H/1077/001-002003/IA/006	Change in name of the DS-manufacturer Novartis Integrated Services Limited - Int	no

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

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