NOVARTIS

Regulatory Affairs

Deferasirox

Summary of the EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Deferasirox
Product(s) concerned (brand name(s)):	Jadenu®, Exjade®
Document status:	Final
Version number of the RMP Public Summary:	20.1
Date of final sign off of the RMP Public Summary	30-Dec-2022

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of “Exjade/Jadenu” is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of “Exjade/Jadenu” in Switzerland is the “Arzneimittelinformation/ Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of “Exjade/Jadenu”.

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I. The medicine and what it is used for

Deferasirox is N-substituted bis-hydroxyphenyl-triazole. It is a tridentate ligand that binds ferric iron with high affinity in a 2:1 ratio and promotes excretion of iron, primarily in the feces.

Deferasirox is indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients with thalassemia, SCD, MDS or other rare anemias, and for the treatment of chronic iron overload in patients with NTDT syndromes.

For transfusional iron overload, recommended initial daily dose for FCT/granules is 14 mg/kg body weight (initial doses of 7 mg/kg or 21 mg/kg may be considered depending on transfusion intensity and treatment goal). Dose adjustments in steps of 3.5-7 mg/kg/day may be considered every 3-6 months. Doses above 28 mg/kg are not recommended because there is only limited experience with doses above this level.

Recommended initial daily dose for FCT/granules is 7 mg/kg body weight. Dose adjustments in steps of 3.5-7 mg/kg/day may be considered every 3-6 months. Doses above 14 mg/kg are not recommended because there is no experience with doses above this level in patients with NTDT syndromes. In patients in whom LIC was not assessed and serum ferritin is = 2000 µg/L, as well as in pediatric patients, dosing should not exceed 7 mg/kg. For patients in whom the dose was increased to > 7 mg/kg, dose reduction to 7 mg/kg or less is recommended when LIC is < 7 mg Fe/g dw or serum ferritin is = 2000 µg/L.

Exjade Dispersible Tablet (DT) has been discontinued in the EU markets and is therefore no longer available for patients. However, generic versions of deferasirox DT may be available. In case of switching patients between Exjade FCT/granules and generic versions of deferasirox DT, the dose of the Exjade FCT/granules should be adjusted. As a reference, the corresponding doses for Exjade FCT/granules and Exjade DT are shown in the tables below.

Transfusional iron overload:

	Exjade film-coated tablets/granules	**Exjade Dispersible tablets**
Starting dose	14 mg/kg/day	20 mg/kg/day
Alternative starting doses	7 mg/kg/day 21 mg/kg/day	10 mg/kg/day 30 mg/kg/day
Adjustment steps	3.5 - 7 mg/kg/day	5 - 10 mg/kg/day
Maximum dose	28 mg/kg/day	40 mg/kg/day

NTDT syndromes:

	Exjade film-coated tablets/granules	**Exjade Dispersible tablets**
Starting dose	7 mg/kg/day	10 mg/kg/day
Adjustment steps	3.5 - 7 mg/kg/day	5 - 10 mg/kg/day

Maximum dose	14 mg/kg/day	20 mg/kg/day

Further information about the evaluation of deferasirox's benefits can be found in deferasirox's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage link to product's EPAR summary landing page on the EMA webpage:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-Summary_for_the_public/human/000670/WC500033927.pdf.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of deferasirox, together with measures to minimize such risks and the proposed studies for learning more about deferasirox's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in thepackage leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size − the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status − the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of deferasirox, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, in Table 7 and Table 8, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine PhV activities.

If important information that may affect the safe use of deferasirox is not yet available, it is listed under 'missing information' in Table 9 and Table 10, below.

II.A: List of important risks and missing information

Important risks of deferasirox are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of deferasirox. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	• Renal disorders (increased serum creatinine, acute renal failure, 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
Important potential risks	• Compliance with posology and biological monitoring • Medication errors due to switching between Exjade FCT/granules and generic versions of deferasirox DT
Missing information	• Long term safety in pediatric NTDT patients aged 10 to 17 years • Safety of new formulation (FCT)

II B: Summary of important risks

Table 2 Important identified: renal disorders (increased serum creatinine, acute renal failure, renal tubular disorders [acquired Fanconis syndrome])

Evidence for linking the risk to the medicine	In thalassemia patients 0.5% of patients are reported to develop renal tubular dysfunction and 3.1% of patients progressed to dialysis therapy and 8% had a reduced CrCl. Renal tubular abnormalities, including increased urinary excretion of proteins and of tubular enzymes, have been reported in 30% of 250 patients with β-thalassemia. Progressive renal insufficiency, generally heralded by the appearance of increasing proteinuria, hypertension and hematuria occurs in 5-18% of patients with SCD and can require hemodialysis or renal transplantation and contributes to 18% of deaths in patients older than 40 years. Acute renal failure has been described as part of a multi-organ failure syndrome that accompanies pain crises in SCD patients and is present in 10% of patients hospitalized with SCD. Renal failure contributes to 18% of deaths in SCD patients older than 40 years. In SCD, 26% of 381 patients were reported to have proteinuria, 13% at or close to the nephritic range. It was reported that 2.3% of MDS patients have renal disorders. Myelodysplastic syndrome patients are generally elderly and have serum creatinine levels that are close to or slightly > ULN due to the normal aging process.
Risk factors and risk groups	Analyses showed that patients receiving high doses of deferasirox DT (20 or 30 mg/kg) and a low iron intake from infrequent blood transfusions were more likely to develop creatinine increases. Elderly patients were more likely to

	develop creatinine values > ULN though, as explained above, the magnitude of increase in comparison to baseline was no higher in these patients. Patients with pre-existing renal conditions or patients who are receiving medicinal products that depress renal function may be at higher risk of complications including ARF. In clinical studies a relationship between iron status (liver iron and ferritin concentrations), the rate of iron removal and renal effects has been observed. As with other iron chelator treatment, the risk of toxicity may be increased when inappropriately high doses of deferasirox are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.2 Posology and method of administration, 4.3 Contraindications, and 4.4 Special warnings and precautions for use. Relevant terms are included as ADRs Section 4.8 Undesirable effects. **Additional risk minimization measures** None

Table 3 Important identified risk: Increased liver transaminases / Hepatic failure

Evidence for linking the risk to the medicine	**Increased liver transaminases** Elevated liver transaminases have been correlated with increased LIC in patients with β-thalassemia. Studies have shown that hepatomegaly is seen in 50% of patients with SCD, hepatitis in 11% of patients, and approximately one third of SCD patients will have a form of hepatic dysfunction. **Hepatic failure** In patients aged > 6 years with beta-thalassemia, 4-6% had evidence of liver failure or cirrhosis. SCD patients can develop sickle cell crises and sequestration events affecting the liver causing massive hepatic enlargement with hepatic failure occurring in up to 10% of patients. Cirrhosis has been reported in 16 to 29% of SCD patients.
Risk factors and risk groups	**Increased liver transaminases** None identified **Hepatic failure** Patients with pre-existing hepatic impairment.
Risk minimization measures	**Increased liver transaminases / Hepatic failure** **Routine risk minimization measures** SmPC Section 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use. Relevant terms are included as ADRs Section 4.8 Undesirable effects. **Additional risk minimization measures** None

Table 4 Important identified risk: Gastrointestinal hemorrhage and ulcers; esophagitis

Evidence for linking the risk to the medicine	No information was found regarding the incidence of this event in the unexposed population.
Risk factors and risk groups	Patients who are taking deferasirox in combination with drugs that have known ulcerogenic potential, such as NSAIDs, corticosteroids or oral bisphosphonates, and in patients receiving anticoagulants.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.4 Special warnings and precautions for use, and 4.5 Interaction with other medicinal products and other forms of interaction. Relevant terms are included as ADRs in SmPC Section 4.8 Undesirable effects. **Additional risk minimization measures**

Table 5 Important identified risk: Hearing loss

Evidence for linking the risk to the medicine	Hearing loss not attributed to chelation therapy has been reported in 28% of patients with beta-thalassemia. A study of 75 adults with SCD demonstrated that the prevalence of hearing loss was 41% and was higher than that of the general population.
Risk factors and risk groups	As with other iron chelator treatment, the risk of toxicity may be increased when inappropriately high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.4 Special warnings and precautions for use. Relevant terms are included as ADRs in Section 4.8 Undesirable effects. **Additional risk minimization measures** None

Table 6 Important identified risk: Lens opacities, retinal changes and optic neuritis

Evidence for linking the risk to the medicine	The background incidence of eye abnormalities in patients with beta-thalassemia is poorly documented. However, several reports document patients with lenticular opacities who have never received chelation therapy though the overall incidence was not provided. Cataracts have not been reported in patients with SCD. In the predominantly elderly patients with MDS, senile cataracts are a relatively frequent event.
Risk factors and risk groups	As with other iron chelator treatments, the risk of toxicity may be increased when inappropriately high doses are given in patients with a low iron burden or with serum ferritin levels that are only slightly elevated.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.4 Special warnings and precautions for use, 5.3 Preclinical safety data. Relevant terms are included as ADRs in Section 4.8 Undesirable effects. **Additional risk minimization measures** None

Table 7 Important potential risk: Compliance with posology and biological monitoring

Evidence for linking the risk to the medicine	Not applicable
Risk factors and risk groups	Patients who are non-compliant with posology and biological monitoring requirements in the SmPC.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.2 Posology and method of administration and 4.4 Special warnings and precautions for use. **Additional risk minimization measures** Educational materials for physicians (which also includes a prescriber checklist) and patients regardless of indication.

Table 8 Important potential risk: Medication errors due to switching between Exjade FCT/granules and generic versions of deferasirox DT

Evidence for linking the risk to the medicine	Not applicable

Risk factors and risk groups	Patients may be at risk of medication errors during switch between Exjade FCT/granules and generic versions of deferasirox DT available on the market by different MAHs and as appropriate depending on the coexistence of these formulations at a national level.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.2 Posology and method of administration. **Additional risk minimization measures** Educational materials for physicians (which also includes a prescriber checklist) and patients clarifying the dose adjustment requirements in case of switch between Exjade FCT/granules and generic versions of deferasirox DT.

Table 9 Missing information: Long term safety in pediatric NTDT patients aged 10 to 17 years

Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use **Additional risk minimization measures** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study CICL670E2422: An observational, multi-center study to evaluate the safety of deferasirox in the treatment of pediatric patients with non-transfusion-dependent iron overload.

Table 10 Missing information: Safety of new formulation (FCT)

Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.2 and 5.2 and Patient Leaflet **Additional risk minimization measures** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study CICL670E2422: An observational, multi-center study to evaluate the safety of deferasirox in the treatment of pediatric patients with non-transfusion-dependent iron overload.

II C: Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

Table 11 Studies which are conditions of the marketing authorization

Study short name	Purpose of the study:
CICL670E2422 (Observational study)	An observational, multicenter study to evaluate the safety of deferasirox DT and FCT in pediatric NTDT patients aged 10 to 17-years old.

II.C.2. Other studies in post-authorization development plan

There are no studies required for deferasirox.