14 September 2017
EMA/639290/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

EXJADE

International non-proprietary name: deferasirox

Procedure No. EMEA/H/C/000670/X/0054

Note

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

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List of abbreviations

AUC	Area under the curve of blood/plasma concentration versus time
CFU	Colony Forming Units
Cmax	Maximum blood/plasma concentration
CPP	Critical process parameter
CQA	Critical Quality Attribute
CV	Coefficient of variation
DT	Dispersible tablet
DoE	Design of experiments
EC	European Commission
ERA	Environmental Risk Assessment
FCT	Film-coated tablet
FDA	Food and Drug Administration
FMEA	Failure mode effects analysis
GI	Gastrointestinal
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
JP	Japanese Pharmacopoeia
MCC	Microcrystalline cellulose
NF	National Formulary
PD	Pharmacodynamics
PDE	Permitted daily exposure
PE	Polyethylene
PET	Polyethylene terephthalate
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
QbD	Quality by design
QTPP	Quality target product profile
RH	Relative Humidity
SAE	Serious adverse Event
SmPC	Summary of Product Characteristics
SOC	System organ class
T½	Elimination half-life
TEAE	Treatment-emergent adverse events
USP	United States Pharmacopoeia
UV	Ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

Novartis Europharm Ltd submitted on 3 October 2016 an extension of the marketing authorisation.

The MAH applied for a change of bioavailability and the addition of a new pharmaceutical form pharmaceutical form: granules (90 mg, 180 mg and 360 mg).

Furthermore, the PI is brought in line with the latest QRD template version 10.

The MAH applied for the following indications for Granules 90 mg, 180 mg and 360 mg: EXJADE 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.

EXJADE is 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.

EXJADE is 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 legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) points (a) change of bioavailability and (d) change or addition of a new pharmaceutical form - Extensions of marketing authorisations

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0175/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0175/2016 was completed.

The PDCO issued an opinion on compliance for the PIP P/0175/2016.

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 MAH 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.

Scientific Advice / Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 25 July 2002, 17 December 2003, 26 June 2008, 23 May 2009 and 19 May 2011. The Protocol Assistance pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP were:

Rapporteur: Alexandre Moreau

- The application was received by the EMA on 3 October 2016.
- The procedure started on 27 October 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 January 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 24 January 2017.
- During the meeting on 9 February 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 23 February 2017, the CHMP agreed on the consolidated List of Questions to be sent to the MAH.
- The MAH submitted the responses to the CHMP consolidated List of Questions on 7 April 2017.
- The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on 30 May 2017.
- During the PRAC meeting on 9 June 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 22 June 2017, the CHMP agreed on a list of outstanding issues to be sent to the MAH.
- MAH submitted the responses to the CHMP List of Outstanding Issues on 7 August 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 31 August 2017.
- During the meeting on 1 September 2017, the PRAC agreed on the PRAC Assessment

Overview and Advice to CHMP.

- During the meeting on 11-14 September 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for an extension of the marketing authorisation for Exjade on 14 September 2017.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Iron overload is the result of many disorders inducing an increased net entry of iron within the body and can lead per se to the development of organ damage and increased mortality. It can be classified as primary or secondary depending whether it results from a primary defect in the regulation of iron balance or is secondary to other genetic or acquired disorders. A known example of primary iron overload is hereditary hemochromatosis (HHC), in which iron is absorbed in excess because of increased iron transfer from the enteral cells to the blood. The secondary includes iron overload either due to, or associated with, ineffective erythropoiesis, chronic liver diseases, parenteral administration or ingestion of excessive amounts of iron. Thalassemia major and sideroblastic anemia are the two best studied examples of iron overload secondary to blood transfusions and ineffective erythropoiesis. Frequent blood transfusions lead to excessive accumulation of iron with a toxic accumulation in 3 to 10 years.

2.1.2. Epidemiology

Transfusional iron overload: Patients with conditions leading to chronic anemia develop transfusional iron overload as a consequence of multiple blood transfusions. The underlying conditions include beta-thalassemia, sickle cell disease, myelodysplastic syndrome, Diamond- Blackfan anemia (DBA) and other anemias..

2.1.3. Management

The aim of treatment of iron storage disease is to remove from the body the excess iron that has accumulated. In the case of patients without primary disorders of haematopoiesis (i.e. primary haemochromatosis), this is best achieved by phlebotomy, since regeneration of erythrocytes by the marrow utilises iron, which is therefore withdrawn from various body pools. Phlebotomy is only occasionally feasible. Patients who have augmented iron stores because of ineffective erythropoiesis and those in whom the iron overload is the result of multiple transfusions require treatment with an iron chelating agent to achieve safe levels of body iron. This is a slow process because only a small proportion of body iron is available for chelation at any moment. By increasing the doses of chelators in an attempt to speed up iron removal, there is a risk of increasing the toxicity of iron chelators by chelating iron, which is needed for normal tissue metabolism. Therefore, while the slow process of decreasing tissue iron to safe levels is being achieved, a second goal is to make the iron as safe as possible by binding the toxic iron pools responsible for causing tissue damage. Iron chelation therapy reduces iron-related morbidity, reduces and retards liver diseases, diabetes and other endocrine failures, normalizes growth and sexual development, prevents, and in some cases reverses, cardiac insufficiency and improves quality of life. Consequently iron chelation therapy dramatically reduces mortality.

About the product

Deferasirox (Exjade) is an orally active chelator that is highly selective for iron III. It 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 and when deferoxamine therapy is contraindicated or inadequate.

Deferasirox is already commercialised and currently available as a dispersible tablet (DT) for once daily administration at strengths of 125 mg, 250mg and 500 mg, and as a film-coated tablet (FCT) for once daily administration at strengths of 90 mg, 180 mg and 360 mg.

Type of Application and aspects on development

To improve palatability and patient compliance, and potentially the safety profile for gastrointestinal (GI) tolerability, the MAH has developed a new lactose-free formulation for oral administration, presented as two different dosage forms: granules packaged in sachets, and a film-coated tablet (FCT). The granules and FCT contain the same compendial excipients in the same proportions (cellulose, microcrystalline; crospovidone; povidone; magnesium stearate; silica, colloidal anhydrous; poloxamer). The only difference in content between the forms (FCT and granules) is the coating material used for the FCT (hypromellose, titanium dioxide (E171), macrogol 4000, talc and indigo carminine aluminum lake (E132)), which is absent from the granules. The new formulation contains deferasirox, the same active substance as in the DT formulation (Exjade).

The film-coated tablet was approved in the USA on 30-Mar-2015 (NDA 206-910), and in Canada on 24-Feb-2016, under the tradename Jadenu. It also received positive CHMP Opinion in the European Union on 28-Jan-2016, followed by European Commission decision on 22-March-2016, under the tradename Exjade. Only the granules are the subject of this submission.

The development program for granules includes a total of five clinical pharmacology studies in healthy adult subjects (Table 3) and an additional pharmacokinetic/pharmacodynamic (PK/PD) investigation in patients diagnosed with transfusion- dependent iron overload, using a pharmacokinetic comparability approach.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as granules containing 90, 180 or 360 mg of deferasirox as active substance.

Other ingredients are: microcrystalline cellulose, crospovidone, povidone, magnesium stearate, colloidal anhydrous silica and poloxamer.

The product is available in PET/Aluminium/PE foil sachets as described in section 6.5 of the SmPC.

2.2.2. Active Substance

Exjade 90, 180 and 360 mg granules contain the same active substance, deferasirox, as that used to manufacture the already-authorised dispersible tablets and film-coated tablets. The active substance is sourced from the same manufacturer, manufactured with the same process and released in accordance with the same active substance specifications. Therefore, the applicant presented no new information in the dossier to support this line extension application.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Exjade granules containing 90, 180 or 360 mg of deferasirox are an immediate release dosage form aimed at patients with difficulty in swallowing tablets. The three presentations are dose proportional and differentiated by the colour of the sachets which are also printed with the respective strengths. The composition is identical to the uncoated tablets cores of Exjade film-coated tablets, approved as a line extension in 2016.

As for the film-coated tablets, the aim of development was to produce a dosage form equivalent to the already-approved dispersible tablets (125, 250 or 500 mg of deferasirox) with improved patient compliance. The dispersible tablets contain lactose and sodium lauryl sulfate which are thought to cause gastro-intestinal side effects. In addition, they are chalky and unpalatable once added to the required large volume of water indicated in the SmPC, and the large observed food effect means they must be taken on an empty stomach. One requirement of the paediatric investigation plan (PIP) was to develop a more palatable orally available dosage form and the line extensions for the film-coated tablets, and thereafter for the granules, fulfil that request. Both the granules proposed in this application, and the film-coated tablets, contain a higher percentage of active substance than the dispersible tablets which reduces the dose burden for patients. The granules remove the requirement to manually crush film-coated tablets for patients who have difficulty swallowing.

Pharmaceutical development of the finished product contains QbD elements. The quality target product profile (QTPP) was defined as an orally available immediate release dosage form, which can be swallowed easily when dispersed on food, with equivalent *in vivo* performance and exposure to dispersible Exjade tablets. The granules should be sufficiently stable in the primary package which should also be child-resistant. Critical quality attributes (CQAs) were identified as appearance and integrity of packaging, identity, assay, content uniformity, impurity profile, dissolution and microbial limits. Identity and microbial limits are unlikely to be impacted by formulation and process variables.

Deferasirox is non-hygroscopic and practically insoluble in water. As a result, the active substance is micronized to reduce its particle size which is controlled by specification. The required polymorph is the more stable of the two identified and is routinely produced by the active substance manufacturing process. It has good permeability and is thus BCS II, exhibiting dissolution limited biopharmaceutics.

The choice of excipients used in the film-coated tablet formulation was based on compatibility test results of binary mixtures with the drug substance. Excipients were chosen to optimize the dissolution profile and stability whilst minimizing adverse effects and are qualitatively and quantitatively identical to those used in the film-coated tablet cores. In contrast to the dispersible tablets, the granules do not contain lactose which will ensure better acceptance in lactose-intolerant patients. The film-coated tablets require less disintegrant as they are intended to be swallowed rather than dispersed. As a result, the percentage of active substance in the formulation increased resulting in smaller tablets which are easier to swallow. Sodium lauryl sulfate was replaced by poloxamer to further reduce gastric irritation. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. Additional particle size limits are set for the two types of MCC and poloxamer. 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 2.1.1 of this report.

For administration, the granules can be sprinkled on soft food such as plain non-fat yoghurt or apple sauce. Compatibility with the proposed vehicles was tested in a stability study which showed no increase in degradants or decrease in assay over 24 hours.

The dissolution method was developed based on the method approved for the film-coated tablets, but with a tighter specification. The combination of a tight dissolution specification, raw material specifications and controlled process parameters was deemed sufficient to ensure adequate and consistent dissolution performance.

Comparability was demonstrated clinically by comparing 4 sachets of the 90 mg strength against a single 500 mg dispersible tablet. The biobatch was manufactured according to the proposed commercial process and at the proposed manufacturing site.

Since the 3 proposed strengths are dose proportional, differing only in fill weight of the sachets, a biowaiver was proposed for the 180 and 360 mg strengths based on comparison of f_2 values of 4 x 90 mg sachets, 2 x 180 mg sachets and 1 x 360 mg sachet at multiple physiologically-relevant pHs. Since these were all >50 (range 63-99), then a biowaiver was considered justified.

The formulation and manufacturing process development were evaluated through the use of risk assessment, performed using failure mode effect analysis (FMEA) and Ishikawa diagrams in order to identify potential critical process parameters (CPPs). The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies of the already-approved film-coated tablets.

Based on the risk assessment, and drawing on knowledge of the identical granules used in the film-coated tablets (where some potential CPPs had already been studied), several parameters were identified for further DoE (Design of Experiments) studies. The final CPPs and suitable set points were defined based on the DoE results and are considered acceptable.

Three pre-validation batches of each strength were then manufactured according to the defined process parameters. All 9 batches passed release testing. In contrast to the approved Exjade presentations, no design space is claimed for the granules.

The primary packaging is PET/Aluminium/PE foil sachets. The materials comply 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.

Manufacture of the product and process controls

The manufacturing process shown below consists of four main steps: blending of deferasirox with intra-granular excipients; wet granulation and drying; blending with extra-granular excipients; filling into sachets. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated on three consecutive production scale batches of each strength. 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 release specifications include appropriate tests for this kind of dosage form and comprise tests for appearance (container and contents), identity (UV, HPLC), mean mass of contents (weight), mass uniformity of contents (Ph. Eur.), dissolution (HPLC), uniformity of delivered dose (HPLC), degradation products (HPLC), microbial enumeration tests (Ph. Eur.), assay (HPLC) and uniformity of dosage units (Ph. Eur.).

Deferasirox is very stable and no impurities have been noted above the identification threshold throughout the lifecycles of other marketed Exjade presentations. A risk assessment was carried out to determine the likelihood of metal contaminants being present in the finished product in accordance with ICH Q3D. Furthermore, analysis data from multiple batches of finished product showed that no class 1-3 elemental impurities, were present above 2% of their permitted daily exposure (PDE) levels. The absence of tests for elemental impurities is considered justified.

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 1 pilot and 6 production scale batches of the 90 mg sachets and 3 production scale batches each of the 180 and 360 mg sachets confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. No impurities were observed above 0.05%.

Stability of the product

Three production scale batches each of 90, 200 and 400 mg sachets were used for stability studies. During development, the 200 and 400 mg presentations were reduced to 180 and 360 mg respectively. All presentations are qualitatively and quantitatively proportional and are packed in the same size sachets proposed for marketing. The 200 mg and 400 mg sachets were manufactured using the proposed commercial process at the proposed settings, the only difference being the amount filled into each sachet and the manufacturing scale which was four times larger. Therefore, data from the 200 and 400 mg sachets is considered representative of the 180 and 360 mg sachets respectively. Additional stability studies using three production scale batches of each strength (90, 180, 360 mg) will be carried out following authorization. Samples were stored for up to 24 months under long term conditions (25 ºC / 60% RH), up to 24 months under intermediate conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines. Samples were tested for appearance (container and contents), dissolution, degradation products and assay. Microbial enumeration tests were carried out at the end of shelf-life. The analytical procedures used are stability indicating. No significant changes to any of the measured parameters were observed in any of the samples tested.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant degradation was observed. Samples were also stored under freeze/thaw conditions (between -20 ^{o}C and ambient temperature) for up to 6 months and no significant changes were observed.

In use stability studies were carried out using 1 batch of the 90, 200 and 400 mg presentations. Sachets were poured onto either apple sauce or yoghurt and stability monitored for up to 24 hours. No significant changes to either assay or impurity measurements indicating that granules are stable when mixed with either vehicle.

Based on available stability data, the proposed shelf-life of 36 months without special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used. The magnesium stearate is of vegetal origin.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. 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. The formulation is based on the already marketed film-coated tablets. The applicant has applied QbD principles in the development of the finished product and its manufacturing process although no design space is claimed. Suitable controls are set for CPPs and the manufacturing process has been validated.

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. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

No new pharmacodynamic studies were submitted for the granule formulation.

2.3.3. Pharmacokinetics

No new studies were submitted for the granule formulation.

Two pharmacokinetic studies [Study 0900739], [Study 1000323] were conducted in dogs using single oral doses of 375 mg deferasirox, to support the development of the film-coated tablets and granule formulation of deferasirox. The results of these studies were presented in the line extension application for film-coated tablets.

A total of six new formulations were tested in dogs, and bioavailability relative to the dispersible tablets was estimated for each formulation. Non-enteric coated tablets showed comparable exposure to the reference dispersible formulation whereas bioavailability of the two enteric-coated tablet formulations was approximately 50% lower than that of the DT formulation [Study 0900739]. Contrary to results with these new tablet formulations, enteric coated pellets resulted in comparable bioavailability to the DT formulation [Study 1000323]. This was likely due to the effect of surfactant used in the enteric-coated pellet formulation. Based on these findings, new formulations were further modified for the use in a pilot pharmacokinetic study in humans.

No additional pharmacokinetic studies in laboratory species were conducted to test new formulations.

2.3.4. Toxicology

No specific toxicology studies have been submitted for the granule formulation.

2.3.5. Ecotoxicity / environmental risk assessment

The calculation of the predicted environmental concentration in the initially submitted ERA as part of the original Marketing Authorisation Application (MAA) for Exjade was based on a forecast peak annual amount in 2013. Current sales forecasts remain well below the initial estimate used as basis for the original ERA. Thus, the previously submitted ERA was based on a very conservative approach for the calculation of the potential environmental exposure. The previously submitted ERA demonstrated no concern for the environment. The current application is not expected to lead to an increase in the initially projected potential environmental exposure.

Therefore, the current application is excluded from the requirement to submit an environmental risk assessment. It is expected that the use of deferasirox does not lead to any significant risk to the environment.

2.3.6. Discussion on non-clinical aspects

According to the guideline on the Environmental Risk Assessment (ERA) of medicinal product for human use (EMEA/CHMP/SWP/4447/00 corr2), the evaluation of the environmental impact should be made if there is an increase in the environmental exposure.

The molecule in this application is similar to the marketed one. Consequently environmental exposure with deferasirox is not expected to increase. The justification provided by the MAH for not submitting an updated ERA is considered acceptable. Therefore, deferasirox formulated as granules is not expected to pose a risk to the environment different from those identified for the initial market approval.

2.3.7. Conclusion on the non-clinical aspects

No new nonclinical data are being included with the present submission for the granules. The toxicology and nonclinical pharmacology studies previously conducted for the dispersible tablets and the pharmacokinetic studies in dogs submitted with the line extension for film-coated tablets are considered to support the safety profile of the granules.

Regarding the ERA, Deferasirox formulated as granules is not expected to increase the environmental exposure compared to the current marketed Exjade form and to pose a risk to the environment different from those already identified in the initial market approval.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 1 Tabular overview of clinical studies

[Study F2104]	Bioavailability and dose-proportionality of the deferasirox granules	Randomized, open-label, single-center, four period cross-over	24	400, 800, 1200 mg granules, 1500 mg DT	Healthy subjects
[Study F2105]	PK comparability of deferasirox granules vs. DT (reference) formulation	Randomized, open-label, single-center, two-period cross-over	41	1200 mg granules, 1500 mg DT	Healthy subjects
[Study F2106]	Food effect of the deferasirox granules	Randomized, two-arm, open-label, single-center, three-period cross-over	48	1200 mg granules	Healthy subjects
[Study F1102-Part 1]	PK comparability of deferasirox granules vs. DT (reference) formulation	Randomized, open-label, single-center, three period cross-over	97	990, 1080 mg granules, 1500 mg DT	Healthy subjects
[Study F1102-Part 2]	PK comparability of deferasirox granules vs. DT (reference) formulation	Randomized, open-label, single-center, two-period cross-over	96	900 mg granules, 1500 mg DT	Healthy subjects
[Study A2409]	Efficacy, and safety of oral deferasirox	One-year, open-label, single arm, multi-center	1744	10-30 mg/kg DT	Patients
[Study F2201]	Overall safety of deferasirox FCT and DT	Randomized, open-label, multi-center, two-arm	173	10-40 mg/kg DT, 7-28 mg/kg FCT	Patients

2.4.2. Pharmacokinetics

Deferasirox is already commercialised and currently available as a dispersible tablet (DT) for once daily administration at strengths of 125, 250 and 500mg. The pharmacokinetics of deferasirox has been well characterised in healthy volunteers and in iron-overloaded patients. It was described in detail in the previously submitted marketing authorisation application and included in the SmPC.

The MAH has developed a new formulation for oral administration, presented as two different dosage forms: granules (G) packaged in sachets and a film-coated tablet (FCT). The granules and FCT contain the same compendial excipients in the same proportions. The only difference in content between the forms (FCT and granules) is the coating material used for the FCT, which is absent from the granules. Based on the improved bioavailability of the new formulation, three strengths as 90 mg, 180 mg and 360 mg (which are compositionally proportional) were developed. The granules dosage form is intended to further enhance patients' convenience of use, especially for the paediatric and geriatric patients, who might have difficulty swallowing the FCT as whole and/or crushing the FCT.

The present submission concerns the registration of the granules form at the same three dosage strengths of 90, 180 and 360mg (compositionally proportional) in line with those of the FCT. It is based on a dose adjusted pharmacokinetic comparability approach to the approved DT formulation. To support the Granules dossier, the MAH submitted five clinical pharmacology studies.

Generally, the used bioanalytical methods appear adequate and comply with acceptance criteria regarding selectivity, sensitivity accuracy and precision. Analytical validation reports were provided with satisfactory results. Short and long-term stability of the analytes in biological matrix were tested and shown to be satisfactory. ISR were performed with satisfactory results. A representative number of chromatograms were provided by the MAH.

Pharmacokinetic parameters such as AUCinf, AUClast, Cmax, T1/2 and Tmax of deferasirox in plasma were estimated using non-compartmental analysis in Phoenix (WinNonlin 6.2).

Primary pharmacokinetic parameters, AUClast, AUCinf, and Cmax, were log-transformed and analysed using a linear mixed effects model including treatment, period, sequence, and subject as effects. Geometric mean ratio (test/reference) and its 90% confidence interval for primary pharmacokinetic parameters were reported. The standard methodology for statistical analysis was used.

Intensive plasma concentration data from healthy subjects were used for PK evaluations of deferasirox. In all studies, blood samples for the determination of deferasirox concentrations in plasma were collected at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 hours post-dose.

In all pharmacokinetic studies, the amount of drug used was selected to be approximately equivalent to the clinically relevant recommended starting dose of 20 mg/kg of the DT (1500 mg in a 75kg subject). The doses of 1080 and 1200mg used for the Granules formulation are estimated to be in the range of 15-25 mg/kg of the DT. The design, number of subjects, strengths and dosing used could be acceptable. The washout period (between 6 to 9 days depending on study) is considered adequate (with expected half-life for deferasirox between 10 and 16h) to allow the complete elimination of the drug before subsequent dosing and to minimise the possibility of a carry-over effect.

In a pilot PK comparability study (F2105) including 41 healthy subjects, the relative bioavailability of a reduced dose 1200mg of the deferasirox granule formulation given with a soft food matrix (apple sauce) versus the reference DT at 1500mg under fasted conditions. The primary PK parameters of the two treatments were not in the range of the reference bioequivalence criteria of [0.8-1.25]. Indeed, the geometric mean ratios and 90% CIs for AUClast, and Cmax (1200 mg deferasirox granules vs 1500 mg deferasirox DT) were 1.22 (90% CI: 1.16, 1.28), and 1.41 (90% CI: 1.33, 1.49), respectively. Thus, the study confirmed the improved bioavailability of the granule formulation (already seen with the FCT) compared to the DT formulation and lead to test lower granules doses.

A pivotal bioavailability study (F1102), conducted in 97 Japanese healthy subjects, was performed to evaluate the PK comparability of two reduced doses (1080 and 990 mg) of the deferasirox granules versus the reference DT (1500mg) under fasted conditions. The exposure (AUCinf, AUClast) of both

1080 and 990mg deferasirox granules were found to be equivalent to the DT, with geometric mean ratios of 1.09 (90% CI: 1.05- 1.14) and 0.99 (0.95-1.05), respectively compared to the DT. However, the peak concentration of the granules was respectively 34 and 24 % higher with the 1080 and 990mg strengths than that of the DT. Based on these findings and to keep the granule dose consistent with the FCT, the 1080 mg granule was chosen as the comparable dose to the 1500mg. this approach is acceptable. Since ethnicity (Asians, Blacks, Caucasians) does not affect the PKs of deferasirox (based on submitted data in original dossier) the fact that PK comparability between the two formulations (Granules versus DT) were conducted in Japanese healthy subjects is not deemed to jeopardize the results.

Study F2106 (food effect study) compared the PKs of deferasirox in 52 healthy subjects who received 1200 mg of deferasirox granules under fasted conditions (three modalities: A- with water, or B- with apple sauce, or C- with yogurt), low-fat breakfast, or high-fat breakfast conditions. The results indicated a lack of food effect when deferasirox granules are administered with soft food (apple sauce or yogurt) compared to the reference fasted conditions with water. When deferasirox granules were given with a low fat meal, the AUC was unchanged (90% CI meet the bioequivalence criteria), and the Cmax decreased slightly by 11% (90% CI: 0.79 -0.99). With a high -fat meal, the AUC was mildly increased by 18%-19% (90% CI: 1.09 -1.29) while the Cmax was similar to under fasted conditions. Overall, systemic availability of the new granules formulation deferasirox under fed conditions appears to be slightly modified and the food effect is not expected to be clinically relevant.

The dose-proportionality of deferasirox PK has been characterised in study F2104 (already submitted in the previous application for the FCT dosage form). The study was conducted on 21 healthy subjects and using the granule formulation. Following a single dose of deferasirox granules, the increase in mean deferasirox exposure (AUC), and peak concentration (Cmax) could be considered dose proportional in the dose range of 400 to 1200 mg. Indeed, the estimated proportionality coefficients (beta) and the 90% confidence interval for AUClast 1.13 (90% CI 1.07, 1.19), AUCinf 1.13 (90% CI 1.07, 1.20) and Cmax 0.90 (90% CI 0.79, 1.01) were within the bioequivalence interval of [0.80 - 1.20].

The new formulation is characterised by an improved bioavailability that leads to about 30% dose reduction, and a reduced food effect than the reference commercialised DT. The deferasirox PK of the granules formulation (AUC and Cmax) is dose proportional in the dose range of 400 to 1200 mg in healthy subjects. Based on dose-adjusted approach, the AUC of deferasirox granules at 1080 mg was equivalent to that of DT 1500 mg based on the bioequivalence criteria of [80-125%]. However, the mean peak concentration of the granules was 34% higher than that of the DT. The clinical impact of this higher Cmax with the FCT was investigated in the PK/PD relationship analysis (A2409 study).

The PKPD relationship for deferasirox has been evaluated using a large clinical trial in the target population (n= 1112). A covariate analysis using a proportional odds model was performed to determine the relative impact of C2h and trough concentrations at steady state (as a surrogate markers of respectively Cmax and exposure of deferasirox) on the efficacy (serum ferritin change from baseline) and safety (serum creatinine and creatinine clearance change from baseline) deferasirox treatment endpoints. The analysis showed that Ctrough had a strong impact on creatinine clearance change in categories ($p<0.0001$) but C2h,ss had minimal impact ($p=0.2544$) after adjusting for Ctrough,ss. Furthermore, a C2h,ss increase by 1.7-fold would provide an odds ratio of worsening from baseline in creatinine clearance categories of 1.146 (0.906, 1.449). A similar conclusion could be drawn regarding the relationship of AUC and Cmax to efficacy. At steady state, Ctrough has a statistically significant impact ($p<0.001$) on the changes in serum ferritin while C2h has no statistically significant impact ($p=0.130$). In particular, after adjusting for Ctrough,ss, an increase in C2h,ss by 70% would lead to a change of -1.28% (90% CI: -2.65%, 0.12%) in the percent change from baseline in serum ferritin which is clinically insignificant.

Based on these results, it appears that overall exposure (AUC) is the key parameter for assessing deferasirox safety and efficacy.

2.4.3. Pharmacodynamics

No new pharmacodynamics data were submitted.

2.4.4. Discussion on clinical pharmacology

The PKs of the new deferasirox granule formulation has been sufficiently characterised in healthy volunteers (see the PK overview for detail). The new formulation is characterised by an improved bioavailability and a reduced food effect than the reference marketed DT. The PK of the granules (AUC and Cmax) is dose proportional in the dose range of 400 to 1200 mg. The AUC of deferasirox granules at 1080 mg was equivalent to that of the DT at 1500 mg, based on the bioequivalence criteria of [80-125%]. However, the mean peak concentration of the granules was 34% higher than that of the DT. Based on a retrospective PKPD analysis in a large clinical trial in the target population, it appears that overall exposure (AUC) is the key parameter for assessing deferasirox safety and efficacy. Thus, the observed higher Cmax (with a similar AUC) with the granules formulation are not likely to result clinically in worsening creatinine laboratory values or in a significant change on serum ferritin from baseline.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology of the granule formulations data are considered appropriate and supportive of this application.

2.5. Clinical efficacy

No new efficacy data were submitted.

2.5.1. Discussion on clinical efficacy

This application cross-referred to the existing efficacy data generated with the dispersible tablet formulation.

An additional [Study A2409 PK/PD analysis] included in this submission confirmed the influence of AUC on efficacy. Efficacy would probably not be affected by the observed Cmax differences. The available data fully support the therapeutic equivalence of the strength-adjusted new granules.

2.5.2. Conclusions on the clinical efficacy

The efficacy of the granule formulation- is considered appropriate and supportive of this application.

2.6. Clinical safety

Safety data collected in healthy volunteer were provided from the following studies:

Study ICL670F2104:

"A randomized, open-label, single-centre, Phase I, four period cross-over study evaluating the bioavailability of new deferasirox granule formulation in comparison to the reference deferasirox (Exjade) marketed formulation in healthy subjects." This study compared the bioavailability after a single dose of the new deferasirox granule formulation vs. the dispersible tablet formulation as a reference. In addition, dose linearity of 400 mg, 800 mg and 1200 mg granules was tested relative to DT.

Study ICL670F2105:

"A randomized, open-label, single-center, Phase I, two-way, cross-over study to evaluate the pharmacokinetic comparability of deferasirox new granule formulation with the reference dispersible formulation in healthy subjects." This study evaluated the pharmacokinetic comparability of deferasirox granule formulation (1200 mg), given with apple sauce (Treatment A), with the reference dispersible tablet formulation of deferasirox (1500 mg) under fasting conditions (Treatment B).

Study ICL670F2106:

"A single-center, open-label, randomized, two arms, cross-over study to investigate the effect of food on the pharmacokinetics of new deferasirox granule formulation in healthy subjects." This was a three period, 12 sequence (six per arm), cross-over study to assess the effect of food on the pharmacokinetics of deferasirox granules (1200 mg) when administered with: 1) apple sauce or yogurt (Arm 1 Treatment B and C) and 2) low-fat 450 kcal breakfast or a highfat 1000 kcal breakfast, compared to fasting conditions (Arm 2 Treatment D and E).

Study ICL670F1102:

"A randomized, open label, six sequences, cross-over study in healthy Japanese subjects to evaluate the pharmacokinetic comparability of deferasirox granule formulation with the reference dispersible tablet formulation (Exjade)." Part 1 of the study evaluated two doses of deferasirox granules (1080 mg and 990 mg) in comparison to the reference dispersible tablet formulation of deferasirox (1500 mg) under fasting conditions in healthy Japanese subjects. Study F1102-Part 1 serves as the pivotal comparability PK study supportive of the present submission. Since the results from Part 1 of the study did not meet the criteria acceptable to file a new formulation application in Japan, a reduced dose of 900 mg granules was further tested in Part 2 of the study. Part 2 was a randomized, open label, two sequences, cross-over study to evaluate the pharmacokinetic comparability of a different dose (900 mg) of the deferasirox granules in comparison to the reference dispersible tablet formulation of deferasirox (1500 mg) under fasted conditions in healthy Japanese subjects. This part of the study is included in the present submission package for completeness.

Patient exposure

In Study F2104, 20 subjects were exposed to doses of 400 mg, 800 mg, and 1200 mg deferasirox granules and 1500 mg deferasirox dispersible tablet. Each subject received a single dose of each dosage in a specific sequence. One subject in this study missed the 800 mg and 1200 mg doses of granules due to a protocol deviation.

In Study F2105, 41 subjects were exposed to doses of 1200 mg deferasirox granules and 1500 mg deferasirox dispersible tablet. Each subject received a single dose of each dosage in a specific sequence.

In Study F2106, 48 subjects were exposed to three doses of 1200 mg deferasirox granules.

In Study F1102-Part 1, 97 subjects were exposed to doses of 990 mg and 1080 mg deferasirox granules and 1500 mg deferasirox dispersible tablet. Each subject received a single dose of each dosage in a specific sequence.

In Study F1102-Part 2, 95 subjects were exposed to doses of 900 mg deferasirox granules and 1500 mg deferasirox dispersible tablet (one patient received 1500 mg DT, then discontinued). Each subject received a single dose of each dosage in a specific sequence.

Adverse events

The population in Studies F2104, F2105, F2106 and F1102-Part 1 and -Part 2 consisted of adult healthy volunteers. Safety assessments included monitoring and recording of all treatment-emergent adverse events (AEs) and serious adverse events (SAEs), blood and urine laboratory monitoring and vital signs, physical examinations and ECGs. No other special safety evaluations were performed in these subjects. Treatment-emergent AEs were summarised and listed by system organ class (SOC) and preferred term.

Adverse event data was coded using MedDRA Version 15 in Study F2104, Version 15.1 in Study F2106 and Version 16 in Study F2105 and Version 16.1 in Study F1102, as those were the MedDRA versions valid when those studies started.

Given the half-life of deferasirox ranging from 8-16 hours and the 6-8 day wash-out between treatment periods, AEs in these cross-over trials are presented by 'treatment arms' as well as by 'all subjects'.

Common adverse events

In Study F2104, the most reported AE was headache. 4 subjects (16.7%) experienced an event of headache assessed as mild and suspected to be related to study drug (400 mg granules, 1 subject; 800 mg granules, 2 subjects; DT, 1 subject) (Table 14). One subject experienced the event twice in different treatment sequences (400 mg and 800 mg granules). In all patients, the duration of the event was 1 to 3 days, except in one subject where it lasted for seven days. No diarrhoea was reported. One subject experienced a mild urinary tract infection assessed as suspected to be related to study drug. The study medication was permanently discontinued due to administration of a prohibited drug.

In Study F2105, subjects were treated with granules and DT. Two subjects in treatment B (1500 mg DT with water) experienced one event of diarrhoea. The other six single events occurred in five subjects in treatment A (1200 mg of deferasirox granules). Diarrhoea was the only reported AE with a suspected relationship to the study drug. No subject discontinued due to an AE.

In Study F2106, one subject in Arm 1 treatment B (1200 mg granules with apple sauce) as well as one subject in Arm 2 treatment A (1200 mg granules with water) experienced an event of diarrhoea. In addition, 2 subjects had an event of dermatitis contact: one in treatment A, and another in treatment E (1200 mg granules with high-fat breakfast). The two subjects with dermatitis contact remained in the study. One subject in treatment D (1200 mg granules with low-fat breakfast) permanently discontinued study drug due to an AE (rash), which also led to administration of a prohibited concomitant medication (diphenhydramine).

In Study F1102-Part 1, subjects received granules and DT. Twelve subjects (12.4%) had an event of diarrhoea, of which 6 subjects had more than one event (Table 17). The events occurred in different treatment groups and sequences (4 events on 990 mg granules, 9 events on 1080 mg granules, and 6 events were on 1500 mg DT). All events were assessed as mild, and most AEs were suspected to be related to study drug. There were also increased alanine aminotransferase and aspartate aminotransferase (both 5.2%) (6 events on 990 mg granules, 2 events on 1080 mg granules, and 2 events on 1500 mg DT) and increased eosinophil count (4.1%) (2 events on 990 mg granules and 2 events on 1500 mg DT). Two subjects discontinued study treatment, one due to the AE increased AST/ALT (not suspected) and the second due to rash which was suspected to be associated with study drug.

In Study F1102-Part 2, subjects were treated with granules and DT. The events diarrhoea and headache occurred with both the 900 mg granules and the deferasirox DT. Six subjects (6.3%) had an event of diarrhoea, of which 3 subjects experienced this more than once. These 9 events of diarrhoea occurred in different treatment groups and sequences (6 events on 900 mg granules and 3 events on 1500 mg DT). Three subjects experienced headache, 2 subjects on 1500 mg DT and 1 subject on 900 mg granules. All events were mild in severity and suspected to be related to study drug. No subject discontinued due to an AE. Part 1 had 18 AEs (19%, N=97) on 1080 mg granules experienced by 14 subjects and Part 2 had 8 AEs (8%, N=95) on 900 mg granules experienced by 8 subjects. (Of note, one patient discontinued in Part 2 and did not receive 900 mg.) Events suspected to be drug-related.

Study F2104: Gastrointestinal disorders was the most commonly observed AE; 7 subjects experienced an event suspected to be related to investigational product: 4 subjects (19.0%) on 400 mg deferasirox

granule, 2 subjects (10.0%) on 800 mg deferasirox granule, 1 subject (5.0%) on 1200 mg granule, and 2 subjects (9.5%) on the reference single dose of 1500 mg DT. Headache was the next most frequently reported AE with a suspected relationship to investigational product: 1 subject (4.8%) on 400 mg granules, 2 subjects (10.0%) on 800 mg granules, no subjects on 1200 mg granules, and 1 subject (4.8%) on DT, respectively.

Study F2105: diarrhoea was the only reported AE with a suspected relationship to the study drug in one subject during treatment with 1500 mg DT.

Study F2106: None of the reported AEs were assessed by the Investigator as suspected to be related to study drug, except for one AE (rash) of a subject on treatment D (single dose of 1200 mg deferasirox granules after a low-fat breakfast) in treatment sequence D/A/E.

Study F1102: In Part 1, most of the AEs (20 of the 21 reported events; see Table 17) were suspected to be drug related. In Part 2, all AEs (see Table 18) were suspected to be drug related.

Severity of AEs

Study F2104: All TEAEs were mild in nature with almost all AEs requiring no action, except for a mild urinary tract infection and mild headache.

Study F2105: All the reported TEAEs were mild in nature.

Study F2106: Overall, the majority of AEs were mild in nature, except for syncope in one subject on treatment C (single dose of 1200 mg deferasirox granules with yogurt). It was assessed as moderate severity and unrelated to study medication.

Study F1102: In both Part 1 and Part 2, all the reported TEAEs were mild in nature except one event of rash in Part 2 which was moderate.

Serious adverse event / deaths / other significant events

In the five pharmacokinetic studies, no deaths occurred within 30 days of the last dose.

In Study F2105, one subject who was not randomized and never received deferasirox, but did receive an iron supplement to counter potential loss of iron due to chelation, reported an SAE, abortion spontaneous. On 25-Sep-2013, an ultrasound showed she was 6 weeks pregnant. An elective abortion was scheduled for 16-Oct-2013, but vaginal bleeding began on 26-Sep-2013 and worsened on 29-Sep-2013, when she went to the local emergency room. A pelvic exam, serum beta human chorionic gonadotropin, and ultrasound suggested that the subject was miscarrying. On 01-Oct-2013, she returned to the emergency room for increased vaginal bleeding and pain. Pelvic exam ultrasound identified a small amount of tissue present, and approximately 50% was removed by forceps under ultrasound guidance. On 02-Oct-2013, the subject fully recovered and was discharged home with instructions to follow-up with obstetrics/ gynaecology. The subject never received deferasirox, but did receive an iron supplement as part of the study. The Investigator did not suspect a relationship between the SAE and study drug (iron supplement).

Laboratory findings

There were no clinically significant findings observed for any of the haematology and clinical chemistry parameters during the studies.

Discontinuation due to adverse events

Study F2104: No subjects had an AE leading to discontinuation.

Study F2105: No subjects had an AE leading to discontinuation.

Study F2106: One subject in Arm 2 permanently discontinued study drug due to mild AE (rash) which also led to administration of prohibited concomitant medication.

The investigator suspected a relationship between the event (rash) and the study medication.

Study F1102:

In Part 1, two subjects had an AE leading to discontinuation of treatment. One subject experienced a mild form of rash (eruption) during treatment B (1080 mg granules), which was suspected to be related to study drug. Another subject experienced mild events of ALT and AST increased (>3x ULN) during treatment C (990 mg granules), which were not suspected to be related to study drug. The study drug was permanently discontinued.

In Part 2, no subjects had an AE leading to discontinuation.

Post marketing experience

Considering the new formulation, post-marketing experience is only available for the film-coated tablet which has been approved in the USA on 30-Mar-2015 (NDA 206-910), in Canada on 24-Feb-2016 (under the tradename Jadenu) and in the European Union on 22-March-2016 (under the tradename Exjade).

2.6.1. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

Concerning the new granule formulation, supplement safety data were provided from clinical pharmacology trials carried on healthy subjects with a total of 301 subjects. No new safety signals have emerged from these studies. AEs in all subjects ranged from 11.5% in study F1102-Part 2 to 41.7% in study F2104. The most commonly reported AE was diarrhoea. All TEAEs were mild in nature except one syncope assessed as moderate and unrelated to study medication (F2106) and one event of rash which was moderate (F1102 Part 2). No death occurred within 30 days of the last dose. Data from these clinical pharmacology studies could not demonstrate the safety profile of the new granule formulation as these studies were not carried out in the target population.

This application is a line extension to the existing marketing authorisation for Exjade 125 mg, 250 mg and 500 mg dispersible tablets and Exjade 90 mg, 180 mg and 360 mg film coated tablets. The granules and FCT contain the same compendial excipients in the same proportions. The only difference in content between the forms (FCT and granules) is the coating material used for the FCT, which is absent from the granules. In the previous X/0043 application, quality data have been generated to confirm that the FCT can be crushed and administered by sprinkling the full dose onto soft food, e.g. yogurt or apple sauce.

The AUC of deferasirox granules at 1080 mg was equivalent to that of the DT at 1500 mg, based on the bioequivalence criteria of [80-125%]. The mean peak concentration of the granules was 34%

higher than that of the DT. Based on a retrospective PKPD analysis in a large clinical trial in the target population, it appears that overall exposure (AUC) is the key parameter for assessing deferasirox safety and efficacy. Thus, the observed higher Cmax (with a similar AUC) with the granules formulation are not likely to result clinically in worsening creatinine laboratory values or in a significant change in serum ferritin from baseline.

The safety of the FCT formulation of deferasirox was recently investigated in a head-to-head comparison in a limited number of patients in F2201 study in thalassemia and MDS. This study randomized 86 patients to DT and 87 patients to FCT treatment. Based on the results of the 24-week treatment period, both treatment arms showed a similar overall adverse event (AE) profile and no new safety signals emerged. The frequencies of serious adverse events were similar between each group (11.6 vs. 12.6%). The most common AEs on DT and FCT (>20% in either arm) were diarrhoea (34.9% vs. 33.3%), nausea (26.7% vs. 27.6%), abdominal pain (26.7 % vs. 26.4%), increased urine protein/creatinine ratio (12.8% vs. 20.7%) and vomiting (22.1% vs. 17.2%), respectively. AEs leading to study drug discontinuation were numerically similar between DT and FCT groups (7% vs. 5.7%). One death (febrile neutropenia in a 63-year-old patient with MDS) occurred during the treatment period; it was in the FCT group and not suspected to be related to study treatment. An imbalance between groups in the urine protein/creatinine ratio (UPCR) increase was noted. This imbalance was further evaluated in the EMEA/H/C/000670/II/0052 procedure. 9/86 (10.5%) patients in the DT arm and 16/87(18.4%) in the FCT arm had normal UPCR at baseline (<=1 mg/mg) but reported at least one post baseline value of UPCR > 1 mg/mg post baseline. However, among these patients, only 2 from DT and none in the FCT arm reported UPCR value of notable range (UPCR >1 mg/mg during 2 consecutive visits). Mean durations of exposure to study drug in patients with at least one UPCR value above 1 mg/mg and/or proteinuria related adverse event were similar in both arms (171 days in the DT group and 160 days in the FCT groups, with a median of 169 days in both treatment arms). This AE was not severe with FCT and did not impact negatively the overall exposure to this formulation.

'Renal disorders' are already considered an important identified risk in the RMP. The SmPC currently recommends extensive monitoring of renal parameters. These measures are considered sufficient to follow the risk of proteinuria.

Considering the pharmacokinetic and quality equivalence of FCT and granule formulation, the CHMP considered that safety data of the granule formulation should be provided in study CICL670F2202, a randomized, open-label, multicenter, two arms, Phase II study allowing to evaluate safety of deferasirox granules in paediatric patients with iron overload.

2.6.2. Conclusions on the clinical safety

Considering the pharmacokinetic and quality equivalence of FCT and granule formulation, the CHMP considered that the safety data of the FCT formulation provided from F2201 study are sufficient to document the tolerance profile of granule formulation. The safety of the new formulations (FCT and granules) is still identified as missing information in the submitted RMP. In addition, study CICL670F2202 has been added in the pharmacovigilance plan in order to evaluate the safety of the granules formulation in the paediatric indication.

2.6.3. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.7. Risk Management Plan

The RMP was updated to take account of the new granule formulation. Clarification is also provided throughout the RMP to distinguish the new formulations film-coated tablets and granules as needed.

Safety concerns

Table 2 Summary of safety concerns

Important identified risks	Renal disorders (increased serum creatinine, acute renal failure, renal tubular disorders [acquired Fanconi's syndrome]) Increased liver transaminases Gastrointestinal hemorrhage and ulcers; esophagitis Hearing loss Lens opacities, retinal changes and optic neuritis Stevens-Johnson syndrome and toxic epidermal necrolysis Hepatic failure Interaction with food Interaction with aluminum-containing antacids Induction of CYP3A4 Inhibition of CYP1A2 UGT inducers Inhibition of CYP2C8 Interaction with cholestyramine
Important potential risks	Peripheral blood cytopenias Compliance with posology and biological monitoring Medication errors Severe cutaneous adverse reactions (DRESS)
Missing information	Long term safety in pediatric NTDT patients aged 10 to 17 years Safety in pregnant women Safety of new formulation (FCT/granules)

Pharmacovigilance plan

The pharmacovigilance plan was updated to reflect study CICL670F2202, a randomized, open-label, multicenter, two arm, Phase II study allowing to evaluate safety of deferasirox granules in paediatric patients with iron overload (as category 3 study).

Table 3 Ongoing and planned additional pharmacovigilance studies / activities in the pharmacovigilance plan

Study / activity (Type, title and category)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
CICL670E2422 (non-interventional, 1) An observational, multi-center study to evaluate the safety of deferasirox in the treatment of pediatric patients with non-transfusion-dependent iron overload.	To study safety of deferasirox in pediatric NTDT patients aged 10 to 17 years-old	Long term safety in pediatric NTDT patients aged 10 to 17 years-old Safety of new formulation (FCT)	Ongoing	Planned final CSR Jun-2021 (Annual progress reports)
Physician survey to assess the impact of educational materials on the prescribers' awareness of doses and biological monitoring recommendations and also to assess the awareness and appropriate use of both formulations (3)	To assess the impact of educational materials on the prescribers' awareness of appropriate doses and biological monitoring recommendations. To assess the awareness and appropriate use of both formulations	Compliance with posology and biological monitoring Medication errors	Planned	Eighteen months after the last launch of film-coated tablets in participating countries
CICL670F2429, A PASS study to assess the safety of deferasirox FCT in the paediatric population (1)	To obtain additional data on the safety profile of FCT, especially when the tablets are crushed, and to further characterize the pediatric safety profile.	Safety of new formulation (FCT)	Planned	Jun-2021 (final study report)
CICL670F2202, a randomized, open-label, multicenter, two arm, Phase II study allowing to evaluate safety of deferasirox granules in pediatric patients with iron overload (3)	To evaluate safety of the granules formulation.	Safety of new formulation (granules)	Ongoing	June 2021 (final CSR-end of core phase)

Risk minimisation measures

The educational material will be updated to reflect the granule formulation.

Table 4 Summary of risk minimisation measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Important identified risks		
Renal disorders (increased serum creatinine, acute renal failure, renal tubular disorders (acquired Fanconi's syndrome))	Wording in sections 4.2, 4.3, 4.4 and 4.8 of the SmPC	None
Increased liver transaminases	Wording in sections 4.2, 4.4 and 4.8 of the SmPC	None
Gastrointestinal hemorrhage and ulcer; esophagitis	Wording in sections 4.4, 4.5 and 4.8 of the SmPC	None
Hearing loss	Wording in sections 4.4 and 4.8 of the SmPC	None
Lens opacities, retinal changes, and optic neuritis	Wording in sections 4.4, 4.8 and 5.3 of the SmPC	None
Stevens-Johnson syndrome and toxic epidermal necrolysis	Wording in sections 4.4 and 4.8 of the SmPC	None
Hepatic failure	Wording in sections 4.2, 4.4 and 4.8 of the SmPC	None
Interaction with food	Wording in sections 4.2, 4.5 and 5.2 of the SmPC	None
Interaction with aluminum-containing antacids	Wording in section 4.5 of the SmPC	None
Induction of CYP3A4	Wording in section 4.5 of the SmPC	None
Inhibition of CYP1A2	Wording in section 4.5 of the SmPC	None
UGT inducers	Wording in section 4.5 of the SmPC	None
Inhibition of CYP2C8	Wording in section 4.5 of the SmPC	None
Interaction with cholestyramine	Wording in sections 4.5 and 5.2 of the SmPC	None
Important potential risks		
Peripheral blood cytopenias	Wording in sections 4.4 and 4.8 of the SmPC	None
Compliance with posology and biological monitoring	Wording in sections 4.2 and 4.4 of the SmPC	Educational materials for physicians and patients regardless of indication.
Medication errors	Wording in section 4.2 of the SmPC	Educational materials for physicians and patients for all the formulations and for all indications describing the new deferasirox formulation (FCT/granules) and appropriate dosing, to be distributed and prior to launch and after substantial safety modifications of the

Safety concern	Routine risk minimization measures	Additional risk minimization measures
		product information. Introductory notification letter to pharmacists explaining the switch between formulations. Introductory notification letter to prescribers which includes a prescriber's guide and a patient's guide. A specific letter to prescribers and pharmacists regarding the timelines for removing Exjade DT from the EU market
Severe cutaneous adverse reactions (DRESS)	Wording in section 4.4 of the SmPC.	None.
Missing information		
Safety in pregnant women	Wording in sections 4.6 and 5.3 of the SmPC	None
Long term safety in pediatric NTDT patients aged 10 to 17 years	Wording in sections 4.2 and 4.4 of the SmPC	None
Safety of new formulation (FCT/granules)	Wording in sections 4.2 and 5.3 of the SmPC and in package leaflet	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 15.3 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH 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.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, EXJADE (deferasirox) is included in the additional monitoring list as it has a PASS imposed.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Iron overload is the result of many disorders inducing an increased net entry of iron within the body and can lead per se to the development of organ damage and increased mortality. It can be classified as primary or secondary depending whether it results from a primary defect in the regulation of iron balance or is secondary to other genetic or acquired disorders. A known example of primary iron overload is hereditary hemochromatosis (HHC), in which iron is absorbed in excess because of increased iron transfer from the enteral cells to the blood. The secondary includes iron overload either due to, or associated with, ineffective erythropoiesis, chronic liver diseases, parenteral administration or ingestion of excessive amounts of iron. Thalassemia major and sideroblastic anemia are the two best studied examples of iron overload secondary to blood transfusions and ineffective erythropoiesis. Frequent blood transfusions lead to excessive accumulation of iron with a toxic accumulation in 3 to 10 years.

3.1.2. Available therapies and unmet medical need

The aim of treatment of iron storage disease is to remove from the body the excess iron that has accumulated. In the case of patients without primary disorders of haematopoiesis (i.e. primary haemochromatosis), this is best achieved by phlebotomy, since regeneration of erythrocytes by the marrow utilises iron, which is therefore withdrawn from various body pools. Phlebotomy is only occasionally feasible. Patients who have augmented iron stores because of ineffective erythropoiesis and those in whom the iron overload is the result of multiple transfusions require treatment with an iron chelating agent to achieve safe levels of body iron.

3.1.3. Main clinical studies

The development program for granules includes a total of five clinical pharmacology studies in healthy adult subjects and an additional PK/PD investigation in patients diagnosed with transfusion- dependent iron overload, using a pharmacokinetic comparability approach.

3.2. Favourable effects

To improve palatability and patient compliance, the MAH developed a new formulation for oral administration, presented as two different dosage forms: granules packaged in sachets, and a film-coated tablet (FCT). This application concerns the granules and is a line extension to the existing marketing authorisation for Exjade 125 mg, 250 mg and 500 mg dispersible tablets and Exjade 90 mg, 180 mg and 360 mg film coated tablets. The granules and FCT contain the same compendial excipients in the same proportions. The only difference in content between the forms (FCT and granules) is the coating material used for the FCT, which is absent from the granules.

Dispersible tablets administration requires the dispersion in high volume (100-250 ml) of liquid and must be taken on an empty stomach due to the substantial food effect. In the previous X/0043 application, quality data have been generated to confirm that the FCT can be crushed and administered by sprinkling the full dose onto soft food, e.g. yogurt or apple sauce. The crushing of FCT facilitates administration for any patient with difficulty in swallowing whole tablets. The granule formulation provides administration advantages, because there is no requirement to manually crush the tablet.

The PKs of the new deferasirox granule formulation has been sufficiently characterised in healthy volunteers. The new formulation is characterised by an improved bioavailability of about 30% and a reduced food effect than the reference marketed DT. The PK of the granules (AUC and Cmax) is dose proportional in the dose range of 400 to 1200 mg. The AUC of deferasirox granules at 1080 mg was equivalent to that of the DT at 1500 mg, based on the bioequivalence criteria of [80-125%]. However, the mean peak concentration of the granules was 34% higher than that of the DT. Based on a retrospective PK/PD analysis in a large clinical trial in the target population, it appears that overall exposure (AUC) is the key parameter for assessing deferasirox safety and efficacy. Thus, the observed higher Cmax (with a similar AUC) with the granules formulation are not likely to result clinically in worsening creatinine laboratory values or in a significant change in serum ferritin from baseline. Finally, systemic availability of the new granules formulation deferasirox under fed conditions was only slightly modified and the food effect is not expected to be clinically relevant.

No specific data focussed on efficacy/activity were submitted as part of this application. This application cross-referred to the existing efficacy data generated with the dispersible tablet formulation.

3.3. Uncertainties and limitations about favourable effects

No specific data focussed on efficacy/activity were submitted as part of this application. However, as mentioned above, the CHMP consider that efficacy would probably not be affected by the observed Cmax differences.

3.4. Unfavourable effects

Considering the quality equivalence and similar pharmacokinetics of FCT and granule formulation, the MAH provided safety data of the FCT formulation provided from F2201 study. This randomized trial included 173 thalassemia and MDS patients. Over the 24-week treatment period, both treatment arms showed a similar overall adverse events profile and no new safety signals emerged. An imbalance between groups in the urine protein/creatinine ratio increase was noted (10.5% patients in DT arm and 18.4% in FCT arm had normal UPCR at baseline (<=1 mg/mg) but reported at least one post baseline value of UPCR > 1 mg/mg post baseline). However, this AE was not severe with FCT and did not impact negatively the overall exposure to this formulation.

3.5. Uncertainties and limitations about unfavourable effects

Concerning the new granule formulation, supplement safety data were provided from clinical pharmacology trials carried out on healthy subjects with a total of 301 subjects. No new safety signals have emerged from these studies. AEs in all subjects ranged from 11.5% in study F1102-Part 2 to 41.7% in study F2104. The most commonly reported AE was diarrhoea. All TEAEs were mild in nature except one syncope assessed as moderate and unrelated to study medication (F2106) and one event of rash which was moderate (F1102 Part 2). No death occurred within 30 days of the last dose. However, data from these clinical pharmacology studies could not demonstrate the safety profile of the new granule formulation as these studies were not carried out in the target population. Hence, the safety of the new formulations (FCT and granules) is still identified as missing information in the submitted RMP. In addition, study CICL670F2202 has been added in the pharmacovigilance plan in order to evaluate the safety of the granules formulation in the paediatric indication.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

In addition to the FCT, the granules are in favour of a better compliance than the DT form.

The safety profile of the granules formulation has not been tested in the target population. However, considering quality equivalence and similar pharmacokinetics of FCT and granule formulation, the CHMP considers that the safety data of the FCT formulation provided from F2201 study are sufficient to document the safety of granule formulation. The safety of the new formulation (FCT and granules) is still identified as missing information in the submitted RMP. In addition, study CICL670F2202 has been added in the pharmacovigilance plan in order to evaluate the safety of the granules in the paediatric indication.

Also, safety post marketing data of these new formulations should be updated in the forthcoming periodic safety update reports.

Risk of error due to wrong dose is low as the granules and FCT contain the same compendial excipients in the same proportions and the granules are intended to be launched after FCT, at the time when DT will likely not be supplied in the respective countries any longer. For these reasons, it was considered that the educational materials for patients and physicians are sufficient to minimise the risk of medication error. The educational materials are updated to reflect the granule formulation.

3.6.2. Balance of benefits and risks

The benefit-risk balance of the granules is considered positive.

3.6.3. Additional considerations on the benefit-risk balance

Not applicable.

3.7. Conclusions

The overall B/R of Exjade is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality , safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of, Exjade new pharmaceutical form is favourable in the following indications:

EXJADE 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.

EXJADE is 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.

EXJADE is 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 CHMP therefore recommends the extension of the marketing authorisation for Exjade 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).

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 must inform the European Medicines Agency and the CHMP of the results of the surveillance programme in each Member State.

As well as the requirements in the legislation, the following serious ADRs should be forwarded on an expedited basis to the appropriate competent authority as well as summarised in the above reports:

- Increase in hepatic enzymes >10x ULN
- Serious rise in creatinine
- Results of renal biopsies, if available
- Cataracts
- Hearing loss
- Gallstones

Prior to launch of EXJADE in each Member State the marketing authorisation holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed to inform healthcare professionals and patients to minimise the risks of:

- Non-compliance of the posology and biological monitoring
- Medication errors due to switching between formulations (dispersible tablets and film-coated tablets/granules).

The MAH shall ensure that, at launch, in each Member State where EXJADE is marketed, all healthcare professionals and patients who are expected to prescribe, dispense and use EXJADE are provided with the following educational package for all available formulations (e.g. dispersible tablets, film-coated tablets and granules) for all indications:

- Physician educational material
- Patient information pack

Additional periodic distributions after launch should be performed, notably after substantial safety modifications of the product information justifying educational material updates.

The MAH shall use distinct outer cartons, blisters and tablets for all formulations (dispersible tablets and film-coated tablets/granules).

The physician educational material should contain:

- The Summary of Product Characteristics
- Guide for healthcare professionals

The Guide for healthcare professionals shall contain the following key elements:

- Description of available deferasirox formulations (e.g. dispersible tablets, film-coated tablets and granules)
    - Different posology regimen
    - Different conditions of administration
    - Dose conversion table when switching from one formulation to another
- The recommended doses and the rules for starting treatment
- The need to monitor serum ferritin monthly
- That deferasirox causes rises in serum creatinine in some patients
    - The need to monitor serum creatinine
        - On two occasions prior to initiation of treatment
        - Every week during the first month of initiation of treatment or after therapy modification
        - Monthly thereafter
    - The need to reduce by 10 mg/kg the dose if serum creatinine rises:
        - Adults: >33% above baseline and creatinine clearance <LLN (90 ml/min)
        - Paediatrics: either >ULN or creatinine clearance falls to <LLN at two consecutive visits.
    - The need to interrupt treatment after a dose reduction if serum creatinine rises:

        - Adults and Paediatrics: remain >33% above baseline or creatinine clearance <LLN (90 ml/min)
    - The need to consider renal biopsy:
        - When serum creatinine is elevated and if another abnormality has been detected (e.g. proteinuria, signs of Fanconi syndrome).
- The importance of measuring creatinine clearance
- Brief overview of methods of measuring creatinine clearance
- That rises in serum transaminases may occur in patients treated with EXJADE
    - The need for liver function tests prior to prescription, then at monthly intervals or more often if clinically indicated
    - Not to prescribe to patients with pre-existing severe hepatic disease
    - The need to interrupt treatment if persistent and progressive increase in liver enzyme were noted.
- The need for annual auditory and ophthalmic testing
- The need for a guidance table highlighting pre-treatment measurements of serum creatinine, creatinine clearance, proteinuria, hepatic enzymes, ferritin, such as:

Before initiating treatment	
Serum creatinine at Day - X	Value 1
Serum creatinine at Day - Y	Value 2

X and Y are the days (to be determined) when pre-treatment measurements should be performed.

- Recommendations for treatment of non-transfusion-dependent thalassaemia (NTDT) syndromes:
    - Information that only one course of treatment is proposed for NTDT patients
    - The recommended doses and the rules for starting treatment
    - The rules for stopping when target liver iron concentration and serum ferritin are reached
    - A warning to minimise the risk of over-chelation
    - A warning on the necessity of closer monitoring of liver iron concentration and serum ferritin in the paediatric population
    - A warning on the currently unknown safety consequences of long-term treatment in the paediatric population

Prior to launch of deferasirox film-coated tablets, healthcare professionals will receive introductory notification letters as follows:

- Pharmacists - a detailed letter explaining the switch between formulations
- Prescribers - a letter including the following dossiers:
    - A prescribers' guide informing about the switch between formulations in order to address the important potential risk of medication error for deferasirox

- A patient's guide informing about the possibility of co-existing formulations in the EU market, and the differences concerning their administration, in order to address the important potential risk of medication error for deferasirox

Additionally, prescribers and pharmacists will be informed via a specific letter regarding the timelines for removing EXJADE dispersible tablets from the EU market.

The patient information pack should contain:

- Patient information leaflet
- Patient guide

Patient guide should contain the following key elements:

- Information on the need for regular monitoring, and when it should be carried out, of serum creatinine, creatinine clearance, proteinuria, hepatic enzymes, ferritin
- Information that renal biopsy may be considered if significant renal abnormalities occur
- Availability of several oral formulations (e.g. dispersible tablets, film-coated tablets and granules) and the main differences associated with these formulations (i.e., different posology regimen, different conditions of administration notably with food).

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Non-interventional post-authorisation safety study (PASS): In order to assess the long-term exposure and safety of deferasirox dispersible and film-coated tablets, the MAH should conduct an observational cohort study in paediatric non-transfusion-dependent thalassaemia patients over 10 years old for whom deferoxamine is contraindicated or inadequate conducted according to a CHMP-agreed protocol. The clinical study report should be submitted by	June 2021
Interventional post-authorisation safety study (PASS): In order to assess the safety of deferasirox film-coated tablets in the paediatric population (especially when the tablets are crushed), the MAH shall conduct and submit the results of a safety study conducted according to an agreed protocol. The clinical study report should be submitted by	June 2021

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

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0175/2016 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.