26 January 2017
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Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

EXJADE

deferasirox

Procedure no: EMEA/H/C/000670/P46/072

Note

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

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1. Introduction

On 11 October 2016, the MAH submitted a completed paediatric study for deferasirox (EXJADE), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study CICL670A1402 : a Japanese surveillance study to confirm the long term (1 year to 5 years) safety and efficacy of deferasirox dispersible tables when orally administered to Japanese patients with chronic iron overload in the clinical setting is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

Exjade is brand name for deferasirox presented as dispersible tablets in 3 doses strengths: 125, 250 and 500mg. The investigational drug was available as tablets at dosage strengths of 125 mg, 250 mg and 500 mg, packaged in high-density polyethylene (HDPE) bottles with an induction seal and child resistant closure.

2.3. Clinical aspects

2.3.1. Introduction

Deferasirox (company research code: ICL670, DFX) is an orally active chelator that is highly selective for iron (III). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Deferasirox promotes excretion of excess iron, primarily in the feces. Deferasirox was developed by Novartis for the treatment of chronic iron overlo ad due to frequent blood transfusions (≥ 7 mL/kg/month of packed red blood cells) in patients with beta thalassemia major aged 6 years and older. It is also indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in the following patient groups:

☐ in pediatric patients with beta thalassemia 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 pediatric patients with beta thalassemia 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 pediatric patients with other anemias aged 2 years and older.

Further it 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 thalassemia syndromes aged 10 years and older.

Deferasirox was first registered on 02-Nov-2005 in the United States and subsequently in the EU via centralized procedure on 28-Aug-2006. Deferasirox is currently approved in over 100 countries.

The MAH submitted a final report for:

• CICL670A1402 : Special Drug use Observational study on Exjade dispersible tablets : a Japanese surveillance study to confirm the long term (1 year to 5 years) safety and efficacy of deferasirox under general practice in Japanese patients with chronic iron overload.

2.3.2. Clinical study

CICL670A1402 : Special Drug use Observational study on Exjade dispersible tablets : a Japanese surveillance study to confirm the long term (1 to 5 years) safety and efficacy of deferasirox under general practice in Japanese patients with chronic iron overload

Description

A post-marketing surveillance study was performed in Japan between the market launch of Exjade in 16 June 2008 and May 24, 2016 (to enroll patients who started treatment with Exjade no later than January 31, 2012) with two studies:

- EXJ-1-01: drug use observational study, all treated patients surveillance, with two follow up periods: from the start of treatment to 0.5 year with data recorded in the CRF01 and from 0.5 to 1 year with data recorded in the CRF02 (CICL670A1401 – cf P46 – 071).

- EXJ-2-01 : special drug use observational study (CICL670A1402).

Methods

Objective(s)

The aim of this special drug observational study is to confirm the safety and efficacy of long-term use under actual use conditions. This study (EXJ-2-01) is being conducted in subjects who have been treated with Exjade starting in the drug use observational study (EXJ-1-01).

Study design

The study design is a drug use observational study after the market launch of Exjade in Japan (June 16, 2008) until 24 May 2016. It concerns subjects who have been treated with Exjade starting in the drug use observational study (EXJ-1-01).

Study population /Sample size

Study A1402 was conducted in patients who were confirmed to be receiving treatment at the time of completion of the 6-month drug use observational surveillance (Study CICL670A1401) with a 1-year observation period, were planned to continue treatment with deferasirox, and were capable of having follow-up continued. For Study A1402, a targeted sample size of 300 patients as those continuously treated for 5 years was considered achievable.

Treatments

The daily dose of Exjade was 14.3 ± 5.41 mg/kg/day (mean ± S.D. n=281), showing that a high percentage of subjects received a lower dose than the approved dose of 20 mg/kg/day. The duration of treatment ranged extremely widely (mean ± S.D., 1053.1 ± 519.51 days, n=317).

Outcomes / endpoints

The aim is to obtain a description of adverse reactions (incidence, seriousness, timing, outcome and incidence by factor), as well as incidence of serious adverse reactions by factor, laboratory values, and adverse events of interest (renal impairment, hepatic impairment, gastrointestinal disorder, eye disorder, hearing impaired, decreased blood cells, leucocytoclastic vasculitis, hypersensitive reaction, agranulocytosis), ferritin levels.

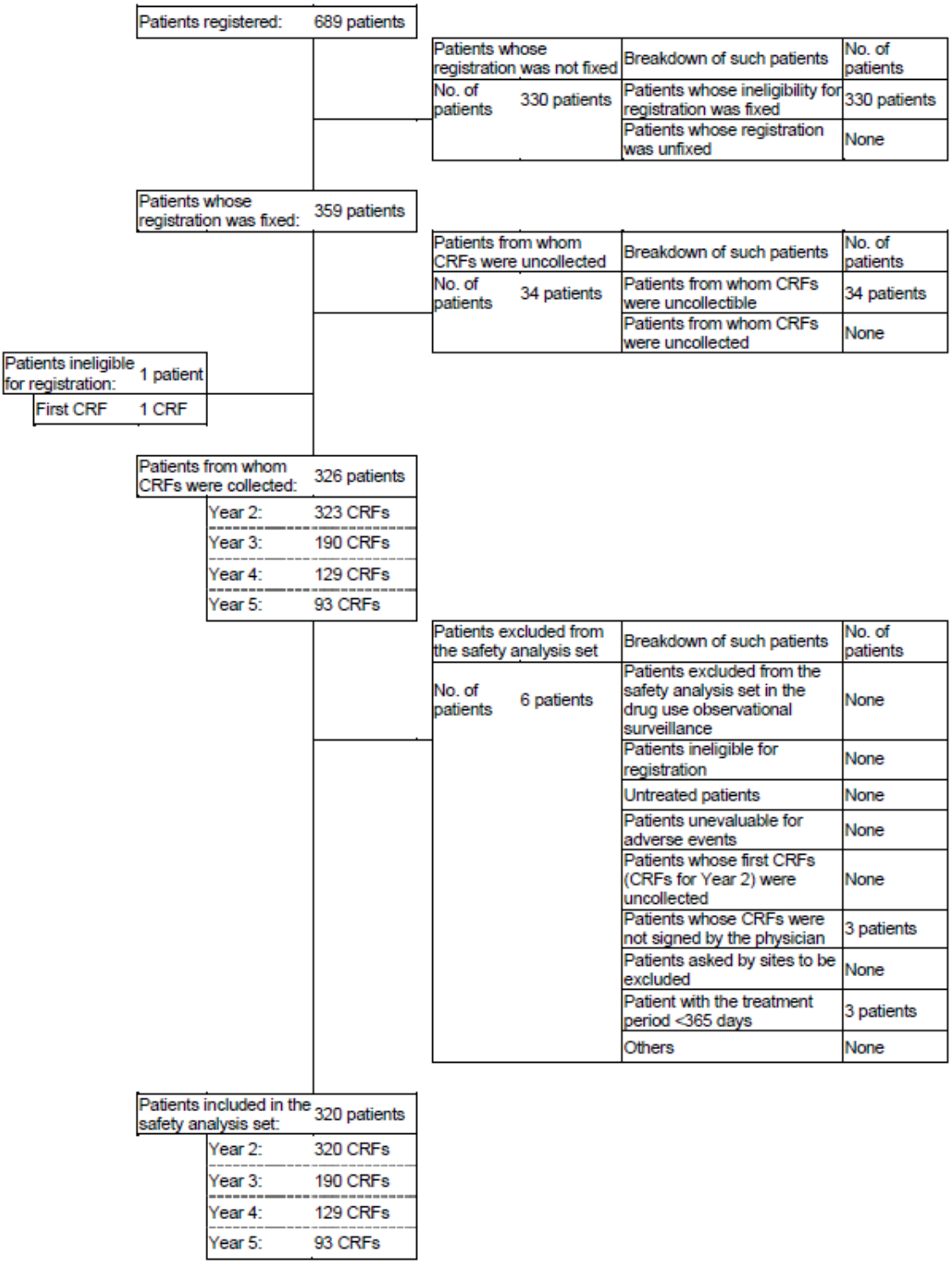
Statistical Methods

Among the pediatric population, efficacy was assessed with ferritin levels. Safety was monitored via adverse events (AE), and adverse drug reactions (ADRs). In addition, a statistical test for adverse drug reactions (ADR) was performed (Fisher's exact test and Mann- Whitney U test).

Results

Recruitment / Number analysed

Figure 10-1 Case composition diagram (patient included in the safety analysis set)



As of May 24, 2016, 689 subjects have been enrolled in the special drug use observational study following 1-year treatment in the drug use observational study (EXJ-1-01). CRFs were collected from 326 of the 689 subjects. Of the 326 subjects from whom the CRFs were collected, 320 subjects were included in safety analysis, excluding a total of 6 subjects: 3 due to CRF not signed and 3 who did receive treatment period <365 days.

Data from 323 CRF-01 (second year), 190 CRF-02 (third year), 129 CRF-03 (fourth year) and 93 CRF-04 (5^{th} year) were tabulated.

Number of children: 3 patients aged under 15 years (0,94%) and 5 patients aged less than 20 years (1.56%).

Efficacy results

Ferritin levels before and after the start of treatment with deferasirox, were measured in 212 patients (efficacy analysis set).

Overall, the mean±SD (median) change in ferritin levels in 212 patients was -704.62±4063.932 (-908.35) ng/mL, with a proportion of patients showing decreased ferritin levels of 68.9% (146/212 patients). Although large variations were noted, serum ferritin levels decreased, despite the fact that 75.0% of patients were receiving lower than the approved 20 mg/kg/day dose, and the majority (66.6%) of patients were receiving 1.7 to 8.3 units of blood per month prior to the start of deferasirox treatment. The mean ferritin levels had a larger decrease in this surveillance (Study A1402) than the drug use observation surveillance (Study A1401), in which the mean ± SD (mean) change in ferritin levels was -292.90±5023.748 (-180.20) ng/mL.

According to the MAH, this is most likely due to: (1) the period of exposure to deferasirox was longer in this surveillance than the drug use observation surveillance and (2) patients who tolerated treatment well in the drug use observational surveillance were included in this surveillance

Children <15 years-old and <18 years-old

The mean±SD (median) changes in ferritin levels in pediatric patients <18 years and adult patients ≥ 18 years were -2706.95 ± 365.928 (-2,706.95) ng/mL and -688.84 ± 4088.019 (-907.00) ng/mL, respectively. Serum ferritin levels decreased in both patient populations. The proportions of pediatric patients <15 years and adult patients ≥ 15 years who had decreased ferritin levels were 100% (2/2 patients) and 68.9% (144/209 patients), respectively.

The ability of deferasirox to remove iron appeared to be superior in pediatric patients, but because ample size was very small, a meaningful comparison could not be made.

CHMP's comment

Due to the small number of paediatric patients in the efficacy analysis set (n=2), no specific analyses of the efficacy in paediatric patients have been conducted.

According to the MAH, a greater reduction in SF levels was observed in the special drug use observational study (A1402) than in the drug observational use study (A1401), indicating that the efficacy was highlighted due to the increased exposure after long term treatment and the fact that patients enrolled well tolerated Exjade.

Safety results

In summary, none of the 3 patients in the pediatric population of this study (<18 years and <15 years of age) had ADRs or serious ADRs reported.

Two patients had aplastic anemia as an underlying disease, and one had pure red blood cell aplasia. One of the three patients reported graft versus host disease, which indicates a prior bone marrow transplant with curative intent. Although no ADRs were reported, it cannot be excluded that potential side effects of the study drug were masked by the many confounders in this patient. In one patient, symptoms were reported as resolved and no longer requiring treatment with study drug at Year 4. This patient was treated with low doses of deferasirox during the 4 years of observation starting at 7.5 mg/kg/day in Year 2 and an average of 14.1 mg/kg/day. No ADRs or AEs were reported in this case, which could be explained by the known lower safety risk of deferasirox at lower doses.

The safety experience in the three pediatric patients in this study was consistent with the currently labeled safety profile of Exjade; however, the low number of pediatric patients do not allow firm conclusions.

CHMP's comment

Only 3 paediatric patients is included in the safety analysis set : one 11 years-old female patient (with aplastic anemia) who has been treated during 1418 days at mean daily dose of 14.08 mg/kg (study discontinuation due to resolution of disease symptoms) ; one 4 years-old male patient (with aplastic anemia) who has been treated during 1826 days at mean daily dose of 19.23 mg/kg (completion of study – He experienced disease complications (liver, cardiac, nervous system)) and a 13 years-old female patient (with PRCA) who has been treated during 658 days at mean daily dose of 27.1 mg/kg. In this latter case, medical history included cholelithiasis, congenital hydrocephalus and bilateral inguinal hernia. On day 631, the patient experienced SAEs : ALT/AST and GGT increased leading to permanent discontinuation on Day 658 due to acute pancreatitis, cholelithiasis, urea nitrogen increased, aggravation of chronic GVHD. SAEs were considered as *not treatment related* but related to concurrent conditions. The SAEs resolved and the patient discharged from hospital.

None adverse reactions were reported in patients under 15 years (or under 18 year-old).

2.3.3. Discussion on clinical aspects

This study is a special drug observational study (post marketing surveillance study) performed in Japan between the market launch of Exjade in 16 June 2008 and May 24, 2016. The aim of this study is to confirm the long term (1 to 5 years) safety and efficacy of Exjade under actual use conditions.

No specific analysis of efficacy in paediatric patients has been performed as only 2 paediatric patients were included in the efficacy analysis set. Similarly for safety, children <15 years old account for only 0.94%. No ADRs were reported in these 3 patients.

Therefore, this observational study did not give any information of long term use of deferasirox in children.

No changes to the paediatric information of the current deferasirox SPC is proposed based on these data.

3. Rapporteur's overall conclusion and recommendation

This study is a special drug observational study (post marketing surveillance study) performed in Japan between the market launch of Exjade in 16 June 2008 and May 24, 2016. The aim of this study is to confirm the long term (1 to 5 years) safety and efficacy of Exjade under actual use conditions.

Overall, this observational study does not bring any new relevant information on efficacy and safety on the long term use in children as children <15 years-old account for only 0.94% of the studied population (3 paediatric patients in safety analysis). No ADRs were reported in these 3 patients.

Based on the data provided for paediatric population, the benefit-risk assessment for deferasirox remains unchanged for the currently approved indications and no changes to the pediatric information of the current deferasirox SPC are proposed as a result of this surveillance.

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**

4. MS comments

During the procedure we have received MS 1 and MS 2 comments. We have not received any comments from other MS:

- **MS 1** agrees with the rapporteur's conclusions and have no further comments.
- **MS 2 comments** :

  In general we can agree with the conclusions as stated by the Rapporteur for the above mentioned procedure. However, we would kindly ask you whether you have considered to provide an integrated report and discussion of the 3 current paediatric worksharing procedures, as it may facilitate decision-making regarding any amendments that might be needed in the SmPC for paediatric patients.

CHMP's comment

After discussion with EMA, it was necessary to have 3 different assessment reports as the applicant submitted P46 071, P46 072 and P46 073 as three separate eCTD sequences (0144, 0145 and 0146 respectively) on 17/10 for P46071 and P46 072 and on 20/10/2017 for P46 073.

However, it could be highlighted that, in all 3 procedures, we are not recommending any PI changes.