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EMA/CHMP/816134/2017
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/P46/074

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 Sep 2017, the MAH submitted a completed paediatric study for deferasirox, 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 CICL670ADE10, 'EXSEPT: Post-authorization non-interventional study on practicability of Exjade treatment in patients with transfusion-dependent iron overload' is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Patients (both adult and pediatric patients) were to be treated with the commercially available product (deferasirox dispersible tablet) according to routine practice and the Summary of Product Characteristics (SmPC). According to the prescribing information, deferasirox dispersible tablet was administered orally as a fine suspension at doses of 10-30 mg/kg body weight.

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 overload 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:

• Study CICL670ADE10: EXSEPT: Post-authorization non-interventional study on practicability of Exjade treatment in patients with transfusion-dependent iron overload.

2.3.2. Study CICL670ADE10: EXSEPT: Post-authorization non-interventional study on practicability of Exjade treatment in patients with transfusion-dependent iron overload

Description

This study was a prospective, multi-center, non-interventional study (NIS) on the practicability of deferasirox for the treatment of patients with transfusion-dependent iron overload. Patients (both adult and pediatric patients) were to be treated with the commercially available product (deferasirox dispersible tablet) according to routine practice and the Summary of Product Characteristics (SmPC). According to the prescribing information, deferasirox dispersible tablet was administered orally as a fine suspension at doses of 10-30 mg/kg body weight. The observation period was scheduled for up to 24 months after start of therapy. According to routine practice, follow-up visits after 3, 6, 9, 12, 18 and 24 months were envisaged.

Diagnostic measures, medically indicated examinations for patient monitoring and prescribed medications in routine clinical practice were documented. The total duration of the study was from July 2010 to March 2017 (end of data collection).

Methods

Objective(s)

The objectives of CICL670ADE10 study were:

- To gain knowledge about the treatment situation of patients with iron overload and prescription characteristics of deferasirox under daily life treatment conditions.

- To evaluate the effectiveness of deferasirox therapy on patients with transfusion - dependent iron overload under daily routine. Treatment effectiveness was assessed by change of serum ferritin from baseline and the number of transfusions (number of erythrocyte concentrates) administered to the patient during the observation period.

- To extend knowledge about the safety profile of deferasirox to be generated by detailed analysis of occurring adverse events (AE), number of therapy discontinuations due to AEs and assessment of hepatorenal parameters (serum creatinine, creatinine clearance, proteinuria, liver transaminase, bilirubin values, and alkaline phosphatases).

- To evaluate the compliance of deferasirox patients by means of number of prescriptions.

Study design

A prospective, multi-center, non-interventional study (NIS) in patients with transfusion-dependent iron overload was appropriate to investigate the research question as close as possible to the daily routine practice. The study did not impose predefined study-related interventions or a visit schedule.

Diagnostic measures and medically indicated examinations performed under daily routine practices were documented. According to routine clinical practice, follow-up visits after 3, 6, 9, 12, 18, and

at the end of observation, i.e., approximately 24 months after start of documentation, were envisaged.

The patients eligible for treatment with oral deferasirox dispersible tablets received an initial dose of 20 mg/kg/day. Study drug dose modifications were observed in accordance with the recommendations by the local deferasirox prescribing information.

Findings from this observational study were analyzed by means of epidemiological methods.

The full analysis set (FAS) comprised of all patients in whom study treatment was started and received at least one dose of deferasirox and there was at least one follow -up visit or an AE. Patients with creatinine clearance <60 mL/min at baseline were excluded from the pediatric FAS. Analysis for efficacy was done in the FAS.

The safety set included all patients with creatinine clearance <60 mL/min at baseline, who received at least one dose of deferasirox, and there was at least one follow-up visit or an AE.

Patients were included in the safety set. All statistical analyses of safety and tolerability were performed in the safety set.

Study population /Sample size

Up to 500 patients of either sex with prior chelation therapy (Deferoxamin or Deferipron) as well as chelation-naïve patients could be documented when starting Exjade therapy. All patients included had to provide informed consent. No further selection criteria were applied apart from contraindications stated in the European Union (EU) SmPC, e.g. patients with a creatinine clearance of <60 mL/min were not to be included. The therapeutic decision had to be independent of the inclusion into the NIS and was to be based solely on the medical necessity for treatment.

Treatments

Patients (both adult and pediatric patients) were to be treated with the commercially available product (deferasirox dispersible tablet) according to routine practice and the Summary of Product Characteristics (SmPC). According to the prescribing information, deferasirox dispersible tablet was administered orally as a fine suspension at doses of 10-30 mg/kg body weight.

Outcomes/endpoints

The present study pursued four main objectives:

- First, to gain knowledge about the treatment situation of patients with iron overload and prescription characteristics of Exjade under daily life treatment conditions.

- Second, to evaluate the effectiveness of Exjade therapy on patients with transfusion-dependent iron overload under daily routine. Main parameters for this objective were the course of serum ferritin and the number of transfusions (number of erythrocyte concentrates) administered to the patient during the observation period.

- Third, extended knowledge about the safety profile of Exjade was to be generated by detailed analysis of occurring adverse events (AE), number of therapy discontinuations due to AEs and assessment of hepatorenal parameters (serum creatinine, creatinine clearance, proteinuria, liver transaminase, bilirubin values, alkaline phosphatases).

- Fourth, compliance of Exjade patients by means of number of prescriptions.

Statistical Methods

The statistical analysis was purely descriptive. For variables with predictive validity, appropriate strata were created and the results were displayed within the strata as well. The output tables were prepared using the statistical software SAS Version 9.4 (SAS Institute Inc., Cary, North Carolina, United States of America).

Full Analysis Set (FAS)

The main analysis set for this NIS was the FAS of patients. This analysis set consists of all patients who met the following criteria:

- Informed consent signed by the patient or parent or legal guardian, respectively
- Treatment with Exjade according to the SmPC (patients with a creatinine clearance <60 mL/min at baseline 7 were excluded from FAS as was one patient with simultaneous treatment with Desferal)
- Documentation of at least one dose of Exjade
- Documentation of at least one follow-up information (follow-up visit or AE)

All tables, figures and listings except for AEs were analyzed for the FAS.

Safety Analysis Set (SAF)

The SAF also included some patients with a creatinine clearance <60 mL/min, i.e., not according to the SmPC. As a result, the SAF comprises the following patients:

- Informed consent signed by the patient or parent or legal guardian, respectively
- Documentation of at least one dose of Exjade
- Documentation of at least one follow-up information (follow-up visit or AE)

All tables for AEs were displayed for the SAF.

Cases excluded from statistical analysis were described in detail in the statistical report. All other patients were included in the evaluation even if they had partially missing data.

Results

Recruitment/ Number analysed

A total of 115 sites participated in this study. Of these, 109 sites had at least 1 patient in the SAF and 108 sites had at least 1 patient in the FAS.

The study database included 505 patients. Of these, 429 patients (84.95%) were included in the SAF. The remaining 76 patients were not included in the SAF. All of these did not have documentation of at least one follow-up information. Additionally, 49 of these patients did not have documentation of at least one dose of Exjade and 7 did not have an informed consent.

The FAS comprised 406 of the 505 patients (80.40%) included in the study database. The remaining 99 patients were not included in the FAS. The most common reasons for non-inclusion were a missing documentation of at least one follow-up information (76 patients, 76.77%) and creatinine clearance <60ml/min (77 patients, 77.78% each).

A total of 12 patients in this study were pediatric patients.

Baseline data

Overall, the patients' median was 73.9 years, with about two thirds of the patients in the age groups of >70 years. A total of 12 patients in this study were pediatric patients. The study included slightly more male (7 patients, 58.33%) than female (41.67%) pediatric patients. The patients' mean age was 6.9±5.32 years (median: 5.1 years).

Slightly more than half of the pediatric patients were Caucasian (58.33%), 33.33% were Black and one patient (8.33%) was in the ethnic group other. For 5 of the 12 pediatric patients (41.67%) beta thalassaemia was the primary disease. A further 3 pediatric patients (25.00%) each suffered from sickle cell disease and other and 1 pediatric patient (8.33%) had MDS as primary disease.

On average, 3.9±4.44 years (median: 1.9 years) had passed since the diagnosis of the primary disease. Concomitant diseases at start of Exjade therapy was reported for 7 of 12 patients (58.33%) in the FAS. At SOC level, hepatobiliary disorders and investigations (2 patients, 16.66%, each) were the only concomitant disease to occur in more than 1 pediatric patient.

The vast majority of patients (11 patients, 91.67%) did not report pre-treatment of transfusion dependent iron overload. For 1 patient (8.33%) such pre-treatment was reported with Exjade® with a duration of 58 days.

CHMP's comment:

As a general comment, the decision to initiate Exjade should not be done in the study. Considering that the majority of patients did not report pre-treatment of transfusion dependent iron overload, it would have been more relevant to include them in the study after the initiation of treatment. The evaluation of the feasibility of the treatment should be tested under usual conditions of care.

Efficacy results

At baseline, more than half of the patients (58.33%) had a moderate need for blood transfusions, 33.33% of patients had a mild need for blood transfusions, and 8.33% of patients had a strong need for blood transfusions. Two thirds of patients had received 20 to 39 packed red blood cells (66.67%) and a third of patients had received <20 packed red blood cells (33.33%) between the diagnosis and the start of Exjade therapy.

The most frequent reason reported for start of Exjade therapy was serum ferritin >1000 ng/ml in the majority of patients (66.67%). In the vast majority of patients the purpose of therapy was given as reduction of serum ferritin (83.33%). The initial daily Exjade dosage was 11.6±6.28 mg/kg (median: 9.8 mg/kg), the last daily Exjade dosage was 23.7±7.56 mg/kg (median: 22.8 mg/kg) and the average daily Exjade dosage (excluding offdays) was 18.1±3.87 mg/kg (median: 19.0 mg/kg).

For pediatric patients, the observation period of this study lasted 556.3±256.40 days (median: 359.5 days) and the duration of exposure was 547.8±254.51 days (median: 624.5 days).

As done for the main analyses, compliance was covered by evaluation of dosage adjustments and differences of the prescribed daily dosage of Exjade at start of therapy versus end of documentation instead. No dosage adjustments were seen in 25.00% of pediatric patients. The reason for dosage increases was dose escalation therapy in 80.00% of patients and chelation too weak in the remaining 20.00% of patients.

Compared to baseline (2048.7±1193.60 µg/L), mean serum ferritin values remained comparable at FU 3 M and FU 6 M. Thereafter, they decreased with increasing length of Exjade treatment from

2064.4±663.11 µg/L at FU 6 M to 1896.3±1960.11 µg/L at FU 24 M. At the last visit, serum ferritin was 2153.7±1595.92 µg/L (median: 1797.0 µg/L) and the mean difference to baseline was 69.7±1684.77 µg/L (median: -412.0 µg/L).

During the observation period, patients received a total median number of packed red blood cells of 20.0. The median number of packed red blood cells per month was 1.0 at all visits. The median change in the number of packed red blood cells per month was 0.0 for all time points.

Transferrin saturation and changes in transferrin saturation values were only available for 8 to 3 patients at the respective time points. Liver iron concentration measurements were performed in 2 or 3 patients. All of these were done by MRT.

CHMP's comment:

EXSEPT is a post-authorization observational study aimed to assess the practicability of Exjade in patients with transfusion-dependent iron overload. This study was not designed to study efficacy of the drug. Only 12 pediatric patients were included and there was no comparator arm.

Because of its non-interventional nature, main limitations of the study included potential selection bias and missing data. Definition of transfusion dependency is not clear in this protocol. As recommended in its SmPC, Exjade should be initiate when serum ferritin >1000 ng/ml or after treatment of more than 20 packed red blood cells. For each child, neither eligibility of inclusion criteria nor drug exposure was detailed for each child.

No clear trend was observed for serum ferritin. Data of other efficacy parameters are poor and disparate.

Based on the data provided in this descriptive study, no conclusion on the efficacy profile of Exjade in pediatric patients can be drawn.

Safety results

A total of 505 patients were included in the study, of which 12 were pediatric patients (<18 years old).

The median daily dose received was 19.0 mg/kg (range: 12.6 mg/kg to 23.6 mg/kg) and the median duration of drug exposure was 624.5 days (range: 50 days to 811.0 days).

During the study, 9 of the 12 pediatric patients (75.00%) in this study reported 37 adverse events (AEs), including 4 out of these 9 patients (33.33%) with at least one serious adverse event. Four (4) patients reported related AEs (n=3 with AE, n=1 with serious adverse event (SAE)):

- One patient presented with SAE, SADR and nSADR

- Two patients presented with nSADRs.

- The remaining 6 patients presented with non-related AE, serious and non-serious

None of the events was fatal.

Table 1: Combinations of Adverse Events Population: Pediatric Safety Analysis Set (N=12)

Parameter	N (%)
Patients (Pediatric Safety Analysis Set)	12 (100.00%)
Patients without AEs	3 (25.00%)
nsAE	3 (25.00%)
nsAE / SAE	2 (16.67%)
SAE	1 (8.33%)
SAE / nsADR / SADR	1 (8.33%)
nsADR	2 (16.67%)

Table 2: Event based incidences of Adverse Events Population: Pediatric Safety Analysis Set (N=12)

Parameter	N (%)
Total number of AEs	37 (100.00%)
nsAE	22 (59.46%)
SAE	8 (21.62%)
nsADR	5 (13.51%)
SADR	2 (5.41%)

Delay of onset of ADRs:

Both SADRs occurred within 6 to 9 months of treatment start.

Three of the nsADRs occurred within the first 3 months, and 1 nsADR occurred within 3 to 6 months.

No recurrent ADR was reported, while 2 pediatric patients presented with recurrent AEs:

- One 2 years patient had 3 recurrent respiratory tract infections

- One 1 year patient had 2 recurrent diarrhoeas, 2 pyrexia and 3 respiratory tract infections

Reported AEs

Regardless of the causality, AEs were mainly reported in the following SOCs (refer to table 8.7.1 of Appendix 1 of the provided clinical summary) (with reccurent AEs counted only once):

- Infections and infestations (6 AE), including 2 AEs of respiratory tract infections

- Gastrointestinal disorders (5 AEs), including 2 AEs of diarrhoea

- Investigations (5 AEs), including 2 AEs of blood bilirubin increased

- General disorders and administration site conditions (4 AEs)

Reported ADRs

Considering related AEs reported, the following nsADRs were reported: Alanine aminotransferase increased (1), Headache (1), Adverse event (1), Bone pain (1), dermatitis (1). Events intensities were mild (2) and moderate (2) when reported, mainly with recovered outcome (3) and not recovered (1) when specified.

Considering related AEs reported, the following SADRs were reported: colitis (1) and haemorrhage (1), both lasting over 21 days and assessed of severe intensity and recovered.

CHMP's comment:

Among the 12 paediatric patients, 9 presented with AEs, including 3 patients with at least 1 non serious ADR and 1 patient with at least 1 serious ADR.

The discussion provided in the clinical overview did not allow to clearly identify the number of patients with related ADRs, and did not provide clear discussion of these 4 cases.

Based on data retrieved from source tables provided in Appendix and from Eudravigilance to get back to the serious ADR detailed description, no unexpected safety trend was identified in the paediatric subgroup from this study.

Among non-serious, related, ADRs:

- a 11 years patient presented with adverse event non further specified,

- a 13 years patient presented with increased alanine aminotransferase; To be noted, increased transaminase is expected as per the section 4.8 of the current SmPC

- a 15 years patient presented with dermatitis, headache and bone pain; To be noted, headache, rash and pruritis are listed in the section 4.8 of the current SmPC. No further details were provided by the sponsor regarding this case.

The serious case reporting SADRs concerned an 11 years old patient who presented non-related gastroenteritis salmonella, leading to salmonella sepsis and diarrhoea. Later the patient presented with colitis and haemorrhage assessed as related and recovered. Exjade dose was decreased due to the events. Of note, ulceration and digestive haemorrhage are described, with dedicated precautions for use, in the current SmPC.

Dose adjustments

More than three dosage increases, two dosage increases and one dosage increase were reported in 25.0%, 16.67 and 25.0% of the patients, respectively. The reason for dosage increases was dose escalation therapy in 80.00% of patients and chelation too weak in the remaining 20.00% of patients No dosage adjustments were reported in 25.0% of the patients. Majority of the patients (91.67%) did not have a dosage decrease (8.33% of the patients had 2 dosage decreases).

Premature discontinuation

Six patients (50.0%) of the patients discontinued the study. The reported reason for premature discontinuation of therapy were lack of compliance, loss of contact, serum ferritin reached target value, stem cell transplantation, physician's decision, other (one patient, 16.67% each).

Clinical laboratory evaluation

Serum creatinine values increased slightly from a mean of 0.33±0.13 mg/dl (median: 0.31 mg/dl, range: 0.20 to 0.66) at baseline to 0.38±0.10 mg/dl (median: 0.39 mg/dl, range: 0.25 to 0.54) at 24 months.

At baseline, for all 12 patients the serum creatinine values were in the ≤ 1.0 × ULN category. At the post-baseline value, 11 patients (91.67%) were in the ≤ 1.0 × ULN category, and one patient had missing values.

There was a decrease in the median creatinine clearance from baseline (183.1 mL/min; range: 152.6 mL/min to 294.1 mL/min) to 24 months (154.8 mL/min; range:128.3 mL/min to 189.2 mL/min) but remained within limits of normal.

Alanine aminotransferase and bilirubin values tended to increase in the course of the study. For the remaining parameters aspartate aminotransferase, alkaline phosphatase, no consistent trend was seen across the time points of the study. There were no cases of Hy's law in this study.

CHMP's comment:

Based on AEs and ADRs reporting, no new safety signal was raised in this paediatric subgroup.

Close monitoring of serum creatinine, creatinine clearance and transaminases is recommended in the SmPC, section 4.4.

2.3.3. Discussion on clinical aspects

No specific analyses of the efficacy in paediatric patients have been conducted. This was a prospective, multicenter and observational study thus non-randomized and non-controlled with limitations including potential selection bias and missing data. No clear trend was observed for serum ferritin. No conclusion on the efficacy profile of Exjade in pediatric patients can be drawn from this study.

Regarding safety data, the discussion provided was minimal, with crossed numbers of patients and AEs making assessment tough. Based on AEs and ADRs reported, no new safety signal was raised in this paediatric subgroup. Main reported ADRs are reflected in the current SmPC.

3. Comments received from other members states

We have received two positive agreements from two member states.

MS1 Comments: The MS agrees with the rapporteur's comments and overall conclusion and has nothing further to add.

MS2 Comments: We agree with the Rapporteur's Assessment report and have no further comments

No further comments were received regarding this procedure.

4. CHMP updated overall conclusion and recommendation

CICL670ADE10, EXSEPT study was submitted in this application as a completed paediatric study for deferasirox, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

This is a prospective, multicenter and observational study thus non-randomized and non-controlled and which was not designated for assess efficacy and safety profile of Exjade in pediatric population.

Data provided from the 12 children included in this study should be considered as supportive.

No conclusion on efficacy of Exjade in paediatric patients could be drawn in this study. Based on AEs and ADRs reporting, no new safety signal was raised in this paediatric subgroup. Main reported ADRs are reflected in the current SmPC.

☒ Fulfilled:

No regulatory action required.