Amsterdam, 30 January 2020
EMA/CHMP/3661/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Praxbind

International non-proprietary name: Idarucizumab

Procedure no.: EMEA/H/C/003986/P46/003

Note

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

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1. Introduction

On 24 October 2019, the MAH submitted completed paediatric study for Praxbind, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study 1321.11 (Safety of potential paediatric patients treated by idarucizumab: a worldwide non-interventional chart review study) is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

The Praxbind (idarucizumab) formulation approved for adults has been used. Praxbind (idarucizumab) 2.5 g/50 mL solution for injection/infusion is a clear to slightly opalescent, colorless to slightly yellow solution. The buffered, isotonic, preservative-free formulation is composed of 25 mM sodium acetate/acetate, 220 mM sorbitol and 0.2 g/L (0.02 w%) polysorbate 20 at pH 5.5. The container closure system consists of a Type 1 glass vial, elastomeric stopper and aluminium overseal with colored button.

The idarucizumab PIP does not foresee development of an age-appropriate formulation.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- study 1321.11: Safety of potential paediatric patients treated by idarucizumab: a worldwide non-interventional chart review study

2.3.2. Clinical study

Study 1321.11: Safety of potential paediatric patients treated by idarucizumab: a worldwide non-interventional chart review study

Description

Methods

Objective(s)

The main objectives of this paediatric observational study were:

- To characterize potential paediatric patients administered with idarucizumab
- To further collect safety data among the paediatric patients until hospital discharge:

- Incidence of thromboembolic events after administration
- Incidence of hypersensitivity / anaphylactic reactions
- Incidence of Adverse Events (AE), Serious Adverse Events (SAE), Adverse Drug Reactions (ADR), and Serious Adverse Drug Reactions (SADR)
- Cause of death and in-hospital mortality rate.

- To compare patient characteristics of paediatric patients with and without safety outcome events.

Amendments and Updates

None

Study design

This non-interventional study was designed as a global, multinational, multi-centre study based on a paediatric cohort using medical chart abstraction.

Neither dabigatran, nor idarucizumab are registered for use in paediatric patients. Identification of paediatric use of idarucizumab were to be performed by hospital pharmacies participating in the idarucizumab drug administration surveillance program (RE-VECTO).

Sites where idarucizumab was administered to paediatric patients were planned to be identified through various methods (e.g. through hospital pharmacies participating in the idarucizumab drug administration surveillance program, spontaneous reporting) and contacted for participation in this paediatric study.

Study population /Sample size

All potential paediatric patients had to meet the following eligibility criteria for the study:

Inclusion criteria

- Male or female, <18 years of age
- Were administered idarucizumab at sites and use identified by various methods (e.g. through the idarucizumab drug administration surveillance program, spontaneous reporting).

Exclusion criteria

- Participation in a dabigatran or idarucizumab clinical trial

Variables and Data Sources

Site characteristics

All hospital pharmacy(ies) (physician/staff administering idarucizumab) characteristics were planned to be collected including:

- Pharmacy characteristics: Country, central pharmacy/Decentralized pharmacy and number of pharmacy units in the hospital (if no central pharmacy) ;
- Idarucizumab stocks, storage location and distribution channels within the hospital;
- Practice type (academic, non-academic, private, public);
- Availability of electronic prescription/medical records at the pharmacy

Paediatric patient characteristics and idarucizumab use

Demographics and medical history:

- Birth month & year or age;
- Gender;
- Name, dose and last intake of previous anticoagulant medications (dabigatran and/or other)
- Medical history pertaining to haemorrhagic risk factors or impact on safety outcomes were planned to be collected
- Concomitant treatment pertaining to haemorrhagic risk factors or impact on safety outcomes were planned to be collected
- Pregnancy status at the time of idarucizumab administration.

Idarucizumab utilisation:

- Department (emergency unit, orthopaedic unit, transplantation unit, cardiovascular unit, or, other patient setting)
- Type of surgery /urgent procedure if applicable
    - Information on bleeding event including: Location: Gastrointestinal tract; intracranial; post-procedural; skin, urogenital tract, retroperitoneal, intraocular, bleeding into the lung, intramuscular (Compartment syndrome), bleeding into the spinal canal (epidural, intraparenchymal), other defined location, undefined location
    - Bleeding severity was planned to be classified according to availability of the following scales in the medical record: International Society on Thrombosis and Haemostasis (ISTH) definition, Thrombolysis In Myocardial Infarction (TIMI) or Global Strategies for Opening Occluded Coronary Arteries (GUSTO) classifications.
- Purpose of use: life-threatening or uncontrolled bleeding requiring urgent medical intervention, emergency surgery or other medical procedure necessitating rapid reversal of the anticoagulant effect of dabigatran prior to surgery/procedure (urgent medical intervention is defined as within the next eight hours), other
- Duration of bleeding event (or start and end of bleeding)
- Dosage and administration (total dose administered and time interval between the administration of the two vials);
- Premature idarucizumab administration discontinuation (yes/no and reason if available)

Other measures:

- Safety outcomes until hospital discharge were planned:
    - Incidence of thromboembolic events (i.e. obstruction of a blood vessel by the formation of a thrombus – e.g. ischemic stroke, MI, DVT, PE) after administration;
    - Incidence of hypersensitivity / anaphylactic reactions
    - Incidence of AE, SAE, ADR, SADR reporting
    - Cause of death and in-hospital mortality rate.

- Comparison of patient characteristics of paediatric patients with and without outcome events (specified above

Data sources:

This study was planned to be based on review of medical charts. The identified local idarucizumab prescriber, investigator or staff were to review the medical charts of the paediatric patients to whom they have administered idarucizumab, over the given time period and extract the desired data elements. The data were planned to be entered pseudonymized into electronic case report forms (eCRFs) via a secure web-based electronic data capture (EDC) system.

Results

The idarucizumab drug administration surveillance program (RE-VECTO) which was the main source for identifying paediatric patients receiving darucizumab in the routine clinical practice has been completed. During his study period no paediatric patients receiving idarucizumab was dentified based on which it was decided to terminate this non- interventional medical chart review study.

This paediatric non-interventional study was open from 29 June 2016 to 30 April 2019. There were no paediatric cases enrolled in this study.

Discussion on clinical aspects

The PIP for idarucizumab (EMEA-001438-PIP01-13) was agreed by the Paediatric Committee of the European Medicines Agency, PDCO on 17 March 2014 (EMA Decision P/0069/2014). Thereafter, 1 PIP modification was submitted and accepted by EMA/PDCO (EMA Decision P/0151/2019 issued on 17 Apr 2019).

The conditions as provided in the PIP are "prevention of dabigatran associated haemorrhage" and "treatment of dabigatran-associated haemorrhage". The targeted indications are the "prevention of haemorrhage in patients who require emergency surgery/procedures when rapid reversal of the anticoagulant effects of dabigatran is needed" and "treatment of uncontrolled or life-threatening bleeding which requires urgent intervention in patients treated with dabiagtran", both in paediatric patients from birth to less than 18 years.

Paediatric clinical programme as agreed in the PIP (EMEA-001438-PIP01-13)

The following 2 measures in paediatric patients from birth to less than 18 years of age were conducted or are ongoing in line with the approved PIP (EMEA-001438-PIP01-13-M01):

- PIP measure 1 is the trial 1321.7, which is a single dose, open label study of administration of idarucizumab as rescue medication to patients in paediatric dabigatran trials to assess safety.

The trial is currently ongoing.

- PIP measure 2 is the paediatric registry 1321.11, which was a non-interventional study with the objective to evaluate the safety of all potential paediatric patients treated with idarucizumab at sites identified by various methods.

This registry data are subject of the current submission. This paediatric non-interventional study was open from 29 June 2016 to 30 April 2019. There were no paediatric cases enrolled in this study.

Given the condition as provided in the PIP this outcome was not unexpected. Idarucizumab is an antidote for dabigatran ("prevention of dabigatran associated haemorrhage" and "treatment of dabigatran-associated haemorrhage". The targeted indications are the "prevention of haemorrhage in

patients who require emergency surgery/procedures when rapid reversal of the anticoagulant effects of dabigatran is needed" and "treatment of uncontrolled or life-threatening bleeding which requires urgent intervention in patients treated with dabiagtran", both in paediatric patients from birth to less than 18 years). Dabigatran has no paediatric indication, it is indicated for primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery." Thus the need for praxbind in children is correspondingly even lower. However paediatric trials of dabigatran are currently ongoing, together with a paediatric trial of idarucizumab (trial 1321.7). Study 1321.7 is designed to allow administration of idarucizumab as rescue medication to patients in paediatric dabigatran trials. The results of these trials are awaited.

3. Rapporteur's overall conclusion and recommendation

This registry data are subject of the current submission. This paediatric non-interventional study was open from 29 June 2016 to 30 April 2019. There were no paediatric cases enrolled in this study.

Given the condition as provided in the PIP this outcome was not unexpected. Idarucizumab is an antidote for dabigatran. However, dabigatran has no paediatric indication. Thus the need for idarucizumab in children is correspondingly even lower.

X Fulfilled:

No regulatory action required.

4. Additional clarification requested

MAH responses to Request for supplementary information