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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

Methylthioninium chloride Proveblue

methylthioninium chloride

Procedure no: EMEA/H/C/002108/P46/010

Note

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

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1. Introduction

On October 2018, the MAH submitted a completed paediatric study for Methylene Blue Proviblue, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert statement was also provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that *Population Modeling & Simulations of Methylene Blue Proviblue in Support of Dose Justification in Pediatric Patients (study number PVP-2015001, Sept 2015)* is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

This was a modeling and simulation study, exposure in children with Methylthioninium chloride Proveblue 5 mg/ml solution for injection was simulated.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Population Modeling & Simulations of Methylene Blue Proviblue® in Support of Dose Justification in Pediatric Patients(study number PVP-2015001, Sept 2015).;

Population PK modeling (report PVP-2015001, Sept 2015) of methylene blue using nonlinear mixed effects modeling was performed based on adult healthy subject data collected from a Phase I bioequivalence study conducted by the Sponsor (StudyPVP- 2014001, IND Number 118,156).

2.3.2. M&S study - Population Modeling & Simulations of Methylene Blue Proviblue in Support of Dose Justification in Paediatric Patients(study number PVP-2015001, Sept 2015)

Description

This modeling and simulation study was to support age-appropriate dose finding in pediatric patients aged 0-18 years by targeting comparable methylene blue exposures as observed in adults.

Objective

The objective of this analysis was to perform population PK modeling and simulation of methylene blue in support of paediatric dosing requirements justification in paediatric patients aged 0 to 18 years.

Methods

Population PK modeling of methylene blue using nonlinear mixed effects modeling was performed based on adult healthy subject data collected from a Phase I bioequivalence study conducted by the Sponsor (StudyPVP-2014001, IND Number 118,156). An allometric function and maturation factor were applied for clearance to account for developmental changes in body size for paediatric subjects and in organ maturation for newborns and infants. A total of 700 plasma concentrations collected from 35 adult healthy subjects were available for population PK model development.

Results

The final model was best described by a three-compartment model with zero-order infusion input. Simulations in pediatric patients older than 3 months of age a dose of 2 mg/kg resulted in similar predicted methylene blue exposure as observed in adults. In newborns and infants younger than 3 months a lower dose of 1 mg/kg should be considered in order to meet target drug concentration ranges.

2.3.3. Discussion on clinical aspects

Methylene Blue (Methylthioninium chloride) is a drug used for a life-threatening methaemoglobinaemia, allowing rapid conversion of methaemoglobin into haemoglobin and rapid improvement of symptoms. The drug is approved in adults and children. Infants above 3 months, children and adolescent have same posology as adults, 1-2 mg/kg given over a period of 5 minutes. The dose for infants less than 3 months of age is 0.3-0.5 mg/kg. The objective of the analysis was to perform population pharmacokinetic (PK) modeling and simulation of methylene blue in support of paediatric dosing in patients aged 0 to 18 years. No PK data in children were available. To simulate pharmacokinetics in pediatric patients, renal maturation was integrated as well as allometric scaled body weight in the developed adult population PK model. Predicted methylene blue exposures (AUC) were evaluated across the ages of 0 to 18 years. Exposure from 1 mg/kg and 2 mg/kg were simulated. In the PK simulations in paediatric subjects, a dose of 2 mg/kg resulted in drug exposures within the adult range in most subjects older than 3 months. In new-born and infants younger than 3 months a lower dose of 1 mg/kg should be considered in order to meet target drug concentration ranges according to the simulations.

The conclusions from the submitted report are only taking PK into account and the MAH states that extra caution due to lower NADPH-methemoglobin reductase levels in the youngest children are warranted. Thus, the adult target exposure range may not be adequate in the youngest children. The MAH has checked AEs(September 2018) including lack of efficacy and states that no lack of efficacy has been reported in the youngest children while 2 serious AEs have been reported, one case of Haemolytic anaemia and one case of Polycytemia with hyperbilirubinaemia. Since the drug is already approved and no lack of efficacy has been reported with the recommended posology and since there could be safety concerns with increased dose, the MAHs suggestion not to change the approved posology is supported. Subsequently the adequacy of the popPK model has not been assessed in detail.

3. Overall conclusion and recommendation

The MAHs suggestion not to change the approved posology is supported.