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Human Medicines Division

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

Vimpat

Iacosamide

Procedure no: EMEA/H/C/000863/P46/032

Note

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

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1. Introduction

On November 2018, the MAH submitted a completed paediatric study for Vimpat, 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 Physiologically based pharmacokinetic (PBPK) prediction of intravenous lacosamide pharmacokinetics and dose adaptations in neonates (aged from birth to 28 days) (study number CL0442, January 2018) is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Not applicable.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted final report(s) for:

- Physiologically based pharmacokinetic (PBPK) prediction of intravenous lacosamide pharmacokinetics and dose adaptations in neonates (aged from birth to 28 days) (study number CL0442, January 2018);

The purpose of CL0442 was to develop a physiologically based pharmacokinetic (PBPK) model for LCM and to use it to predict iv pharmacokinetics (PK) in neonates (age 0 to 28 days) and propose suitable dose adaptions to match PK exposure in older children and adults after oral dosing.

2.3.2. Clinical study

Physiologically based pharmacokinetic (PBPK) prediction of intravenous lacosamide pharmacokinetics and dose adaptations in neonates (aged from birth to 28 days) (study number CL0442, January 2018)

Description

The purpose of CL0442 was to develop a physiologically based pharmacokinetic (PBPK) model for LCM and to use it to predict iv pharmacokinetics (PK) in neonates (age 0 to 28 days) and propose suitable dose adaptions to match PK exposure in older children and adults after oral dosing.

Methods

Objective(s)

- To develop a PBPK model for lacosamide.

- To use the PBPK model to predict intravenous lacosamide pharmacokinetics and dose adaptions in neonates (aged from birth to 28 days) relative to oral doses given to older children and adults.

Statistical Methods

Physico-chemical, in vitro and clinical in vivo PK data for lacosamide were used to develop a PBPK model for lacosamide. The model was validated using adult and paediatric PK data. The model was used to predict intravenous lacosamide pharmacokinetics and dose adaptions in neonates (aged from birth to 28 days).

Results

The PBPK model was used to simulate iv (200mg, 30-minute infusion) PK for healthy adults and the results compared to clinical study SP658 that studied this dose regimen. The model simulation was close to the PK in study SP658.

The model was modified to include the in vitro cytochrome P450 (CYP) metabolism (fms) data and the simulation re-run. The model prediction was good when compared to iv (Table 1) and oral PK data from study SP658.

Table 1: Comparison of PBPK prediction and study SP658 PK data for 200mg iv infusion

Parameter	**PBPK model (200mg iv 30min infusion)**	**SP658 (200mg iv 30min infusion)**
C_{max} (mg/L)	5.43	6.0
AUC (mg/L/h)	81.8	89.0

iv=intravenous; PBPK=physiologically based pharmacokinetic

Data source: CL0442 Table 5-1

In order to fit the early part of the iv and oral PK profiles, a v_{sac} (volume of single adjusting compartment) value (0.1L/kg) was included with K_{in} and K_{out} set to 0.011/h.

Based on in vitro metabolism experiments, CYP3A4 is the main metabolic enzyme for LCM with approximately 70% of metabolism estimated to be due to CYP3A4 (CL0442 Study Report Figure 5-2). It is noteworthy that the CYP3A4 sensitivity analysis performed within this PBPK analysis did not indicate that PBPK predictions were sensitive to the proportion of metabolism attributed to CYP3A4.

The model was used to simulate PK in children 4 to 18 years of age following oral dosing with comparison made to clinical PK data from this population in population PK analysis CL0430. The PBPK model provided a similar prediction of clearance to the estimates made in CL0430 providing confidence in the performance of the model (CL0442 Study Report Figure 5-3).

The model was next used to simulate PK in neonates following a range of iv doses and exposures compared to those seen in adults. The predicted clearance was fairly uniform across the age 0 to 28-day age range with the mean of approximately 0.02 L/h/kg somewhat lower than the mean 0.04L/h/kg seen in older (4 to 17 years) children in CL0430 (CL0442 Study Report Figure 5-4). The predicted clearance of approximately 0.02 L/h/kg in neonates being approximately half of that

observed in older (4+ years) children is plausible for a drug with a mixture of renal (40% in adults) and metabolic (60% in adults) clearance.

Predictions were made for a range of iv bid doses in neonates with the aim to provide a close match of exposure to those in adults. In addition table 1 and table 2 illustrate these neonate PK predictions versus adult initiation (50mg bid) and maximum recommended dose (200mg bid) respectively. Table 2 provides the associated PK parameters. Neonate doses of 0.25mg/kg bid and 0.5mg/kg bid provide close matches of exposure to adult doses of 50mg bid, and neonate doses of 1mg/kg bid and 2mg/kg bid provide close matches of exposure to adult doses of 200mg bid.

Table 2: Comparison of PBPK predicted PK parameters in adults (oral) and neonates (iv)

Parameter	**Adult 50mg bid po**	**Adult 200mg bid po**	**Neonates 0.25mg/kg bid iv**	**Neonates 0.5mg/kg bid iv**	**Neonates 1mg/kg bid iv**	**Neonates 2mg/kg bid iv**
C_{max}	2.00	8.00	0.80	1.60	3.20	6.40
AUC_{tau}	18.78	75.12	6.93	13.87	27.73	55.46

iv=intravenous; PBPK=physiologically based pharmacokinetic; PK=pharmacokinetic

Data source: CL0442 Table 5-2

2.3.3. Discussion on clinical aspects

A PBPK model was developed for LCM and used to predict intravenous PK in neonates (0-28 days). In order to provide a good match of steady state exposure to initiation adult dose of 50mg bd a dose of 0.25-0.5mg/kg is proposed. Clearance was lower and exposure higher for equivalent dose in neonates relative to older children.

A potential limitation of the model may come from lack of certainty of the proportion of metabolism that goes via specific CYPs (fms) used in the study. This is because the excretion balance study did not derive accurate fm values and clinical DDI data is not available to corroborate the fm values used.

There are a number of views on ontogeny of CYP3A4 in literature. The software employed (Simcyp version 15) used the data published by Johnson 2005. Alternative literature by Upreti 2016 reports different ontogeny profiles for CYP3A4 so there is some potential for different exposure to be derived depending on the ontogeny assumptions made.

The aim of the PBPK simulation was to predict doses to be used in future studies in neonates from birth to 28 days old. In this age category, it is not accepted that the SmPC is updated on the basis of predicted (simulated) doses only and hence the suggestion of no change to the approved posology is supported.

3. Rapporteur's overall conclusion and recommendation

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

☒ Fulfilled:

No regulatory action required.