1 April 2016
EMA/CHMP/280639/2016
Procedure Management and Committees Support Division

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

Celsentri

maraviroc

Procedure no: EMEA/H/C/000811/P46/041

Note

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

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1. Introduction

On 05 January 2016, the MAH submitted a completed paediatric study (A4001031) in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. A short critical expert overview was also provided.

According to the obligations under Article 46 the study report should be submitted within 6 months of last patient last visit (LSLV) in the study.

This submission does not include an updated SmPC proposal.

The MAH has communicated the intention to file an extension application for the new formulations and variation (C.I.6) to the prescribing information for a new paediatric indication in April 2016.

CHMP comment

The complete assessment of study A4001031 will be conducted as part of the upcoming new indication variation. Thus, this report only contains some comments related to the pharmacokinetic dataset, which should be addressed in the upcoming variation.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study A4001031 is part of a clinical development program. A line listing is annexed.

2.2. Information on the pharmaceutical formulation used in the study

- Tablets, 25 mg and 75 mg
- Oral solution 20 mg/mL

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- A4001031; An open label, multicentre, multiple dose pharmacokinetic, safety and efficacy trial of maraviroc in combination with optimized background therapy for the treatment of antiretroviral experienced CCR5 tropic HIV-1 infected children 2 - <18 years of age.

CHMP comment

This report only contains a limited number of comments to point out some uncertainties and requirements that will need to be addressed in the new indication variation planned by the MAH to be submitted in April 2016.

Thus, this report does not present a final assessment of the submitted study results. The submitted clinical study report will be assessed as part of the upcoming new indication variation.

2.3.2. Clinical study number A4001031

An open label, multicentre, multiple dose pharmacokinetic, safety and efficacy trial of maraviroc in combination with optimized background therapy for the treatment of antiretroviral experienced CCR5 tropic HIV-1 infected children 2 - <18 years of age.

This was an open-label, 2-stage, age-stratified, non-comparative, multi-center study to evaluate the safety, efficacy, tolerability, and PK/dosing of multiple doses of MVC combined with OBT in ARV treatment-experienced children and adolescents (2 to <18 years) who were failing current ARV therapy or had failed their most recent ARV regimen, defined by plasma HIV-1 RNA ≥1000 copies/mL, were infected with only R5 HIV-1, and had ARV experience ≥6 months, or intolerance to at least 2 ARV drug classes.

Participants received MVC twice daily in combination with OBT. The dose of MVC was scaled down (from adult doses for a BSA of 1.73 m^2) to body size based on BSA bands (mg/m^2) and adjusted for OBT and/or concomitant medication category as shown in Table 1.

Table 1: Initial Maraviroc Doses by BSA and presence/absence of CYP3A interactants in OBT Regimen

Body surface area (m^2)	Dose in absence of potent CYP3A inhibitors or inducers (prior to CSP amendment 5)*	Dose in absence of potent CYP3A inhibitors or inducers	Dose with potent CYP3A inhibitors[a]	Dose with CYP3A inducers[c] (in absence of potent CYP3A inhibitors[a])
<0.22	20 mg BID[b]	40 mg BID[b]	10 mg BID[b]	40 mg BID[b]
0.22 – 0.43	50 mg BID	100 mg BID	25 mg BID	100 mg BID
0.44 – 0.72	100 mg BID	200 mg BID	50 mg BID	200 mg BID
0.73 – 1.19	150 mg BID	300 mg BID	75 mg BID	300 mg BID
1.20 – 1.30	200 mg BID	300 mg BID	100 mg BID	375 mg BID
1.31 – 1.73	300 mg BID	300 mg BID	125 mg BID	450 mg BID
>1.73	300 mg BID	300 mg BID	150 mg BID	600 mg BID

Source: CSP Section 1.3 and Table 5, Appendix 16.1.1.
Abbreviations: BID=twice a day; BSA=body surface area; CSP=clinical study protocol; CYP3A=cytochrome P450 3A; MVC=maraviroc; OBT=optimized background therapy.
*Original starting doses which were no longer used after CSP amendment 5.
[a] eg, atazanavir, darunavir, indinavir, lopinavir/ritonavir, nelfinavir, saquinavir, ketoconazole, itraconazole, clarithromycin, and telithromycin.
[b] dose available in liquid formulation only.
[c] eg, efavirenz, etravirine, rifampicin, carbamazepine, phenobarbital, and phenytoin.

CHMP comment

Table 1 is referred to in the comments below.

3. CHMP overall conclusion and recommendation

This assessment report concludes the current procedure.

The MAH has communicated the intention to file an extension application for the new formulations and variation (C.I.6) to the prescribing information for a new paediatric indication in April 2016.

The full review and final assessment of the submitted study (A4001031) will be conducted as part of the upcoming new indication variation. As part of the upcoming variation the MAH is asked to present additional information and justifications for the maraviroc PK from the study, as listed below:

- The report describing the development process and validation of the popPK model used to analyse the sparse PK data in stage 2 should be submitted. Also, the MAH should present popPK data based on all subjects for which sparse PK data was obtained in stage 2.
- The MAH should present PK parameter data (AUC, Cmax, t½ etc), and comparisons of these between groups (by e.g. CYP interactants, BSA group, age), for the full PK profiles in subjects recruited into stage 1. In addition, the PK (including PK parameters) in children should be compared to the PK in adults (historical data) to further strengthen the PK bridge between adults and children.
- PK parameter data (AUC, Cmax, tmax etc) comparing the tablet and liquid formulation should be presented to allow an assessment of the comparability between the formulations.
- As limited data on subjects taking CYP3A neutral and especially CYP3A4 inducers are available in study A4001031, the MAH is asked to clearly support the suitability of the proposed doses in patients with either CYP3A neutral or CYP3A4 inducer OBT.
- The MAH is asked to explain the rationale for the suggested different BSA categories used for dosing (Table 1) as the ranges of these are very different in size.

Recommendation

☒ Fulfilled:

No regulatory action required.

This study will be fully reviewed in the future new indication variation.