22 October 2009
EMA/823358/2012
Committee for Medicinal Products for Human Use (CHMP)

Ebixa

(memantine)

Procedure No. EMEA/H/C/000463/P45 029.1

CHMP assessment report for paediatric use studies submitted according to Article 45 of the Regulation (EC) No 1901/2006

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

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

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INTRODUCTION

On May 2009, the MAH submitted 13 completed paediatric studies for Ebixa, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Ebixa and that there is no consequential regulatory action.
This investigation involves three areas: Attention-Deficit/Hyperactivity, motorfunction abnormalities and autistic spectrum disorder. These indications are not approved in adults or elderly patients. Efficacy and safety results coming from the submitted studies conducted in the paediatric population are inconclusive. The benefit/risk of the product does not require to be updated in this respect.

Some information about pharmacokinetic characterisation in children and adolescent subjects seem to be generated by different pharmacokinetic studies (or analyses). These data were not submitted within this variation. The MAH was asked to provide the data and to further discuss them. Also, the MAH was asked to comment on the suitability of the marketed formulations for children as well as the eventual development of an oral formulation especially suitable for this population

ASSESSMENT OF THE MAH RESPONSES

1. The MAH should comment on the suitability of the marketed formulations for children as well as the eventual development of an oral formulation especially suitable for this population.

Company's responses

The reflection paper *EMEA/CHMP/PEG/194810/2005*: "formulation of choice for the paediatric population", page 22 describes: solutions/drops for the age class of "newborn infants" up to "adolescents" in group 4 to 5 as „good/preferred acceptability" and „dosage form of choice".

Hence, considering the existing Memantine oral drops/solution we already have a presentation for the complete paediatric population.

Assessor's comment
The question has been satisfactorily answered. Point solved

2. Some information about pharmacokinetic characterisation in children and adolescent subjects seem to have be generated in different PK studies (or analyses). These data have not been submitted in this procedure. The MAH is therefore asked to provide the data and to further discuss them.

Company's responses

Recent sponsor-initiated studies

a) MEM-MD 24
There is one recent clinical study to assess the short-term effects and the pharmacokinetics of memantine in children (*MEM-MD 24*, published by Findling et al.). The trial was completed in 2005 by Forest Laboratories, Jersey City, NJ, USA. Spare plasma samples were withdrawn in this study and analysed by population pharmacokinetic methods. To enrich the spare PK data of this study, data from the two phase I studies MEM-PK-07 and MEM-PK-16 were included in the model development.
MEM-PK-07 was a study of the pharmacokinetic interaction of Memantine and Aricept® in Healthy Young Subjects. MEM-PK-16 was an open-label, randomized, two-way crossover, and multiple dose

bioequivalence study comparing once daily and twice daily dosing regimens of Memantine in healthy subjects.

Study design: In a single-centre, open-label, uncontrolled dose-finding study, children aged between 6 and 12 years of age and diagnosed with *Attention-Deficit/Hyperactivity Disorder* (ADHD, combined type) in accordance with DSM-IV-TR criteria were treated with Memantine on an outpatient basis for a total of 8 weeks . Children enrolled did not receive other concomitant psychoptropic medication.
Study MEM-MD-24 was conducted in two cohorts of patients. Patients were titrated over 4 weeks to 10 mg of Memantine in Cohort 1 and 20 mg of Memantine in Cohort 2, administered once daily. Following the titration period, patients had a 4-week maintenance period using the highest tolerated daily dose. Patients in Study MEM-MD-24 contributed a total of 37 plasma samples obtained from 11 patients at random times post dose. In this study, 3 patients from Cohort 1 and 1 patient from Cohort 2 contributed one sample each at early termination. Seven patients from Cohort 2 contributed 4 to 5 PK samples each at Weeks 1 (Visit 3), 2 (Visit 4), 3 (Visit 5), 4 (Visit 6), and 5 (Visit 7) or early termination at random times post dose. In Study MEM-PK-07, 23 healthy adult subjects contributed 343 plasma samples following administration of a single dose of 10 mg Memantine alone. In Study MEM-PK-16, 25 healthy adult subjects contributed 375 steady-state plasma samples following administration of 20 mg Memantine once daily, the same dosing frequency as in Study MEM-MD-24.

Pharmacostatistics: A nonlinear mixed-effects model was fit to the data using NONMEM® software (NONMEM Version V, Level 1.1; University of California at San Francisco/GloboMax®). Data were analyzed with the one compartment model with first-order absorption and elimination and a lag time in absorption (ALAG). Population PK analysis was performed using the first-order conditional estimation method with interaction. Intersubject variability was described using the exponential error model. Residual variability was described using the proportional error model. Covariates tested during the analysis included weight (WT), age, sex, and creatinine clearance (CrCL).

Model selection criteria: The selection of an appropriate population PK model was based on a significant reduction in the objective function value based on the likelihood ratio test (for nested models; $p<0.001$), the goodness-of-fit plots, and a 95% confidence interval (CI) of the estimated parameters.

Summary and Conclusions: Memantine Cmax levels were higher in paediatric patients with ADHD than in healthy adult subjects following administration of equal doses of Memantine. The differences in drug exposure could be attributed to a large extent to differences in WT, with CL/F and V/F significantly ($p < 0.001$) smaller in paediatric patients with ADHD compared with healthy adult subjects. In the final model of CL/F and V/F, which included WT as a covariate, intersubject variability in CL/F and V/F was reduced by 0.9% and 4.0%, respectively, relative to the basic PK model (no covariates). The greatest reduction was observed in residual variability for paediatric patients with ADHD; residual variability was 95.8% in the basic PK model and only 37.0% in the final PK model.
Based on the final PK model, values of CL/F and V/F determined for healthy adult subjects were similar to those obtained in Study MEM-PK-07 using traditional, non-compartmental, PK analyses. In addition, following administration of 20 mg Memantine once daily in healthy adult subjects, the model-predicted Cmax and AUC0-24 values were similar to those obtained in Study MEM-PK-16 by non-compartmental analysis following the same Memantine dose and dosing frequency.
Given the small number of data from paediatric patients, more studies will need to be performed to better define the PK of Memantine in this patient population. When larger data sets become available, additional covariates, besides weight, may be found to explain differences in Memantine exposure in children and adults. It is also possible that the relationship of CL/F and/or V/F to weight may be different in adults and children.
Graphical relationships between the primary efficacy parameter (change from baseline in ADHD-IV-RS total score) and drug exposure (model-predicted Cmax and AUC0-24) suggest that efficacy can be observed only after a threshold concentration is achieved (around 120-130 ng/mL); thereafter, efficacy seems to improve with increasing drug exposure. The data indicate that Memantine Cmax levels around

150 to 180 ng/mL may be needed for efficacy in ADHD. More data is needed to better describe the relationship between the efficacy of Memantine in paediatric patients with ADHD and drug exposure.

b) MEM-PK-21
Currently the pharmacokinetics in children is investigated in the study MEM-PK-21. This is a single dose, open-label study evaluating the pharmacokinetics of an oral Memantine HCl modified-release formulation in paediatric patients with autistic spectrum disorders.

Status of the Study: Until now 10 children were included in the study. The PK study offers no benefit for the children. Therefore, the recruiting of children was very low and is still ongoing.
Up to now, no report is available.

Assessor's comment
The Company reports two trials in children: Study MEM-PK-21 in paediatric patients with autistic spectrum disorders and MEM-MD-24 in ADHD children. MEM-PK-21 is ongoing and results are not available yet. MEM-MD-24 has provided some PK data coming from 37 samples from 11 patients between 6 an 12 years of age.
From these data, exposure to Memantine in children appears to be higher than that achieved in young adults to equivalent doses. Additional data in paediatric population are expected to be available in next future when study MEM-PK-21 is concluded.
Thus, it seems reasonable to wait in order to have a better PK characterisation of Memantine in this population. Whether the SmPC should be updated accordingly will require further evaluation.

In summary at this stage it seems premature to include any particular information regarding the PK profile of Memantine in children. Additional data are expected to be available in next future.

Rapporteur's Overall Conclusion and Recommendation

The MAH has submitted information about the available results from the clinical investigation in paediatric population. This investigation involves three areas: Attention-Deficit/Hyperactivity, motorfunction abnormalities and autistic spectrum disorder. These indications are not approved in adults or elderly patients. Efficacy and safety results coming from the submitted studies conducted in the paediatric population are inconclusive. The benefit/risk of the product does not require to be updated in this respect. No sound PK data in this population are available at this stage. Therefore no changes in the PI are deemed necessary for the time being.