



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

21 March 2013  
EMA/328117/2013  
Committee for Medicinal Products for Human Use (CHMP)

## Memantine ratiopharm

memantine

Procedure No. EMEA/H/C/002671/0000

Assessment report for initial marketing authorisation application

**Assessment report as adopted by the CHMP with  
all commercially confidential information deleted**



## Table of contents

<b>1. Background information on the procedure .....</b>	<b>3</b>
1.1. Submission of the dossier .....	3
1.2. Steps taken for the assessment of the product .....	4
<b>2. Scientific discussion .....</b>	<b>5</b>
2.1. Introduction .....	5
2.2. Quality aspects .....	5
2.2.1. Introduction .....	5
2.2.2. Active substance .....	5
2.2.3. Finished medicinal product .....	7
2.2.4. Discussion on chemical, and pharmaceutical aspects .....	9
2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects .....	9
2.3. Non-clinical aspects .....	9
2.3.1. Introduction .....	9
2.3.2. Ecotoxicity/environmental risk assessment .....	9
2.3.3. Conclusion on the non-clinical aspects .....	10
2.4. Clinical aspects .....	10
2.4.1. Introduction .....	10
2.4.2. Pharmacokinetics .....	11
2.4.3. Pharmacodynamics .....	15
2.4.4. Post marketing experience .....	15
2.4.5. Discussion on clinical aspects .....	16
2.4.6. Conclusions on clinical aspects .....	17
2.5. Pharmacovigilance .....	17
<b>3. Benefit-risk balance .....</b>	<b>17</b>
<b>4. Recommendation .....</b>	<b>18</b>

## List of abbreviations

AR	Assessment Report
ASMF	Active Substance Master File
AUC	Area Under Curve
BCS	Biopharmaceutics Classification System
BE	Bioequivalence
$C_{\max}$	Maximum plasma concentration of drug after administration
CV	Co-variance
DSC	Differential Scanning Calorimetry
EMA	European Medicines Agency
GC	Gas Chromatography
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HPLC	High Performance Liquid Chromatography
ICH	The International Conference on Harmonisation of Technical Requirements for
LOQ	Limit of Quantification
LLOQ	Lower Limit of Quantification
NMR	Nuclear Magnetic Resonance
NMT	Not More Than
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
QC	Quality Control
RH	Relative humidity
RP	Restricted Part
SD	Standard Deviation
SmPC	Summary of Product Characteristics
$T_{\max}$	Time after administration of drug when maximum plasma concentration is reached
TSE	Transmissible Spongiform Encephalopathy
UV	Ultraviolet
XRPD	X-ray powder diffraction

# 1. Background information on the procedure

## 1.1. Submission of the dossier

The applicant ratiopharm GmbH submitted on 21 May 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Memantine ratiopharm, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– ‘Generic of a Centrally authorised product’. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 27 January 2012.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication: treatment of Alzheimer’s disease.

### The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Ebixa instead of non-clinical and clinical data unless justified otherwise

### Information on paediatric requirements

Not applicable

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:

Product name, strength, pharmaceutical form: **Ebixa 5 mg/10 mg/15 mg/20 mg**

#### film-coated tablets

- Marketing authorisation holder: **H.Lundbeck A/S**
- Date of authorisation: 15/05/2002
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: **EU/1/02/219**

- Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

Product name, strength, pharmaceutical form: **Ebixa 5 mg/10 mg/15 mg/20 mg**

#### film-coated tablets

- Marketing authorisation holder: **H.Lundbeck A/S**
- Date of authorisation: 15/05/2002
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: **EU/1/02/219**

- Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

Product name, strength, pharmaceutical form: **Ebixa 10 mg film-coated tablets**

- Marketing authorisation holder: **H.Lundbeck A/S**
- Date of authorisation: 15/05/2002
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number: **EU/1/02/219**
- Member State of source: **France**
- Bioavailability studies reference number/EudraCT number: **70303 (study code: DEV399501-1MEM07)**

### ***Scientific advice***

The applicant did not seek scientific advice at the CHMP.

### ***Licensing status***

The product was not licensed in any country at the time of submission of the application.

## ***1.2. Steps taken for the assessment of the product***

The Rapporteur appointed by the CHMP and the evaluation team were:

Rapporteur: Walter Janssens

- The application was received by the EMA on 21 May 2012.
- The procedure started on 20 June 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 7 September 2012.
- During the meeting on 18 October 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 14 November 2012.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 19 December 2012.
- During the CHMP meeting on 17 January 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 19 February 2013.
- During the meeting on 18-21 March 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Memantine ratiopharm.

## 2. Scientific discussion

### 2.1. Introduction

Memantine ratiopharm 5 mg; 10 mg; 15 mg; 20 mg film-coated tablets is a generic medicinal product of Ebixa 5 mg; 10 mg; 15 mg; 20 mg which has been authorised in the EU since 15 May 2002.

The active substance of Memantine ratiopharm is memantine hydrochloride, a psychoanaleptic, anti-dementia drug (N06DX01). Memantine is a voltage-dependent, moderate-affinity non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, modulating the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction.

The safety and efficacy profile of memantine has been demonstrated in several clinical trials details of which can be found in the EPAR of Ebixa. In addition, there is a long-term post-marketing experience contributing to the knowledge of the clinical use of this product. Since this application is a generic application referring to the reference product Ebixa, summary of the clinical data is available and no new clinical studies regarding pharmacology, pharmacokinetics, efficacy and safety have to be conducted, which was considered acceptable.

The approved indication is: Treatment of patients with moderate to severe Alzheimer's disease.

The indication proposed for Memantine ratiopharm is the same as authorized for the reference medicinal product. Proposed pack sizes are consistent with the dosage regimen and duration of use as per the SmPC.

### 2.2. Quality aspects

#### 2.2.1. Introduction

The finished product Memantine ratiopharm is presented as film-coated tablets containing 5 mg; 10 mg; 15 mg; 20 mg of memantine as the active substance. The composition is described in section 6.1 of the SmPC.

The product is available in Alu/Alu blisters or HDPE bottles as described in section 6.5 of the SmPC.

#### 2.2.2. Active substance

The active substance memantine (as hydrochloride) or 1-Amino-3,5-dimethyl tricycle (3,3,1,1<sup>3,7</sup>) decane hydrochloride, 3,5-Dimethyl-1-adamantamine HCl, 1-Amino-3,5-dimethyl adamantane HCl is a white, crystalline powder, soluble in water and methanol, practically insoluble in acetone.

It is a non-hygroscopic substance. Memantine contains two stereocenters. It has a symmetry axis C<sub>2</sub> and a symmetry plane, therefore it is achiral.

The active substance is consistently obtained as a single polymorphic form.

The elucidation of the structure of Memantine hydrochloride has been confirmed by Elemental analysis, IR, UV, <sup>1</sup>H & <sup>13</sup>C NMR, XRPD, DSC & Mass spectrum. The results are all-consistent with the chemical

structure assigned. All DSC peaks show that a single polymorphic form is present and that no change could be observed after storage.

A comprehensive discussion has been presented regarding impurities including potential genotox impurities and residual solvents. The limits remained below the ICH limits and therefore no safety concern is expected.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure from two suppliers within the current manufacturing authorisation application.

## ***Manufacture***

The information on the manufacturing process of the active substance is provided in the restricted part of the ASMF provided for both manufacturers. Memantine hydrochloride is synthesised in 5 steps including the salt formation using well-defined commercially available starting materials.

The synthetic process and the starting materials used in the manufacture of the active substance are sufficiently described by both suppliers. Critical steps and intermediates are presented in a satisfactory manner. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Both suppliers established satisfactory control on the manufacturing process of memantine hydrochloride through adequate in-process and intermediates specifications. Information regarding process validation has also been presented and considered acceptable. Batch analysis data confirm the active substance is manufactured reproducibly.

## ***Specification***

The finished product manufacturer set up a specification that is a combination of the specifications of the 2 active substance manufacturers. The specification includes the following parameters: appearance (visual), solubility, clarity and colour of solution (Ph.Eur.), pH, identification (IR, and chloride method), water content (Ph.Eur. 2.5.12), sulphated ash (Ph.Eur. 2.4.14), chloride content (titration, Ph.Eur. 2.2.20), assay (titration, Ph.Eur. 2.2.20), related substances (GC in-house), related substances (GC, in house), residual solvents (GC, in-house), particle size (laser in-house )

The specification from the finished product manufacturer is suitable to control the quality of memantine. The analytical methods have been described and the in-house methods have been validated in accordance with ICH guidelines.

Two Certificates of analysis of memantine obtained from each ASMF supplier and issued by the proposed finished product manufacturer were presented, confirming compliance with the proposed specification.

## ***Stability***

For the first active substance manufacturer, 12 pilot batches of memantine packed in the commercial package were put on ICH long term (25°C/60%RH, up to 5 years) and accelerated (40°C/75%RH, 6 months) stability studies.

The following parameters were tested: clarity and colour of solution, pH, loss on drying, related substances and assay. The analytical methods were the same as those used for release testing.

All the available results are within specifications (accelerated and long term studies) and no significant trends are observed. Stress stability studies were conducted under heat, acidic, alkaline, and oxidative conditions, No significant degradation could be observed apart from oxidative conditions

For the second ASMF supplier, 3 pilot batches (only 2 batches for the accelerated studies) of memantine packed in commercial package were put on ICH long term (25°C/60%RH, up to 36 months) and accelerated (40°C/75%RH, 6 months) stability studies.

The stability samples are tested for appearance, water content, assay by titration, chlorides content and purity & related substances by GC. The analytical methods and the specifications are those applied at release.

All the available results were within specifications (accelerated and long term studies) and no significant trends are observed.

In conclusion, based on the available stability data, the proposed re-test period and storage conditions by each supplier when the active substance is packed in the proposed packaging materials are considered acceptable.

### **2.2.3. Finished medicinal product**

#### ***Pharmaceutical development***

The objective was to develop a tablet formulation containing memantine that is essentially similar to the reference product Ebixa film-coated tablets. The manufacturing process retained after different trial formulations was a process by direct compression.

The active substance memantine hydrochloride is classified as a highly soluble drug substance (BCS class I). In addition, parameters such as water content, and particle size of the active substance were studied and controlled during the pharmaceutical development and their results were consistent for both manufacturers.

With regard to polymorphism, DSC thermograms and XR-diffractograms of consecutive batches confirmed the same crystalline form is used in the manufacturing process.

The first prototypes formulations were evaluated for dissolution profiles compared to the reference product. In order to improve dissolution, these formulae were further optimized for the composition. Satisfactory dissolution and stability at 40°C/75%RH were achieved with the final formulation.

Memantine Hydrochloride 5, 15 and 20mg tablet cores are dose proportional to memantine Hydrochloride 10mg tablet cores. Similar dissolution profiles for the 5, 15 & 20mg tablets versus reference Ebixa tablets were demonstrated.

The dissolution profiles at all the pH media including QC medium for product release between the Memantine ratiopharm and Ebixa film-coated tablets are similar for all dosage strengths. Pilot batches of the drug product show dissolution of more than 85% within 15 minutes. The discriminative power of the dissolution method is deemed demonstrated with different prototype trial formulae, proposed formula and reference product.

The chosen excipients are widely used for this immediate-release dosage form, and they are microcrystalline cellulose and lactose anhydrous as filler, pregelatinised starch as disintegrant/binder, magnesium stearate as lubricant, white film-coating powder Opadry including partial hydrolysed polyvinyl alcohol, titanium dioxide, talc, lecithin, xanthan gum and purified water as coating solvent and polysorbate 80 as wetting agent. All the excipients are of compendial grade. There are no compatibility concerns with the proposed excipients, as is demonstrated in long-term and accelerated testing and supporting compatibility screening studies of binary mixtures. The excipients used are



standard pharmacopoeial excipients for solid oral dosage forms. Opadry is not described in any pharmacopoeia but the individual ingredients are.

The formulation used during the bioequivalence study (biobatch V00407002; 120 000 tablets) is the same as the final formulation used for marketing.

Bioequivalence study was therefore performed showing bioequivalence between the European Reference Product (Ebixa) and the proposed commercial formulation.

The primary packaging proposed is PVC/PVdC/Alu blister or HDPE bottle. The materials comply with Ph.Eur. requirements. Stability studies have been performed and confirm the appropriateness of the packaging.

### ***Adventitious agents***

The only material from animal origin is lactose. It is confirmed that the lactose is produced from milk from healthy animal in the same conditions as those used to collect milk for human consumption and the lactose has been prepared without the use of ruminant material other than calf rennet according to the current Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products. No TSE risk is foreseen.

### ***Manufacture of the product***

The manufacture of Memantine ratiopharm film-coated tablets is a standard process and can be summarised in the following main steps: blending and sifting of the ingredients, mixing, compression, coating of the tablets, packaging.

Appropriate in-process controls such as assay, density, uniformity of weight, hardness have been applied during the manufacture of the tablets.

A process validation protocol at pilot scale has been provided as well as validation results on three pilot batches for the 5 and 10mg tablets. Results showed that the tablets could be manufactured reproducibly according to the agreed finished product specification. The first three commercial batches will be produced and subjected to validation as outlined in the validation protocol.

### ***Product specification***

The finished product release and shelf-life specification for Memantine ratiopharm 5, 10, 15 & 20mg film-coated tablet include the appropriate tests for description (visual), identification of memantine (IR and HPLC), identification of colorant, average weight, uniformity of dosage units (Ph.Eur. 2.9.40), water content (Karl-Fischer), assay (HPLC), related substances (GC), dissolution (Ph. Eur. 2.9.3), microbial contamination (Ph.Eur. 2.6.12 and 2.6.13).

Analytical methods were described and for non pharmacopoeial methods, description and validation reports were presented.

Batch results on four pilot batches of Memantine ratiopharm of each strength produced at Ratiopharm using the active substance from the two proposed suppliers confirm consistency and uniformity of the manufacture, and indicate that the process is under control. The limits for the related substances remained within the ICH limits and raised no safety concerns.

## ***Stability of the product***

Stability of four pilot batches of each strength kept in the commercial packaging (blisters or bottles) stored under ICH long term (up to 48 months at 25°C/60%RH), and accelerated conditions (6 months at 40°C/75%RH) were presented. The parameters tested were identical to those from the finished product specification. All results were in compliance with the specifications. There were no significant trends observed. The analytical methods used were stability indicating.

Stability data of 2 batches of bulk coated tablets of each strength stored for 6 months at 25°C/60%RH, 30°C/65%RH or 40°C/75%RH revealed no significant changes.

In-use stability study were performed on 2 pilot batches of 5, 10 & 20mg tablets packed in open HDPE bottles and stored for 6 months at 25°C/60%RH. The tested parameters were appearance, identity, water content, assay and degradation products, dissolution and microbial purity. No trend in stability was observed during storage in open bottles, except for moisture content that increased. The product should be kept in the closed packaging to protect it from moisture.

Based on the available stability data, the proposed shelf-life, the in-use shelf life and the storage conditions as stated in the SmPC are acceptable.

### **2.2.4. Discussion on chemical, and pharmaceutical aspects**

Information and development, manufacture, and control of the active substance and the finished product has been presented in a satisfactory manner. The results of the tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a uniform and satisfactory performance in the clinic.

### **2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects**

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been provided to give reassurance on viral/TSE safety.

## ***2.3. Non-clinical aspects***

### **2.3.1. Introduction**

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable further to the applicant clarification in its answer to the List of Questions.

Therefore, the CHMP agreed that no further non-clinical studies are required.

### **2.3.2. Ecotoxicity/environmental risk assessment**

No Environmental Risk Assessment (ERA) was submitted. This was justified by the applicant as the introduction of Memantine ratiopharm manufactured by Ratiopharm GmbH is considered unlikely to

result in any significant increase in the combined sales volumes for all memantine containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

### **2.3.3. Conclusion on the non-clinical aspects**

There are no objections to approval of Memantine ratiopharm from a non-clinical point of view.

## **2.4. Clinical aspects**

### **2.4.1. Introduction**

This is a generic application for film-coated tablet containing memantine. To support the marketing authorisation application the applicant conducted two bioequivalence studies with cross-over design under fasting conditions with the 10mg strength (study n°70303 and study n°120087). Study 120087 was the pivotal study for the application and study 70303 was supportive. The applicant applied for a biowaiver for the additional strengths (5mg, 15mg, and 20mg).

No formal scientific advice by the CHMP was given for this medicinal product.

For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

### **GCP**

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

### **Exemption**

According to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr \*\*) if the pharmacokinetic of the active substance is linear and that the bioequivalence is demonstrated for one strength, *in vivo* bioequivalence studies for the other strengths could be waived. An exemption from the requirement to perform bioequivalence studies would be justified when the following conditions are met: the pharmaceutical products have the same manufacturer, same qualitative composition, same ratio between active substance and excipients and *in vitro* dissolution profile comparable to the reference product.

A biowaiver was applied for the 5 mg, 10 mg and 15 mg strengths. The applicant provided tabular listing of the composition of the four strengths. Similarity factors were not calculated as more than 85% of the drug was dissolved within 15 minutes at all pH values tested. According to literature (Robinsons and Keating, 2006) the dose/plasma concentration relationship is linear over the range of 10-40 mg. During the procedure the applicant provided published data which demonstrated PK linearity over the range 5mg-40mg (FDA website). During the procedure, the applicant also provided the comparative dissolution profiles at pH 1.2, 4.5 and 6.8 of the four strengths for the batches used in both BE studies.

Based on these results, the CHMP concluded that the general biowaiver criteria were met. Therefore, one bioequivalence study and a biowaiver for the additional strengths were considered adequate.

## Clinical studies

To support the application, the applicant has submitted two bioequivalence studies, neither pharmacodynamic studies, nor therapeutic equivalence studies. The applicant conducted a first pivotal bioequivalence study with cross-over design under fasting conditions with the 10 mg strength (study n°70303). However during the assessment it was observed that an incurred sample reanalysis was missing in the bioanalytical method part of the study. The validation of the analytical method used was therefore not in accordance with the Guideline on Bioanalytical method validation (EMA/CHMP/EWP/192217/2009). As the plasma samples were not available anymore for a re-assay, the applicant repeated the study (study n°120087). Thus this study was considered pivotal for the application and the results of the initial study were considered supportive.

**Table 1.** Tabular overview of clinical studies

Type of study	Location of study report	Objectives of the study	Study design and type of control	Test product, dosage regimen; route of administration	Number of subjects	Healthy subjects or patients' diagnosis	Duration of treatment	Study status; type of report
BE	5.3.1.2	To compare the rate and extent of absorption of memantine 10 mg tablet (ratiopharm GmbH; test), versus Ebixa 10 mg tablet (H. Lundbeck-A/S, Denmark; marketed in France; reference)	Single centre, bioequivalence, open-label, single-dose, randomised, 2- way crossover study, performed under fasting conditions.	Test: Memantine Hydrochloride 10 mg film coated-tablets, ratiopharm, Pvt. Ltd., India; 1 x 10 mg oral;  Reference: Ebixa® 10 mg filmcoated tablets; H. Lundbeck-A/S, Denmark for marketing in France; 1 x 10 mg oral;	Enrolled and randomised: 32 subjects (16 females and 16 males) were included in the study  Drop-out: 0 subject  Withdrawal: 1 subject  Completed: 31 subjects	Healthy subjects	Single dose	Complete; Full
BE	5.3.1.2	To compare the rate and extent of absorption of memantine 10 mg tablet (ratiopharm GmbH; test), versus Ebixa 10 mg tablet (H. Lundbeck-A/S, Denmark; marketed in France; reference)	Single centre, bioequivalence, open-label, single-dose, randomised, 2- way crossover study, performed under fasting conditions.	Test: Memantine Hydrochloride 10 mg film coated-tablets, ratiopharm, Pvt. Ltd., India; 1 x 10 mg oral;  Reference: Ebixa® 10 mg filmcoated tablets; H. Lundbeck-A/S, Denmark for marketing in France; 1 x 10 mg oral;	Enrolled and randomised: 24 subjects (10 females and 14 males) were included in the study  Drop-out: 0 subject  Withdrawal: 0 subject  Completed: 24 subjects	Healthy subjects	Single dose	Complete; Full

## 2.4.2. Pharmacokinetics

### Study 70303

#### Methods

#### Study design

Study 70303 was a randomized, open-label, 2-way crossover, bioequivalence study of memantine 10 mg tablet and Ebixa (reference) following a single dose in healthy subjects under fasting conditions. It was conducted with Ratiopharm GmbH, as sponsor, from 29/08/2007 to 18/10/2007.

Blood samples were collected at 0.00 (pre-dose), 1.00, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.0, 12.0, 14.0, 24.0, 48.0, 72.0, 144, 216, 288 and 360 hours following drug administration in each period. The two periods were separated by a wash-out period of 35 days.

Memantine was analysed in plasma.

### ***Test and reference products***

Memantine ratiopharm 10mg manufactured by Ratiopharm, Pvt. Ltd. (batch No. V00407002, manufacturing date: 04/2007; exp. date 04/2008) has been compared to Ebixa 10mg manufactured by H. Lundbeck-A/S (Batch No: 609451, exp. date 08/2010.).

### ***Populations studied***

Based on data from previous studies, the intra-subject coefficients of variation should be approximately 10% and 16% for AUC and  $C_{max}$ , respectively. Thus, with these expected coefficients of variation and an expected ratio of AUC and  $C_{max}$  within 0.90 and 1.11, the study should have a power of at least 85% to show bioequivalence with 28 subjects.

In order to account for possible dropouts, a total of 32 healthy adult subjects (16 males and 16 females) aged between 18-55 years were included into the study. Thirty-one (Subject n° 11 excluded) completed both treatment periods of this study and have been included in the statistical analysis. Subject n°11 was withdrawn from the study in Period I due to positive urine drug screen (benzodiazepine).

### ***Analytical methods***

The plasma concentrations of memantine in the study samples were quantified by a validated LC/MS/MS method after a liquid-liquid extraction using memantine-d6 as the internal standard.

The analytical method used has been shown to be sensitive, accurate and selective for the plasma level determination of memantine in the concentration range of 0.101-20.144 ng/mL. The lower limit of quantification (LLOQ) was 0.101 ng/mL of plasma.

### ***Pharmacokinetic variables***

The pharmacokinetic parameters were calculated from the drug-concentration-time profile by non-compartmental model.

Pharmacokinetics: AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, C<sub>max</sub>, Residual area, T<sub>max</sub>, T<sub>1/2 el</sub> and K<sub>el</sub>.

### ***Statistical methods***

ANOVA was performed on ln-transformed AUC<sub>0-t</sub>, AUC<sub>0-inf</sub> and C<sub>max</sub>.

ANOVA was also carried out on the untransformed data of T<sub>1/2 el</sub> and K<sub>el</sub>.

A non-parametric test (Wilcoxon's Signed-Rank test) was carried out to compare the T<sub>max</sub> between treatments. Ratios of least-squares means and 90% geometric confidence intervals were calculated for ln-transformed AUC<sub>0-t</sub>, AUC<sub>0-inf</sub> and C<sub>max</sub>.

Inter and intra-subject CVs were also calculated.

Bioequivalence of Test Product-A vs. Reference Product-A was concluded, if the 90% geometric confidence intervals of the ratio of least-squares means for ln-transformed  $AUC_{0-t}$  and  $C_{max}$  were within the acceptable range of 80% and 125%.

## Results

**Table 2.** Pharmacokinetic parameters for memantine hydrochloride (non-transformed values)

Pharmacokinetic parameter	Test (Memantine ratiopharm (A))		Reference (Ebixa (B))	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-t)}$	1157.257	204.929	1162.949	232.725
$AUC_{(0-\infty)}$	1191.632	224.411	1204.374	260.456
$C_{max}$	13.324	2.047	13.471	2.174
$T_{max}^*$	5.50 (2.00 – 8.00)	1.68	5.50 (2.00 – 12.00)	2.44
$AUC_{0-t}$	area under the plasma concentration-time curve from time zero to t hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
$C_{max}$	maximum plasma concentration			
$T_{max}$	time for maximum concentration (* median, (min - max))			

**Table 3.** Statistical analysis for memantine hydrochloride (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference*	Confidence Intervals**	Intra-Subject CV%***
$AUC_{(0-t)}$	99.88 %	97.51 % to 102.30 %	5.56 %
$AUC_{(0-\infty)}$	99.42 %	97.02 % to 101.88 %	5.66 %
$C_{max}$	99.02 %	96.39 % to 101.71 %	6.22 %
* Calculated using least-squares means according to the formula: $e^{(Memantine\ HCl\ (A) - Ebixa\ (B))} \times 100$			
** 90% Geometric Confidence Interval using ln-transformed data			
*** estimated from the Residual Mean Squares			

## Safety data

A total of 43 treatment emergent adverse events (TEAEs) were reported by 19 of the 32 subjects who received at least one dose of the study medication (safety population). Twenty-three adverse events were reported by 40.6% (n=13) of the 32 subjects who received the test product and 20 adverse events were reported by 35.5% (n=11) of the 31 subjects who received the reference product. Of the 43 post-dose adverse events reported, 34 were graded as mild and 9 were graded as moderate. The most commonly reported adverse event was "Somnolence" reported by 18.8% (n=6) of subjects who constituted the safety population (n=32). No deaths or serious adverse events were reported during the conduct of the trial.

## Study 120087

## Methods

## Study design

Study 120087 was an open-label, randomized, two-way, single oral dose, crossover BE study under fasting conditions. Blood samples were collected prior to study drug administration and at 1.00, 2.00,

2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 8.00, 10.0, 16.0, 24.0, 36.0, 48.0, and 72.0 hour post-dose in each period. The treatment phases were separated by a washout period of 35 days.

Memantine and its internal standard memantine-d6 were analysed in plasma.

### ***Test and reference products***

Memantine ratiopharm 10 mg manufactured by TEVA India private Ltd, Goa for Ratiopharm GmbH (batch No. 3120018, manufacturing date 04/2012; exp. date not available, retest date: 04/2015) has been compared to Ebixa 10 mg manufactured by H. Lundbeck A/S, Denmark (Batch No: 153287, exp. date 05/2015).

### ***Populations studied***

Based on data from literature, the intra-subject CVs should be 10% and 16% for AUC and  $C_{max}$ , respectively. Thus, with these expected CVs and an expected ratio of AUC and  $C_{max}$  within 0.95 and 1.05, with an alpha error of 5%, the study should have a power of at least 90% to show BE with 18 subjects. In order to account for possible dropouts, 24 healthy subjects (10 females and 14 males) were included in the study. All subjects completed the study and were included in the safety population.

Some protocol deviations in the blood sampling schedule occurred during the study (11 samples were taken with over 30 mn delay and 1 sample was not obtained).

### ***Analytical methods***

Pharmacokinetics:

- Parametric ANOVA on  $AUC_{0-72}$  and  $C_{max}$ ; geometric confidence intervals for  $AUC_{0-72}$  and  $C_{max}$ ; and non-parametric test (Wilcoxon) for  $T_{max}$ ;
- Factors in the ANOVA model: sequence, subject within sequence, period, and treatment;
- Ln-transformed parameters:  $AUC_{0-72}$  and  $C_{max}$ .

Criteria for bioequivalence for memantine: 90% geometric confidence intervals of the ratio (A/B) of least-squares means from the ANOVA of the Ln-transformed  $AUC_{0-72}$  and  $C_{max}$  should be within 80.00% to 125.00%.

### ***Pharmacokinetic variables***

Pharmacokinetics:  $AUC_{0-72}$ ,  $C_{max}$ ,  $T_{max}$

### ***Statistical methods***

ANOVA was performed on Ln-transformed  $AUC_{0-t}$ ,  $AUC_{0-\infty}$  and  $C_{max}$ .

ANOVA was also carried out on the untransformed data of  $T_{1/2\text{ el}}$  and  $K_{el}$ .

Ratios of least-squares means and 90% geometric confidence intervals were calculated for Ln-transformed  $AUC_{0-t}$ ,  $AUC_{0-\infty}$  and  $C_{max}$ . Inter and intra-subject CVs were also calculated.

A non-parametric test (Wilcoxon's Signed-Rank test) was carried out to compare the  $T_{max}$  between treatments.

## Results

**Table 4.** Pharmacokinetic parameters for memantine (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	geometric mean	SD CV%	geometric mean	SD CV%
AUC <sub>(0-72h)</sub>	600.180	76.747 12.79	605.802	91.241 15.06
C <sub>max</sub>	12.907	1.743 13.50	13.125	1.891 14.41
T <sub>max</sub> *	7.00 (2.00 – 10.0)		7.00 (3.00 – 16.0)	
AUC <sub>0-72h</sub> area under the plasma concentration-time curve from time zero to 72 hours				
C <sub>max</sub> maximum plasma concentration				
T <sub>max</sub> time for maximum concentration (* median, range)				

**Table** Statistical analysis for memantine (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	Intra-CV% *
AUC <sub>(0-72h)</sub>	99.35%	97.03% to 101.73%	4.77%
C <sub>max</sub>	98.44%	95.57% to 101.40%	5.97%
* estimated from the Residual Mean Squares			

## Safety data

A total of 21 TEAEs were recorded by 9 subjects during the study: 13 TEAEs reported by 29.2% of subjects following administration of Treatment A and 8 TEAEs reported by 16.7% of subjects following administration of Treatment B. The most commonly reported TEAEs was “headache” reported by 25.0% (n=6) of subjects who constituted the safety population. Of the 21 TEAEs reported, 19 were graded as mild and 2 were graded as moderate. No deaths, serious or significant AEs were reported during this study.

## Conclusions

Based on the presented bioequivalence studies Memantine ratiopharm is considered bioequivalent with Ebixa.

The results of study 120087 with the 10mg formulation can be extrapolated to other strengths 5mg, 15mg and 20mg, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6.

### 2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

### 2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.



## 2.4.5. Discussion on clinical aspects

In this application no new efficacy or safety data were submitted which was considered acceptable. The applicant provided an acceptable review of clinical trial published in literature, describing the efficacy and safety profile of Memantine Ratiopharm. No new dose recommendations compared with the reference product were made for this generic application.

### Bioequivalence study 70303

The applicant conducted a first open-label, single-dose, randomised, 2- way crossover study, under fasting conditions with the 10 mg strength. The study design, population chosen, sample size, and statistical methods were well described and appropriate according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr \*\*). However, no incurred sample reanalysis was reported as the study was performed before the current guideline was available. Nevertheless, this is now a regulatory requirement in the European guideline (Questions & Answers EMA/618604/2008 Rev. 6, 10 December 2012). Therefore the applicant was requested to provide the ISR of a scientific justification for the lack of ISR.

The 90% confidence intervals around the geometric means ratio T/R for memantine were in the acceptance range of 80-125% for the primary parameters  $AUC_{0-t}$ ,  $AUC_{0-\infty}$  and  $C_{max}$ . The AUC derived from the measurements is at least 80% of the AUC extrapolated to infinity. The median values of  $T_{max}$  were sufficiently similar for test and reference product. These results were considered as supportive.

### Bioequivalence study 120087

Further to the major objection on the lack of ISR, as the samples were no longer available, the applicant submitted during the procedure a new bioequivalence study including an ISR analysis (study n°120087) in the validation of the bioanalytical method. Study 120087 was an open-label, randomized, two-way, single oral dose, crossover BE study with the 10 mg strength, under fasting conditions. According to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr \*\*) the study design was appropriate for an immediate release product. This Guideline states that the bioequivalence study should in general be conducted at the highest strength, however for products with linear pharmacokinetics and where the drug substance is highly soluble as it is the case for memantine, selection of a lower strength than the highest is also acceptable. Hence, one bioequivalence study with the 10 mg strength was considered appropriate to establish bioequivalence. Since memantine may be taken with or without food according to the SmPC of the reference medicinal product, a study under fasted conditions was adequate. Taking into account the terminal half-life ranges from 60 to 100 hours for memantine, the sampling scheme and the wash-out period were considered appropriate. The determination of sample size was based on a power of at least 90%, an alpha level of 0.05, a T/R ratio between 95-105% and a low within-subject CV based on in-house estimates, this was acceptable. The reported deviations were minor and considered not to affect the results and conclusions of the study as the accurate sampling times were used in the analysis.

This new bioequivalence study was conducted according to the Note for Guidance on the Investigation of Bioequivalence, CPMP/EWP/QWP/1401/98 Rev.1. The analytical and statistical methods were well described and appropriate. A total of 100.00% of the reanalysed samples (96 samples) met the criteria of assay reproducibility.

The 90% confidence intervals of the ratios of geometric means were well in the acceptance range of 80-125% for the primary parameters  $AUC_{0-72}$  and  $C_{max}$ .

Based on the results obtained, it was concluded that the test product (Memantine ratiopharm 10 mg film-coated tablets) is bioequivalent to the reference product (Ebixa 10 mg film-coated tablets). The test and reference product were found to be clinically comparable in their safety profile.

#### Additional strengths biowaiver

The general biowaiver criteria were met and the pharmacokinetics over the therapeutic dose range is linear. Therefore, a biowaiver for the strengths 5 mg, 15 mg and 20 mg is adequate.

### **2.4.6. Conclusions on clinical aspects**

Based on the submitted bioequivalence studies and the presented additional strength biowaiver, Memantine ratiopharm 10 mg and 20mg film-coated tablets are considered bioequivalent with Ebixa 10mg and 20mg film-coated tablets.

## **2.5. Pharmacovigilance**

### ***Summary of the pharmacovigilance system***

The CHMP considered that the Summary of the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

### ***Risk management plan***

The CHMP did not require the applicant to submit a risk management plan because there are no safety concerns with the reference medicinal product, which has led to additional risk minimisation activities, beyond routine risk minimisation activities.

### ***PSUR submission***

The CHMP considered that PSUR submission is not required for generics of this active substance. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product were to be included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

### ***User consultation***

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Memantine hydrochloride 10mg/ml. The bridging report submitted by the applicant has been found acceptable.

## **3. Benefit-risk balance**

This application concerns a generic version of memantine film-coated tablets. The reference product Ebixa is indicated in the treatment of adults with moderate to severe Alzheimer's disease. No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study 120087 forms the pivotal basis with a single centre, open-label, single-dose, randomised, 2- way crossover design, under fasting conditions with the 10 mg strength. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Memantine ratiopharm met the protocol-defined criteria for bioequivalence when compared with Ebixa. The point estimates and their 90% confidence intervals for the parameters  $AUC_{0-72}$  and  $C_{max}$  were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

## 4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers that the benefit-risk balance of Memantine ratiopharm in the treatment of adults with moderate to severe Alzheimer's disease is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

### ***Conditions or restrictions regarding supply and use***

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

### ***Conditions and requirements of the Marketing Authorisation***

#### ***PSUR cycle***

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 and published on the European medicines web-portal.

### ***Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the member states.***

- **Risk Management Plan (RMP)**

Not applicable