London, 21 February 2013

EMA/229868/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Memantine Mylan

International non-proprietary name: **Memantine**

Procedure No. EMEA/H/C/002660

Assessment Report as adopted by the CHMP with all commercially confidential information removed

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8545
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table of contents

List of abbreviations

AAS	Atomic Absorption Spectrometry
AP	Applicant's Part
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File
AUC	Area Under Curve
BCS	Biopharmaceutics Classification System
BE	Bioequivalence
CTD	Common Technical Document
C_{max}	Maximum plasma concentration of drug after administration
CV	Co-variance
DSC	Differential Scanning Calorimetry
EMA	European Medicines Agency
FT-IR	Fourier Transform Infrared Spectroscopy
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 Registration of Pharmaceuticals for Human Use.
IPCs	In-Process Controls
KF	Karl-Fischer titration
LOD	Limit of Detection
LOQ	Limit of Quantification
LLOQ	Lower Limit of Quantification
NMR	Nuclear Magnetic Resonance
NMT	Not More Than
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
QOS	Quality Overall Summary

QC	Quality Control
QP	Qualified Person
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
USP	United States Pharmacopeia
UV	Ultraviolet
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Generics (UK) Limited submitted on 22 May 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Memantine Mylan, 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 17 November 2011.

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).

The applicant applied for the following indication.

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 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 10mg, 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/1/02/219/001-003
    EU/1/02/219/007-012
    EU/1/02/219/014-021
    EU/1/02/219/023-035
    EU/1/02/219/037-049

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

- Product name, strength, pharmaceutical form Ebixa 10mg, 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/1/02/219/001-003
    EU/1/02/219/007-012
    EU/1/02/219/014-021
    EU/1/02/219/023-035
    EU/1/02/219/037-049

■ 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 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(s): EU/1/02/219/034
- Bioavailability study number(s): MEMA-11225 & MEMA-12036

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

Memantine Mylan has a Marketing Authorisation pending in the United States of America.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was Concepcion Prieto Yerro

- The application was received by the EMA on 22 May 2012.
- The procedure started on 18 July 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 5 October 2012.
- During the meeting on 12-15 November 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 15 November 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 December 2012.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 31 January 2013.
- During the meeting on 18-21 February 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 Mylan.

2. Scientific discussion

2.1. Introduction

Memantine Mylan, 10 mg and 20 mg film-coated tablets, is a generic medicinal product of Ebixa, which has been authorised in the EU since 15th May 2002.

The active substance of Memantine Mylan is memantine hydrochloride, a psychoanaleptic anti-dementia drug (ATC code: N06DX01) for the treatment of moderate to severe Alzheimers disease. Memantine is an amantadine derivative and antagonist of *N*-methyl-*D*-aspartate (NMDA) receptors.

The safety and efficacy profile of memantine has been demonstrated in several clinical trials, details of which can be found in the EPAR for 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 medicinal product Ebixa, a summary of the clinical data of memantine is available and no new clinical studies regarding pharmacology, pharmacokinetics and efficacy and safety have been conducted.

Memantine Mylan 10 mg and 20 mg film-coated tablets have the same qualitative and quantitative composition, in terms of active substance, and the same pharmaceutical form as the reference product Ebixa. Bioequivalence of the 20 mg dose with the reference 20 mg Ebixa tablet was demonstrated clinically. Demonstration of bioequivalence of the 10 mg dose was waived since the drug substance is highly soluble, the two strengths are manufactured by the same method, and the compositions of the two strengths are quantitatively proportional.

The indication proposed for Memantine Mylan is the same as authorized for the reference medicinal product, Ebixa. In addition to the pack presentations authorised for Ebixa, the applicant has applied for 7, 10 and 60 tablet pack sizes for both strengths. The proposed pack sizes are consistent with the dosage regimen and duration of use of the reference medicinal product.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 10 mg and 20 mg of memantine hydrochloride as active substance. The composition is described in section 6.1. of the SmPC.

The product is available in PVdC clear film push through foil lidding blister packs.

2.2.2. Active substance

This medicinal product contains memantine hydrochloride as active substance. Memantine hydrochloride is a white to off-white crystalline powder soluble in water and methanol. The chemical name is 3,5-dimethyl-1-adamantamine hydrochloride, 3,5-dimethyltricyclo-[3.3.1.1]-decan-1-amine hydrochloride, or 1-amino-3,5-dimethyladamantane hydrochloride.

The structure of memantine hydrochloride was unambiguously confirmed by ^{1}H and ^{13}C NMR, FT-IR spectroscopy, mass spectrometry, elemental analysis, and XRPD.

Memantine is achiral, therefore no stereoisomerism was observed. Polymorphism has been observed although the manufacturing process consistently produces the required crystalline form.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure within the current Marketing Authorisation Application.

Manufacture

The active substance is supplied by one active substance manufacturer. Detailed information about the manufacturing process, control of starting materials, reagents and solvents, control of critical steps and intermediates along with process development and validation for the active substance has been supplied in the form of an active substance master file (ASMF). Memantine hydrochloride is synthesized in three steps. The manufacturing process is adequately described. Adequate in-process controls are in place and appropriate specifications have been adopted for the starting materials, solvents and reagents. All relevant impurities, degradation products and residual solvents have been appropriately characterised. Batch analysis data is provided on three consecutive production scale batches using the proposed synthetic route, and the batch analysis data show that the active ingredient can be manufactured reproducibly.

Specification

The active substance specification includes tests for appearance, solubility, identity (IR, GC), water content (KF), residue on ignition, heavy metals, impurities (HPLC), assay (HPLC), residual solvents (GC), chloride content (titrimetry), bulk density (tapped and un-tapped), and particle size (Malvern).The specifications and tests proposed are compliant with the relevant ICH guidelines and general requirements of Ph.Eur. The specifications are adequate to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety.

Batch analysis data on three commercial scale batches of the active substance are provided. The results comply with the proposed specification specifications and confirm consistency and uniformity of the active substance manufacture.

Stability

Four commercial scale batches of the active substance packed in the intended commercial package from the ASMF holder were put on stability testing as per ICH conditions: three batches were stored under long term conditions (25 °C / 60% RH) for 60 months, and under accelerated conditions (40 °C / 75% RH) for 6 months. A further batch was stored under long term conditions (25 °C / 60% RH) for 12 months, and under accelerated conditions (40 °C / 75% RH) for 6 months. Stability was also tested under stressed conditions in solution: acid hydrolysis; base hydrolysis, oxidation (peroxide); heat degradation (60 ^{o}C) and UV light. Solid state stability was investigated by exposure to white fluorescent light, UV light (365 nm), and heat degradation (105 ^{o}C).
The following parameters were tested: description (identity by IR; GC and XRPD); clarity and colour of solution; water content (KF); related substances (GC); assay (HPLC). The active substance is stable under all conditions, except that it undergoes rapid degradation on exposure to peroxide and slow degradation on exposure to base at 60 ^{o}C. In conclusion, no special storage conditions are required.

The stability studies indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished medicinal product

Pharmaceutical development

The objectives of formulation development were to develop an immediate-release memantine hydrochloride tablet bioequivalent to the reference Ebixa tablets. Furthermore, compositionally proportional formulations for 10 mg and 20 mg strengths were required, along with acceptable content uniformity, rapid and complete active substance release, and adequate product stability throughout the intended shelf-life. The qualitative composition is similar to that of Ebixa with the addition of talc and different colour coating for the 20 mg strength.

The active substance is a crystalline solid, routinely manufactured as form I with consistent particle size distribution. It is highly soluble in all tested media from pH 1.1-7.4 (BCS class I), and the dissolution characteristics were shown to depend on its inherent solubility, rather than the composition of excipients, since changes to the formulation and tablet hardness had little effect on solubility. Dissolution rates were demonstrated as equivalent to the reference product. Both Ebixa and Memantine Mylan are immediate release tablets with functionally similar excipients, similar physico-chemical properties, and similar dissolution profiles. Thus, the physico-chemical properties of the active substance are unlikely to have any impact on therapeutic equivalence. No compatibility issue between drug substance and excipients was observed during development

Memantine Mylan 10 mg and 20 mg film-coated tablets have the same quantitative and qualitative composition in active substance and the same pharmaceutical form as the reference product. Bioequivalence was demonstrated by comparing 20 mg Memantine Mylan tablets with 20 mg Ebixa tablets. The bioequivalence of the 10 mg strength was waived since its manufacture and proportional composition is the same as the 20 mg strength.

All the chosen excipients are well-known, and widely used in film-coated tablets. The excipients include: microcrystalline cellulose (filler); croscarmellose sodium (disintegrant); magnesium stearate (lubricant); micronized talc (glidant); colloidal anhydrous silica (glidant), and film-coating agents (yellow Opadry II, red Opadry II and clear Opadry). All the excipients are controlled in accordance with Ph. Eur. monographs except for the coating agents which meet in-house specifications.

Direct compression and high shear wet granulation were first investigated for tablet manufacture. However, as a result of poor flowability and low assay values, a dry granulation roller compaction method was selected which gave acceptable content uniformity, hardness, and assay results.The film-coated tablets are packaged in blisters comprised of PVC-PVdC clear film with a foil push-through lidding material to seal the film surface. The material complies with Ph.Eur. requirements and is adequate to support the stability and use of the product.

Adventitious agents

No excipients derived from animal or human origin have been used.

Manufacture of the product

The finished product is manufactured by dry granulation and the manufacturing process consists of dispensing, screening, final blending, compression, coating and packaging. A description and flow diagram of the manufacturing process is provided. The manufacturing process is considered standard.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process using three batches of each strength and is satisfactory. The in process controls are adequate for this product.

The batch analysis data provided show that this tablet can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.The applicant committed to perform process validation studies on the first three production scale batches at the proposed commercial batch size.

Product specification

The finished product release specification includes appropriate tests for appearance (visual description), identification (HPLC and IR), assay (HPLC), uniformity of dosage unit (HPLC), dissolution, water content (KF), related compounds (HPLC), and microbiological quality (Ph.Eur.).

Batch analysis results from two pilot scale batches of the 10 mg strength and two pilot scale batches of the 20 mg strength confirm consistency and uniformity of manufacture and indicate that the process is capable and under control.

Stability of the product

Stability data from two pilot scale batches of the 10 mg strength in proposed commercial packaging stored under long-term conditions (25 ºC / 60% RH) for up to 12 months and under accelerated conditions (40 ºC / 75% RH) for up to 24 weeks according to ICH guidelines were provided. Additionally, stability data from two pilot scale batches of the 20 mg strength in proposed commercial packaging stored under long-term conditions (25 ºC / 60% RH) for up to 12 months, under intermediate conditions (30 ºC / 65% RH) for up to 12 months, and under accelerated conditions (40 ºC / 75% RH) for up to 24 weeks according to ICH guidelines were provided.

Samples were tested for appearance, dissolution, assay, related compounds, and water content. The analytical procedures used were stability indicating.

The applicant commits to further testing at up to 36 months under long-term conditions (25 ºC / 60% RH) for each of the aforementioned batches.

Furthermore, the applicant has carried out stability studies on the bulk drug product intermediates to justify holding times of longer than 30 days and ensure stability in the in-process container closure system.

The CHMP recommends that the applicant further tests the bulk drug product intermediate on commercial batches at up to 12 months under long-term conditions (25 ºC / 60% RH) for commercial batches post-opinion.

In addition, two batches of each strength of drug product were exposed to both UV and visible light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant changes in Memantine Mylan film-coated tablet quality attributes were observed and thus, the product is not sensitive to light.

The breakability of the scored 10 mg tablets was also assessed after storage under long-term conditions (25 ºC / 60% RH) after 12 months, given an observed increase in water content on long-term storage, and found to be acceptable. The applicant is recommended to further breakability testing after 18 and 24 months, and thereafter, annually until the end of shelf-life.

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

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of 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 satisfactory and uniform 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 presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The applicant is recommended to further testing of bulk drug product intermediate at up to 12 months under long-term conditions (25 ºC / 60% RH) for commercial batches post-opinion. This is to give further confidence that the bulk intermediate can be held for up to 1 year under the proposed in-process storage conditions without detrimental effects on finished product quality. The bulk intermediate stability has already been demonstrated on pilot batches up to 9 months.
- Taking into account the increase in the water content of the product during storage, the applicant is recommended to perform subdivision testing on lots 1000769 and 1000770 of scored 10 mg tablets after 18 and 24 months, and thereafter, annually until the end of shelf-life.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview based on up-to-date and adequate scientific literature on the pharmacology, pharmacokinetics and toxicology was provided. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics (PK) 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.

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 Mylan manufactured by Mylan Pharmaceuticals Inc. 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 environmental risk is expected to be similar and not increased. The CHMP endorsed this view.

2.3.3. Discussion on non-clinical aspects

N/A

2.3.4. Conclusion on the non-clinical aspects

The non-clinical overview presented by the applicant is largely based on published scientific literature which is acceptable since memantine is a well-known active substance. There are no objections to the approval of Memantine Mylan from a non-clinical point of view. The SmPC of Memantine Mylan is similar to that of the originator product Ebixa and is therefore acceptable.

2.4. Clinical aspects

Introduction

This is a generic application for film-coated tablets containing memantine. To support the marketing authorisation application the applicant conducted two bioequivalence studies with parallel design under fasting conditions with the 20 mg strength (study MEMA-11225 and study MEMA-12036). Study MEMA-12036 was the pivotal study for this application.

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/Corr**) 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 (Doc. Ref.: 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 has been applied for the 10 mg strength. The applicant provided a tabular listing of the composition of the two strengths and their dissolution curves at pH 1.2, 4.5 and 6.8. Similarity factors were not calculated because more than 85% of the drug was dissolved within 15 minutes at all pH values tested.

Based on these results, the CHMP concluded that the general biowaiver criteria were met. Therefore, one bioequivalence study with the highest dose of 20 mg and a biowaiver for the additional strength was considered adequate.

Clinical studies

To support the application, the applicant submitted two bioequivalence studies (MEMA-11225 and MEMA-12036).,Neither pharmacodymanic studies, nor therapeutic equivalence studies were submitted.

The applicant conducted two studies as the lower 90% CI for log transformed AUC_{0-72} was narrowly outside (79.71-101.61%) the acceptable bioequivalence limit (80-125%) for the first study (MEMA-11225). The applicant stated that this issue was due to the inter-subject variability (20.43%) and that the relative geometric least square mean ratio of the test and reference observed for pharmacokinetic parameter $LnAUC_{0-72}$ in the study was larger than the anticipated (16%), therefore, a sample size of 32 subjects was considered not adequate to meet the required bioequivalence standards.

Table 1. Tabular overview of clinical studies

Type of study	Study identifier	eCTD	Objective of the study	Study design	Test product: dosage regimen; route of administration	Number of subjects	Healthy subjects of diagnosis of patients	Duration of treatment	Study status; type of report
BE	MEMA-11225	5.3.1.2	BE versus reference product under fasting conditions	Parallel	Tablet 20 mg, single dose, oral	32	Healthy subjects	Single dose	Complete, full
BE	MEMA-12036	5.3.1.2	BE versus reference product under fasting conditions	Parallel	Tablet 20 mg, single dose, oral	64	Healthy subjects	Single dose	Complete, full

Pharmacokinetics

Methods

Studies design

Study MEMA-11225 and Study MEMA-12036

These were open-label, single dose, randomized, single-period, two-treatment parallel studies investigating the bioequivalence of Mylan's Memantine hydrochloride film-coated tablets, 20 mg to H. Lundbeck A/S' Ebixa® 20 mg film-coated tablets in adult subjects under fasting conditions.

Blood samples were collected within 120 minutes prior to dose administration (0 hour) and after dose administration at study hours : 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18, 24, 36, 48, and 72 hours.

Memantine was analysed in plasma

Test and reference products

Study MEMA-11225 and Study MEMA-12036

Memantine Mylan 20 mg film coated tablet manufactured by Mylan Pharmaceuticals Inc. Lot No.: 2003060 (Batch No.1000771), manufacturing date 06/10/2011; exp. date 10/2014) has been compared to Ebixa 20 mg film coated tablet manufactured by H. Lundbeck A/S (Batch No: 052230, exp. date 30/09/2014).

Population studied

Study MEMA-11225

Assuming a true ratio between 0.94 and 1.06 and an inter-subject variability of 16% or less for Cmax, a minimum of 28 subjects was required to conclude bioequivalence with approximately 80% power. To account for subject withdrawal and dropouts due to adverse events, non-compliance or personal reasons, 32 subjects were planned to be randomized and dosed. The data from thirty-two subjects (Subjects 1-32) were included in the pharmacokinetic and statistical analysis.

Thirty-two (32) healthy, non-tobacco using subjects were enrolled in the study.

The number of protocol deviations was similar in the reference group (6 meal deviation and 7 PK sample collection deviation) than in the test group (5 meal deviation and 6 PK sample collection deviation).

Study MEMA-12036

Assuming a true ratio between 0.93 and 1.07 and an inter-subject variability of 21% or less for C_{max} and AUC_{0-t}, a minimum of 60 subjects were required to conclude bioequivalence with approximately 80% power. To account for subject withdrawal and dropouts due to adverse events, non-compliance or personal reasons, 64 subjects were planned to be randomized and dosed.

Sixty-four healthy subjects were enrolled in the study.

Subject 29 (test group) was excluded from the bioanalysis of plasma sample and pharmacokinetic analysis as they did not return to the clinical facility for blood sample collection 72 hour time point and hence truncated AUC 72 could not be calculated precisely for the subject. There was 1 other protocol deviation in the test group and 3 in the reference group.

Analytical methods

Study MEMA-11225 and Study MEMA-12036

Pre-study validation

The assay employed a LC-MS/MS method for the determination of memantine in K2EDTA. The complete analytical method (Project # 09-022-02 dated on March 19th, 2012) associated with this validation was provided. The method validation was performed in accordance with SOP L-301-06, which fulfils the acceptance criteria in US FDA, May 2001. The method was validated over the concentration range of 0.4 ng/mL to 40.0 ng/mL. A weighting of 1/c2 was used.

In-study validation

Biostudy samples were assayed using HPLC-MS/MS in K2EDTA plasma. The method used a standard range of 0.4 ng/mL to 40 ng/mL. A weighted (1/c2) linear regression was used.

Pharmacokinetic variables

Study MEMA-11225 and Study MEMA-12036

Single-dose pharmacokinetic parameters for Memantine were calculated using non-compartmental method. The primary pharmacokinetic variables for assessment of bioequivalence are C_{max} and AUC_{0-72}. The secondary pharmacokinetic variable was T_{max}.

Statistical methods

Study MEMA-11225 and Study MEMA-12036

Statistical analyses were performed on the pharmacokinetic parameters of Memantine using the General Linear Models Procedure (PROC GLM) of SAS Software (SAS Institute, Cary, NC). The model tests for treatment effects in the parameter means at an alpha level of 0.05. The parameters' T_{max} was analysed statistically using the non-transformed data. The natural log transformed parameters AUC_{0-72} and C_{max} were statistically analyzed. The tests were performed to analyze for statistically significant differences in the pharmacokinetic parameters using Least Squares Means. Ninety percent confidence intervals (90%CI) were constructed for C_{max} and AUC_{0-72} using the two one-sided tests procedure to assess average bioequivalence between the two products.

Assessment of bioequivalence was conforming to the Regulatory requirements set forth by the region of submission. The primary pharmacokinetic variables for assessment of bioequivalence were C_{max} and AUC_{0-72}. The primary assessment of bioequivalence was based on the 90% confidence interval of the ratio (T/R) of least-squares means from the ANOVA of the natural log transformed C_{max} and AUC_{0-72} being within 80% - 125%.

Results

Study MEMA-11225

Table 2. Pharmacokinetic parameters for Memantine (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD CV%	arithmetic mean	SD CV%
$AUC_{(0\text{-}72h)}$	1266.107	258.911 20.45	1402.757	273.455 19.49
C_{max}	30.743	6.968 22.67	31.978	6.665 20.84
T_{max} *	4.938 (2.00–10.00)	46.46	5.250 (3.00–8.00)	23.59
$AUC_{0\text{-}72h}$ area under the plasma concentration-time curve from time zero to 72 hours C_{max} maximum plasma concentration T_{max} time for maximum concentration (* median, range)				

Table 3. Statistical analysis for Memantinte (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	90% Confidence Intervals	CV%*
$AUC_{(0\text{-}72h)}$	90.00%	79.71%-101.61%	-
C_{max}	95.52%	83.32%-109.52%	-
* estimated from the Residual Mean Squares			

Study MEMA-12036

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

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD CV%	arithmetic mean	SD CV%
$AUC_{(0\text{-}72h)}$	1293.239	200.553 15.51	1234.602	212.564 17.22
C_{max}	29.050	5.246 18.06	28.245	4.499 15.93
T_{max} *	5.581 (2.00 – 9.00)	2.013 36.07	5.219 (2.00 – 10.00)	2.366 45.33
$AUC_{0\text{-}72h}$ area under the plasma concentration-time curve from time zero to 72 hours C_{max} maximum plasma concentration T_{max} time for maximum concentration (* median, range)				

Table 5. Statistical analysis for Memantine (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	90% Confidence Intervals	CV%*
$AUC_{(0-72h)}$	104.98%	97.84%-112.65%	-
C_{max}	102.49%	95.45%-110.06%	-
* estimated from the Residual Mean Squares			

Safety data

Study MEMA-11225

Seven subjects experienced a total of 8 adverse events (AEs) over the course of the study. All 8 AEs were considered mild in severity. No AE was reported more than once following administration of the test treatment. The most frequently reported AE following administration of the reference treatment was headache, which was reported by 2/16 (12.5%) subjects. No AEs were reported during post-study procedures. No SAEs were reported.

Study MEMA-12036

Twelve subjects experienced a total of twenty-one adverse events (AEs) over the course of the study. All adverse events were considered mild in severity. Dizziness, headache and neutrophil count decreased were the most frequent AE experienced by subjects following administration of test treatment and were each reported by 2/32 (6.3%) subjects. The most frequently reported AE following administration of reference treatment was headache and dyspnoea which were each reported by 2/32 (6.3%) subjects.

There were 8 AEs considered possibly related to the study medication in both groups. There was 1 AE (euphoric mood) considered probably related to the oral administration of Ebixa 20 mg film-coated tablets (H. Lundbeck A/S). No serious adverse events were reported.

Conclusions

Study MEMA-11225

This study was not sufficient to conclude on the bioequivalence of Memantine Mylan as AUC(0-72h) 90% confidence interval being slightly outside of the accepted range with Ebixa. The results of this study with the 20 mg formulation are considered supportive.

Study MEMA-12036

Based on the presented bioequivalence study, Memantine Mylan 20 mg tablet is considered bioequivalent with Ebixa 20 mg tablet.

The results of study MEMA-12036 with the 20 mg formulation can be extrapolated to the 10 mg strength, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1/Corr**, section 4.1.6.

Pharmacodynamics

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

Post marketing experience

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

Discussion on clinical aspects

In this application no new efficacy or safety data were submitted and none are required. The applicant provided an acceptable review of clinical trials published in literature, describing the efficacy and safety profile of Memantine Mylan. No new dose recommendations compared with the reference product were made for this generic application.

Bioequivalence studies

According to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) although a two-period, cross-over design is recommended, alternative well-established designs can be accepted in certain cases (i.e., long half-life products) provided that they are scientifically sound and that the statistical analysis is, too. Memantine exhibits linear and dose proportional pharmacokinetics over the dose range of 10 to 40 mg after oral administration with a terminal $t_{1/2}$ of 60 to 100 hours and as described in the innovator's SmPC there is no indication that food influences the absorption of Memantine, therefore one parallel single dose in fasting condition at the highest strength could be accepted.

For both studies, the study population, with regards to demographic characteristics and the exclusion and exclusion criteria were considered acceptable. Considering the expected time to peak concentration (3-8 hours) and the elimination half-life of Memantine, the sampling schedule and the sampling time period truncated at 72 hours is acceptable to estimate PK parameters. The test and reference product are adequate for a generic application. Protocol deviations were reported, however these are not considered to impact on study validity. There were no concomitant medications. Statement on GLP compliance and bio-analytical audits were given. There were no subjects excluded from the pharmacokinetic analysis in the first study. In study MEMA-12036 subject 29 was excluded from the pharmacokinetic analysis, this is considered acceptable as it was pre-specified in the study protocol.

For both studies, the pre-study validation of the analytical method was satisfactory. The in-study validation showed an acceptable calibration standards and QC values (in all runs for both studies, there were no calibration standards outside the acceptance criteria and only two QCs were rejected for study MEMA-12036). The LLOQ (0.40 ng/mL) was lower than 5% of the minimum Cmax (0.90 ng/mL and 0.97ng/mL respectively for study 11225 and 12036). The reasons for re-analysis of samples were acceptable. Dilution samples were necessary (1/5 dilution was validated). In both studies, the study samples were analysed, with a calibration curve, and four of non-zero QCs in duplicate (8 QCs). Since study samples from three subjects (57 samples) were analysed in each run, the number of QCs samples relative to the number of study samples is adequate. Incurred Sample Reproducibility is acceptable.

Chromatograms of calibrators, QCs, and subject samples (and corresponding sample sequences) from at least 20% of the subject samples analysed were included (from subject 01 to subject 09, both inclusive).

The pharmacokinetic software employed was not specified. Pharmacokinetics variables were appropriate for a single dose bioequivalence study. The non-compartmental linear-trapezoidal rule for calculation was adequate. AUC truncated at 72 hours was acceptable for drugs with a long half-life.

The statistical software and method is considered acceptable. Using PROC GLM of SAS Software (SAS Institute, Cary, NC) was acceptable. ANOVA analysis was performed correctly and linear and log-linear plots were submitted.

Based on the statistical analysis submitted by the Applicant for study 11225, the test product was not considered equivalent to the reference with respect to the extent of exposure. The 90% confidence intervals calculated for AUC0-72 of Memantine was narrowly out of the normal range of acceptability (80.00 – 125.00). As the applicant stated, this was probably due to differences in subjects of the two treatment groups since this is a parallel design were randomization is not able to ensure sensitivity between groups due to the small sample size.

However, based on the statistical analysis of the pivotal study (12036) the test product was found equivalent to the reference product with respect to the extent and rate of absorption/exposure as the 90% confidence intervals for the ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are within the acceptance range of 80-125%.

The safety profile of both products was considered to be comparable, although the design was not powered to compare the safety profile. No difference in the safety profile can be anticipated.

Biowaiver for additional strength

The general biowaiver criteria are met and the pharmacokinetics over the therapeutic dose range is linear. Therefore, a biowaiver for the additional strength is adequate.

Conclusions on clinical aspects

Based on the results of the pivotal bioequivalence study submitted, Memantine Mylan 10 mg and 20mg film-coated tablets are considered bioequivalent with Ebixa 10mg and 20mg film-coated tablets.

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that 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 the product is a generic of a well-known active substance, already on the market for more than 20 years.

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 Ebixa. The bridging report submitted by the applicant has been found to be acceptable, since the safety messages are the same as for the reference product and the wording, design, and layout have no impact on readability.

3. Benefit-risk balance

This application concerns a generic version of Memantine film-coated tablet. The reference product Ebixa is indicated in the treatment of adults with for 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 nor on 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 studies form the pivotal basis with a parallel, randomised, open label, two treatment, single dose, single period design under fasting condition. The studies' 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 periods were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Memantine Mylan met the protocol-defined criteria for bioequivalence when compared with the 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 Mylan in the treatment of patients 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 products subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

Pharmacovigilance System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

- **Periodic Safety Update Reports**

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/EC and published on the European medicines web-portal.

- **Risk Management Plan (RMP)**

Not applicable