17 January 2013
EMA/293975/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Maruxa

International non-proprietary name: Memantine

Procedure No. EMEA/H/C/002658

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

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

Product information

Marketing authorisation application

Name of the medicinal product:	Maruxa
Applicant:	Krka d.d. Novo mesto Šmarješka cesta 6 8501 Novo mesto SLOVENIA
Active substance:	Memantine hydrochloride
International Nonproprietary Name:	Memantine
Pharmaco-therapeutic group (ATC Code):	Other anti-dementia drugs(N06DX01)
Therapeutic indication(s):	Treatment of patients with moderate to severe Alzheimer's disease.
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	10 mg and 20 mg
Route(s) of administration:	Oral use
Packaging:	blister (PVC/PVDC/Alu)
Package size(s):	14 tablets, 28 tablets, 30 tablets, 42 tablets, 50 tablets, 56 tablets, 60 tablets, 70 tablets, 84 tablets, 90 tablets, 98 tablets, 100 tablets and 112 tablets

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List of abbreviations

HPLC	High Performance Liquid Chromatography
UV	Ultraviolet spectroscopy
MS	Mass spectroscopy
NMR	Nuclear magnetic resonance spectroscopy
IR	Infrared spectroscopy
XRPD	X-ray powder diffraction spectroscopy
DSC	Differential scanning calorimetry
GC	Gas Chromatography

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Krka d.d. Novo mesto submitted on 30 May 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Maruxa, 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) of Directive 2001/83/EC.

The applicant applied for the following indication

Treatment of patients with moderate to severe 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 and 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 film-coated tablets
- Marketing authorisation holder: H. Lundbeck A/S
- Date of authorisation: 2002-05-17
- Marketing authorisation granted by:
  - Community
    - Community Marketing authorisation number: EU/1/02/219/001-004, 007-012, 014-021

■ 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, 20mg film-coated tablets
- Marketing authorisation holder: H. Lundbeck A/S
- Date of authorisation: 2002-05-17
- Marketing authorisation granted by:
  - Community
    - Community Marketing authorisation number: EU/1/02/219/001-004, 007-012, 014-021, 023-035, 037-049

Scientific advice

The applicant received Scientific Advice from the CHMP on 16 February 2012. The Scientific Advice pertained to quality and clinical aspects of the dossier.

Licensing status

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

1.2. Manufacturers

Manufacturers responsible for batch release

Krka d.d. Novo mesto
Šmarješka cesta 6
8501 Novo mesto
SLOVENIA

TAD Pharma GmbH
Heinz-Lohmann-Strasse 5
27472 Cuxhaven
GERMANY

1.3. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was Andrea Laslop.

- The application was received by the EMA on 30 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 final consolidated List of Questions was sent to the applicant on 19 October 2012.
- 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 20 December 2012.
- During the meeting on 17 January 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 Maruxa.

2. Scientific discussion

2.1. Introduction

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

The active substance of Maruxa 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 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, 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 meets all the criteria for classification as BCS class I and the qualitative and quantitative differences of critical excipients in the test and reference product do not preclude the BCS-based biowaver as they are considered not to have an impact on the bioavailability of mematine, therefore, a bioequivalence study versus the reference product Ebixa was not required.

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

The indication proposed for Maruxa is the same as authorized for 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 blisters (PVC/PVDC-Al foil) in packs of 14, 28, 30, 42, 50, 56, 60, 70, 84, 90, 98, 100 and 112 film-coated tablets.

2.2.2. Active substance

The active substance is a white or almost white powder, not hygroscopic, soluble in water and methanol, sparingly soluble in acetic acid, practically insoluble in acetone. The chemical name is 3,5-dimethyl-1-adamantamine hydrochloride.

The structure of memantine hydrochloride was confirmed by elemental analysis (CHN), MS (mass spectroscopy), 1H-NMR (Proton nuclear magnetic resonance spectroscopy) and 13C-NMR (Carbon13 nuclear magnetic resonance spectroscopy), IR (Infrared spectroscopy), XRPD (X-ray powder diffraction spectroscopy) and DSC (differential scanning calorimetry).

Memantine has a non-chiral molecular structure. Polymorphism has not been observed for active substance. The manufacturing process consistently produces the same crystalline form of memantine hydrochloride. The crystalline form does not change upon storage.

Manufacture

Memantine is synthesized in 7 main steps using commercially available starting materials. The manufacturing process consists of both synthetic and recrystallisation steps.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Batch analysis data was provided on three pilot scale batches produced with 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 (visual examination), identity (IR, reaction on chlorides), assay for memantine hydrochloride (potentiometric titration), assay for chloride (potentiometric titration), impurities (GC), residual solvents (GC, HPLC), water content (Ph Eur), heavy metals (Ph Eur), pH value (Ph Eur) and sulphated ash (Ph Eur).

Batch analysis data is provided on three pilot scale batches of the active substance. The results are within the specifications and consistent from batch to batch.

Stability

Five pilot scale batches of the active substance from the proposed manufacturer, were put on stability testing as per ICH conditions: under long term (25°C/60%RH) for up to 24 months, and accelerated (40°C/75%RH) for up to 6 months. Photostability test following ICH guidelines Q1B was performed on three batches.

From the studies it is concluded that memantine hydrochloride does not require special storage conditions.

The stability results 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 formulation of Maruxa was designed to obtain an essentially similar product to the reference medicinal product, Ebixa film-coated tablets.

Maruxa film coated tablets are an immediate release oral solid dosage form, containing memantine (as hydrochloride) as the active ingredient. The qualitative composition of Maruxa is identical to the composition of Ebixa when the product was initially approved.

Excipients used in the formulation were all compendial, well-known and widely used for this dosage form. The excipients used include: lactose monohydrate (filler), microcrystalline cellulose (filler, disintegrant and binder), colloidal anhydrous silica (glidant), magnesium stearate (lubricant) and talc (glidant). The film coating components (methacrylic acid-ethyl acrylate copolymer, sodium lauryl sulphate, polysorbate 80, talc, simethicone emulsion, and triacetin) are of compendial quality with the exception of the simethicone emulsion which meets USP requirements. Compatibility studies between the excipients and active substance were conducted and no compatibility issue was observed.

Two bioequivalence studies were conducted (one for each strength, i.e. 10 mg and 20 mg). The test formulations were shown to be bioequivalent to the reference product Ebixa 10 mg and 20 mg film coated tablets, respectively. However, a BCS-based biowaiver was applied for this product, and therefore the results of both studies were used as supportive data for this application.

Dissolution studies were performed in order to demonstrate in vitro equivalence between the reference product and memantine hydrochloride film coated tablets with regard to memantine release from the

product. The discriminatory nature of the method was evaluated. Solubility studies indicated that the solubility of memantine hydrochloride is very high in all tested media covering physiological pH range from pH 1.2 to 7.4 and is pH independent. Sink conditions were achieved in all tested media, since more than 10 times of the highest single dose (20 mg) of memantine hydrochloride was found to be soluble in 900 ml of dissolution medium. In vitro dissolution studies performed at different media showed that the dissolution profiles were similar.

The primary packaging proposed is described as stated in the SmPC. The material complies with PhEur requirements, and it is adequate to support the stability and use of the product.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Manufacture of the product

The manufacturing process consists of four main steps: (1) mixing, (2) compression, (3) film coating and (4) packaging. The process is considered to be a standard manufacturing process.

The manufacturing process has been adequately described and the critical steps have been identified. Adequate flow-charts were provided and the different steps of the manufacturing process are described, together with equipment type and operating parameters.

The validation protocol proposed for the full scale batches has been provided and the quality of the production batches will be evaluated through the results of in-process testing as well as the results of finished product testing.

Product specification

The finished product release specification includes appropriate tests for appearance (visual description), identification (HPLC and GC), assay (HPLC), uniformity of dosage unit (PhEur), related substances (GC), subdivision of tablets (PhEur), dissolution (PhEur) and microbiological quality (PhEur). Analytical methods have been well described and validated.

The proposed limits for the impurities are in accordance with the ICHQ3B guideline.

Batch analysis results of two full scale batches of memantine hydrochloride 10mg film coated tablets and three pilot scale batches of 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 of two full scale batches of memantine hydrochloride 10mg film coated tablets and three pilot scale batches of memantine hydrochloride 20mg film coated stored under long term conditions for 48 months at 25ºC/60%RH and for up to 6 months under accelerated conditions at 40ºC/75%RH according to ICH guidelines were provided. The batches of memantine hydrochloride are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, water content, hardness, related substances, dissolution, assay and microbiological purity. The same analytical methods are used in the stability program as for the finished product release. The analytical procedures used were stability indicating.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Photostability testing results have shown that the product is not sensitive to light.

Based on available stability data, the proposed shelf-life as stated in the SmPC is 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

Not applicable.

2.3. Non- clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, based on up-to-date and adequate scientific literature. 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 Maruxa manufactured by KRKA 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

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 Maruxa from a non-clinical point of view. The SmPC of Maruxa is similar to that of the originator product Ebixa and is therefore acceptable.

2.4. Clinical aspects

2.4.1. Introduction

This is a generic application for film-coated tablets containing memantine. The applicant applied for a BCS-based (Biopharmaceutics Classification System) biowaiver which represents a surrogate for *in vivo* bioequivalence studies and conducted two supportive bioequivalence studies with cross-over design under fasting conditions.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of Maruxa based on published literature. In general, the clinical aspects of the generic product's SmPC are in accordance with the reference product's SmPC.

Formal scientific advice by the CHMP was given for this medicinal product (EMEA/H/SA/2276/1/2012/II) concerning BCS-based biowaiver.

For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1/Corr**) is of particular relevance.

GCP

The applicant 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 **, Appendix III), an application for a BCS-based biowaiver is restricted to highly soluble drug substances with known human absorption and considered not to have a narrow therapeutic index.

Memantine does not belong to the group of narrow therapeutic index drugs. Furthermore, the applicant provided justification that Maruxa meet relevant general requirements as detailed below:

A BCS-based biowaiver is applicable for immediate release, solid pharmaceutical products for oral administration with systemic action having the same pharmaceutical form if:

• The drug substance has been proven to exhibit high solubility and complete absorption (BCS class I) and

• Either very rapid (> 85 % within 15 min) or similarly rapid (85 % within 30 min) in vitro dissolution characteristics of the test and reference product has been demonstrated considering specific requirements and

• Excipients that might affect bioavailability are qualitatively and quantitatively the same. In general, the use of the same excipients in similar amounts is preferred.

<u>BCS classification:</u>

Memantine hydrochloride is highly soluble and shows complete human absorption, generally related to high permeability.

Evaluation of *in vitro* dissolution results:

The applicant provided a Dissolution Study Report (DSR-00001). Two batches of test and reference product were analysed per strength (10 mg and 20 mg tablets).

In vitro dissolution results of all batches tested are provided. Similarity of dissolution profiles was confirmed.

Excipients:

The composition of Memantine hydrochloride film-coated tablets 10 mg and 20 mg is linearly proportional for all ingredients.

There are differences in the composition of test and reference product in both core and coating layer. However, well-established excipients in usual amounts are employed in both products and the function of the different excipients can be considered the same.

Clinical studies

To support the application, the applicant has submitted two bioequivalence studies, no pharmacodynamic studies, no therapeutic equivalence studies. As a BCS-based biowaiver is applied for both strengths, the submitted BE studies are considered as supportive data only.

Table 1. Tabular overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective of the Study	Study Design; Type of Control	Test Product(s); Dosage Regimen; Rout of Administration	No. of Subjects	Healthy Subjects/ Diagnosis Of Patients	Duration of Treatment	Study Status; Type of report
BE	11-341*	Section 5.3.1.2.	Assessment of single-dose relative bioavailability of two 20mg memantine hxdrochloride tablet formulations after administration under fasting conditions	Crossover; Fasting state with a 35-days washout period	**Test** Memantine 20mg film-coated tablets (B.No.: 1215 03 P004 1211) **Reference** Ebixa® 10mg film-coated tablets (B.No.: 153461)	24	Healthy subjects	Single Dose	Complete; Full
BE	07-192*	Section 5.3.1.2.	Assessment of single-dose relative bioavailability of two 10mg memantine hxdrochloride tablet formulations after administration under fasting conditions	Crossover; Fasting state with a 35-days washout period	**Test** Memantine 10mg film-coated tablets (B.No.: H5821) **Reference** Ebixa® 10mg film-coated tablets (B.No.: 502571)	26	Healthy subjects		Complete; Full

***As BCS-based biowaiver is applied for this product, the results of both studies will only serve as supportive data for this submission.** The study for 10 mg tablets was conducted, as explained in Module 3, several years ago, before the originator changed the composition. This study cannot be considered as pivotal due to several minor changes in the development since 2008. On the other hand, in vivo study with 20 mg tablets was conducted recently with relevant reference product and is therefore the representative study.

2.4.2. Pharmacokinetics

2.4.2.1. Study 110572/11-341

Methods

Study design

Study 110572/11-341 was a randomised open-label, 2-way crossover bioequivalence study of two memantine 20 mg formulations following single 20 mg doses in healthy subject under fasting condition.

A single dose of 20 mg Memantine Hydrochloride was administered in each period with 240 ml water. Subjects fasted for at least 10 hours before drug administration and for at least 4 hours afterwards. Treatment phases were separated by a washout period of 35 days.

Sampling schedule: The 0.00h blood samples for pharmacokinetic analysis were collected within 1 hour prior to dosing and the post-dose samples at 0.750, 1.50, 2.25, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 10.00, 12.00, 24.00, 48.00 and 72.00h after dosing in each period.

Analyte and matrix: Memantine in plasma, quantitated using validated method.

Test and reference products

Maruxa film-coated tablet 20 mg manufactured by KRKA (batch No. 1215 03 P004 1211, Manufacturing date: December 2011; exp. Date: n.a. (Retest date: December 2014)) has been compared to Ebixa film-coated tablet 20 mg manufactured by H. Lundbeck A/S (Batch No: 153461 (German market)., exp. date May 2015).

The applicant confirmed that the test product was identical to the formulation intended to be marketed in its responses to the list of question.

Population studied

Twenty-eight healthy adult male subjects were enrolled and 24 subjects were randomised. All subjects received at least one dose of study medication and constituted the safety population. One subject (subject No. 22) was withdrawn due to adverse events (fainting, convulsion and nausea) in period 02 before dosing, 2 subjects (subjects No. 10 and 24) withdrew consent due to personal reasons and 1 subject (subject No. 14) did not show up for confinement in period 02. Thus, 20 subjects completed the study and were analysed for statistical analyses. Three protocol deviations were reported.

Analytical methods

Plasma concentrations of memantine and its internal standard memantine-d6 were determined with an HPLC/MS/MS method.

Pharmacokinetic variables

Primary pharmacokinetic parameters: AUC_{0-72h}, C_{max}

Secondary pharmacokinetic parameters: T_{max}

Statistical methods

Determination of Sample Size: based on data from the literature, the intra-subject coefficient of variation (CV) was assumed up to 13% for Memantine's pharmacokinetics parameters. Thus, with expected CV up to 16% and an expected ratio of AUC and C_{max} within 0.95 and 1.05, the study was calculated to have a power of at least 90% to show bioequivalence with 18 subjects. In order to account for possible dropouts, 24 subjects were included in the study.

Analysis of variance (ANOVA): for all analyses, effects were considered statistically significant if the probability associated with 'F' was less than 0.05. Based on pairwise comparisons of the ln-transformed AUC_{0-72h} and C_{max} data, the ratios of the least-squares means, calculated according to the formula "$e^{(X-Y)}$ X 100", as well as the 90% geometric confidence intervals for ln-transformed AUC_{0-72h} and C_{max} were determined. Finally, the inter- and intra-subject CVs were also determined.

90% Confidence Intervals: ratios of least-squares means and 90% geometric confidence intervals were calculated for ln-transformed AUC_{0-72h} and C_{max}. Inter- and intra-subject CVs were also calculated. BE was to be concluded if the 90% geometric confidence intervals of the ratio (A/B) of least-squares means for ln-transformed AUC_{0-72h} and C_{max} were within the acceptable range of 80.00% to 125.00%.

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

Results

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

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD CV%	arithmetic mean	SD CV%
$AUC_{(0-72h)}$	1136448.21	149403.93 13.15	1160025.60	139414.48 12.02
$AUC_{(0-\infty)}$	n.a.	n.a.	n.a.	n.a.
C_{max}	24635.65	3054.40 12.40	24784.67	2746.72 11.08
T_{max}*	6.25	2.25 – 12.0	7.25	1.50 – 12.0

AUC_{0-72h} area under the plasma concentration-time curve from time zero to 72 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, range)

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

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-72h)}$	97.88	95.66 – 100.15	4.16

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
C_{max}	99.08	95.67 - 102.62	6.37
* estimated from the Residual Mean Squares			

Safety data

A total of 15 TEAEs (treatment emergent adverse event) were reported by 10 of the 24 subjects who received at least one dose of the study medication (safety population). Five TEAEs were reported by 17.4% (n=4) of the 23 subjects who received Treatment A and 10 TEAEs were reported by 33.3% (n=7) of the 21 subjects who received Treatment B.

The most commonly reported TEAEs were “Somnolence”, reported by 12.5% (n=3) of subjects who constituted the safety population, and “Nausea” and “Headache” each reported by 8.3% (n=2) of subjects who constituted the safety population (N=24).

Of the 15 TEAEs reported, 12 were graded as mild, 1 was graded as moderate, and 2 were graded as severe.

2.4.2.2. Study 70475/07-192

Methods

Study design

Study 70475/07-192 was a randomised open-label, 2-way crossover bioequivalence study of memantine 10 mg tablet and Ebixa following single 10 mg doses in healthy subject under fasting condition.

A single dose of 10mg Memantine Hydrochloride was administered in each period with 240ml water. Subjects fasted for at least 10 hours before drug administration and for at least 4 hours afterwards. Treatment phases were separated by a washout period of 35 days.

Sampling schedule: the blood samples for pharmacokinetic analysis were collected prior to dosing and at 1.00, 2.00, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 10.00, 12.00, 14.00, 24.00, 48.00 (±0.5), 72.00 (±0.5), 144.00 (±0.5), 216 (±0.5), 288.00 (±0.5) and 360 (±0.5) hours post dose in each period. Actual sampling time was used for statistical analyses.

Analyte and matrix: memantine in plasma, quantitated using validated method.

Test and reference products

Maruxa film-coated tablet 10 mg manufactured by KRKA (batch No. H5821, Manufacturing date: September 2007; exp. Date: n.a. (Retest date: February 2008)) has been compared to Ebixa film-coated tablet 10 mg manufactured by H. Lundbeck A/S (Batch No: 502571 (German market)., exp. date January 2009).

Neither the test product is identical to the formulation intended to be marketed due to several minor changes in the development after this study was conducted, nor is the reference product used in this study the actual formulation on the market due to composition changes.

Population studied

Twenty-six healthy adult male subjects were randomised. All subjects received at least one dose of study medication and constituted the safety population. One subject (subject No. 02) was withdrawn due to an adverse event in period 01 and 1 subject (subjects No. 12) did not check in for period 02. Subject No. 23 was replaced pre-dose of period 01 (elected to withdraw due to personal reasons). Thus, 24 subjects completed the study and were analysed for statistical analyses. Eight protocol deviations were reported.

Analytical methods

Plasma concentrations of memantine and its internal standard memantine-d6 were determined with an HPLC/MS/MS method.

Pharmacokinetic variables

Pharmacokinetic parameters: AUC0-t, AUC0-∞, C_{max}, Residual area, T_{max}, K_{el}, $T_{1/2\ el}$

Statistical methods

Determination of Sample Size: based on data from previous studies, the intra-subject coefficients of variation were assumed approximately 6% and 7% for AUC and C_{max}, respectively. Thus, with these expected coefficients of variation and an expected ratio of AUC and C_{max} within 0.95 and 1.05, the study was calculated to have a power of at least 90% to show bioequivalence. In order to complete with at least 24 subjects, a total of 26 subjects were enrolled into the study.

Statistical analysis: analysis of variance was performed on the ln-transformed data of AUC_{0-t}, AUC_{0-inf} and C_{max}. ANOVA was also carried out on the untransformed data of $T_{1/2}$ el and K_{el}. All ANOVAs were performed with the SAS (release 8.2 for Windows) General Linear Models Procedure (GLM). The model included sequence, subject within sequence, period and treatment as factors. The sequence effect was tested using subjects within sequence effect as the error term. The treatment and period effects were tested against the residual mean square error. All sums of squares (Types I, II, III and IV) were reported. Probability (p) values were derived from Type III sums of squares. A non-parametric test (Wilcoxon's Signed-Rank test) was carried out to compare the T_{max} between treatments. For all analyses, effects were considered statistically significant if the probability associated with 'F' was less than 0.05. Based on pairwise comparisons of the ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} data, the ratios of the least-squares means, calculated according to the formula "$e^{(X-Y)}$ X 100", as well as the 90% geometric confidence intervals for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} were determined. The inter- and intra-subject CVs were also determined.

Results

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

Pharmacokinetic parameter	Test		Reference	
	geometric mean	SD CV%	geometric mean	SD CV%
$AUC_{(0-t)}$	1203698.08	264273.85 21.96	1202106.95	226248.10 18.82

Pharmacokinetic	Test		Reference	
$AUC_{(0-\infty)}$	1241649.25	295627.94 23.81	1242655.02	251337.55 20.23
C_{max}	12736.39	1286.88 10.10	12845.16	1428.16 11.12
T_{max}*	6.00	2.50	5.50	2.50
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, range)			

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

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	100.14	97.11 – 103.26	6.17
C_{max}	99.46	96.93 – 102.06	5.20
* estimated from the Residual Mean Squares			

Safety data

A total of 14 TEAEs were reported by 6 of the 26 subjects who received at least one dose of the study medication (safety population). Eight TEAEs were reported by 12.5% (n=3) of subjects following administration of treatment A and 6 TEAEs were reported by 15.4% (n=4) of subjects following administration of treatment B.

The most commonly reported TEAE was "Headache", reported by 19.2% (n=5) of subjects who constituted the safety population.

The severity of adverse events was graded according to the following categories: mild, moderate, or severe. Of the 14 TEAEs reported, 9 were graded as mild and 5 were graded as moderate.

Of the 14 TEAEs reported, the relationship of 11 was judged as "possible" and 3 as "unrelated". No deaths or serious adverse events were reported during this study.

Conclusions

Based on the presented bioequivalence studies the test product can be considered bioequivalent to the reference product.

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 have been submitted and none are required. The applicant has provided an acceptable review of clinical trial published in literature, describing the efficacy and safety profile of Maruxa. No new dose recommendations compared with the reference product have been made for this generic application.

BCS-based biowaiver

Based on the results of the solubility study, memantine hydrochloride can be classified as a highly soluble drug since the requirements of the Guideline on the Investigation of Bioequivalence (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, Appendix III) are fulfilled.

No definite conclusions can be drawn based on the three absolute bioavailability studies as the results of these studies show values for absolute bioavailability superior to 100%. However, according to the EPAR of the originator, absolute bioavailability of memantine is approximately 100% and data of the conducted in vitro permeability studies show a passive permeability across Caco-2 monolayers greater than Metoprolol. Although in vitro data are supportive only, these data are considered more reliable and conclusive than the human data provided, therefore complete drug absorption (defined as extent of absorption is $\geq$ 85%) of memantine hydrochloride is considered established.

Based on data on solubility and absorption/permeability characteristics, Memantine meets all criteria for classification as BCS-class I since it exhibits high solubility and high permeability (complete absorption) and requirements on the drug product regarding *in vitro* dissolution and excipients for BCS-class I drugs are applicable.

Although excipients that might affect drug bioavailability, are comprised in the coating layer of reference and test product these are in very small amount and the guideline accepts to neglect possible differences in coating components in case of proportionality biowaiver. Therefore, they are considered to have no impact on the bioavailability of Memantine. Qualitative and quantitative differences of critical excipients in test and reference product do not preclude the BCS-based biowaiver.

As all requirements described in the Guideline on the Investigation of Bioequivalence (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, Appendix III) are fulfilled, a BCS-based biowaiver approach is acceptable.

Bioequivalence studies

As a BCS-based biowaiver is applied for both strengths, the submitted BE studies are considered as supportive data only.

According to the Guideline on the Investigation of Bioequivalence (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) the study design of the BE-study 110572/11-341 with the 20 mg tablets is appropriate for an immediate release product and the pharmacokinetic variables are adequate. Use of a truncated AUC (AUC0-72h) is justified due to the long half-life of the active substance. The 90% confidence intervals for AUC0-72h and Cmax are within the pre-set acceptance range of 80.00 and 125.00%. Results of in vitro dissolution tests reflect bioequivalence. The reported protocol deviations and the deviations in the blood sampling schedule are not considered relevant for the overall results.

Based on the results obtained, it can be concluded that the test product (Maruxa 20 mg film-coated tablets) is bioequivalent to the reference product (Ebixa 20 mg film-coated tablets). The test and reference product are clinically comparable in their safety profile.

Study 70475/07-192 was conducted in 2008 in line with then in force “Note for Guidance on the Investigation of Bioavailability and Bioequivalence” (Doc. Ref.: CPMP/EWP/QWP/1401/98). Hence, some requirements in the study design of the Guideline on the Investigation of Bioequivalence (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) are not fulfilled. Moreover this study was performed with a previous formulation of the reference product and of the test product. Therefore the results of this study cannot be considered relevant for the assessment of bioequivalence. However, these deviations are not considered important as this study serves as supportive data only. The reported blood draw deviations are not considered relevant for the overall results.

Based on the results obtained, it can be concluded that the test product is bioequivalent to the reference product. The test and reference product are clinically comparable in their safety profile.

2.4.6. Conclusions on clinical aspects

Based on the presented BCS-based biowaiver and supported by the submitted bioequivalence studies, Maruxa 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

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a generic version of memantine film coated tablets. The reference product Ebixa is indicated for treatment of patients 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 presented BCS-based biowaiver and supportive bioequivalence study were considered adequate to evaluate the bioequivalence of this formulation and were in line with the respective European requirements. Bioequivalence of Maruxa 10 mg and 20mg film-coated tablets and Ebixa 10mg and 20mg film-coated tablets 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 by consensus that the benefit-risk balance of Maruxa 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 product 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.

Risk management system

Not applicable.

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