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EMA/227468/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Memantine LEK

International non-proprietary name: **Memantine**

Procedure No. EMEA/H/C/002630

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

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List of abbreviations

AEs	adverse events
Al or Alu	Aluminium
ASMF	active substance master file
AUC0-t	Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC0-∞	Area under the plasma concentration curve extrapolated to infinite time
BE	Bioequivalence
BMI	body mass index
Cmax	Maximum plasma concentration
CLcr	creatinine clearance
CHMP or CPMP	Committee for Medicinal Products for Human Use
DSC	Differential Scanning Calorimetry
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EP or Ph. Eur.	European Pharmacopoeia
HPLC	high pressure liquid chromatography
GC	gas chromatography
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
ICH	International Conference on Harmonisation
IPC	in-process controls
IR	infra-red
Kel	elimination constant
MAH	Marketing Authorisation Holder
Ph+	Philadelphia chromosome (bcr-abl) positive
PK	pharmacokinetics
PSUR	periodic safety update report
PVC	Polyvynilchloride
PVDC	Polyvinylidene Chloride
RH	relative humidity
RMP	Risk Management Plan
SAEs	serious adverse events
SmPC or SPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
tmax	Time until Cmax is reached
TSE	transmissible spongiform encephalopathy
UV	ultra violet
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pharmathen S.A. submitted on 22 May 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Memantine LEK, 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 22 September 2011.

The application concerns a generic medicinal product as defined in Article 10(1) 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, complete quality data and a bioequivalence study with the reference medicinal product Axura 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: Axura 10mg, 20 mg film-coated tablets

- Marketing authorisation holder: Merz Pharmaceuticals GmbH
- Date of authorisation: 15/05/2002
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number: EU/1/02/218/001-003
    EU/1/02/218/007-010
    EU/1/02/218/012-015
    EU/1/02/218/030
    EU/1/02/218/017-022
    EU/1/02/218/024-029

■ 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: Axura 10 mg film-coated tablets
- Marketing authorisation holder: Merz Pharmaceuticals GmbH
- Date of authorisation: 15/05/2002
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number(s): EU/1/02/218
- Bioavailability study number(s): GE/09/MEM/2/10 – EudraCT number: 2012-023194-19

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 was Martina Weise.

- The application was received by the EMA on 22 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 15- 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 21 December 2012.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 February 2013 and subsequent updates on 8 and 21 February 2013.
- During the meeting 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 LEK.

2. Scientific discussion

2.1. Introduction

Memantine LEK 10 mg 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 Memantine LEK 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.

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

The indication proposed for Memantine LEK 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 is presented as film coated tablets with a score line 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 PVC/PVDC-Al foil blisters.

2.2.2. Active substance

The active substance is a white to off-white slightly hygroscopic powder, highly soluble in water .The chemical name of memantine hydrochloride is 3,5-dimethyl-1-adamantamine hydrochloride., the chemical formula is $C_{12}H_{21}N \cdot HCl$ and the relative molecular mass 215.77 g/mol.

Memantine has a non-chiral molecular structure. Polymorphism has been observed; it exists in anhydrous and in monohydrate form. The active substance form manufactured is consistently the same and does not change upon storage.

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 synthetic process and the starting materials used in the manufacture of the active substance are sufficiently described. 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. Satisfactory control on the manufacturing process of memantine hydrochloride through adequate in–process and intermediates specifications has been established. Information regarding process validation has also been presented and considered acceptable. Batch analysis data confirm the active substance is manufactured reproducibly.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Specification

The specification of the active substance as set up by the drug product manufacturer includes tests and limits for appearance (visual), identification (IR, HPLC), assay (HPLC, potentiometric titration), related substances (HPLC), water content (Ph. Eur.), chloride content (potentiometric titration), sulphated ash (Ph. Eur.), heavy metals (Ph. Eur.), residual solvents (GC), and loss on drying (Ph. Eur.).

The proposed specifications for impurities in the active substance are in accordance with EU/ICH Q6A and Q3A guidelines and 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. The analytical methods for assay, related substances and residual solvents used for the active substance are satisfactorily described and validated in accordance with the relevant EU/ICH guidelines on Analytical validation.

Batch analysis data is presented by each supplier on three production batches. In addition data of two batches analysed by the applicant as per the proposed specifications have also been presented. All the results are all within the specifications.

Stability

Three consecutive batches manufactured by the first supplier as per the proposed manufacturing process have been studied under long term (25° ± 2°C and 60% ± 5% RH) for up 36 months and under accelerated (40° ± 2°C and 75% ± 5% RH) storage conditions for up 6 moths in the proposed packaging. The parameters tested are the same as for release.

The stability data generated for memantine hydrochloride is in line with ICH Q1A (R2) requirements.

A full photostability study was not performed because the active substance appears stable enough under stress conditions of UV light. Therefore based on ICH guideline Q1B for Photostability there is no need to perform a photostability study.
From available data it is evident that there is no significant change observed under accelerated and long term storage conditions and the active substance t is stable during the proposed retest period.

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

2.2.3. Finished medicinal product

Pharmaceutical development

The aim of the development was to develop a generic memantine immediate release film-coated tablets for Alzheimer treatment as that would be bioequivalent to the reference product.

Although memantine hydrochloride exhibits two different polymorphic forms, the drug substance manufactured is consistently the same. The polymorphic form of memantine has been monitored during the manufacturing and stability of Memantine LEK tablets, taking into account batches manufactured with active substance from both sources. It has been demonstrated that no inter-conversion occurs in the drug product during manufacture or storage.

All the excipients of the formulation are included in the reference product too. They are widely used and have monographs in the European Pharmacopeia. Sufficient information regarding the compatibility of the active substance and the excipients has been provided. The results are supported by current stability data.

During development active substance from a second manufacturer (not applied for registration) was also used.
A bioequivalence study has been performed on the 10 mg strength.
The dissolution was very fast and complete. The dissolution profiles of tablets manufactured with drug substance from the two different suppliers were similar with each other and with the biobatch in all tested pH-media. In addition, the discriminatory power of the dissolution method has been sufficiently demonstrated. It can be concluded that the drug product dissolution is complete and independent from pH of the dissolution medium, strength or the manufacturer of the drug substance. Based on the presented comparative dissolution results and considering the high solubility of memantine the bioequivalence study can therefore be accepted.

Memantine LEK application concerns two strengths (10 mg and 20 mg). A biowaiver has been applied for the second strength. Since the biowaiver criteria as per the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr) are met, only one bioequivalence study for one strength (10 mg) was conducted. The dissolution profiles of the Memantine LEK 10 mg film coated tablets and of the reference Axura 10 mg used in the bioequivalence study GE/09/MEM/2/10 have been compared in order to demonstrate similarity.
The dissolution profiles of the higher strength (20 mg) have also been compared to Memantine LEK 10 mg which has been used in the bioequivalence study (biobatch) as per the bioequivalence guideline. It can be can concluded that the dissolution was complete and the dissolution profiles of both strengths were similar in all tested pH-Media (HCl 0.1 N, pH 4.5 buffer solution and pH 6.8). Thus, the biowaiver for the 20 mg strength is accepted. The manufacturing process is a conventional method for preparing immediate release dosage forms. It has been optimised in order to yield a homogeneous final mixture and to ensure robust manufacture.
The product is packaged in a PVC/PVDC - Aluminium blister. This material has been shown to be suitable and conforms to relevant EU regulations.

Adventitious agents

None of the excipients used in the manufacture of Memantine LEK film coated tablets are of human or animal origin. Appropriate declarations from the manufacturers of excipients have been provided.

Manufacture of the product

The manufacturing process is a conventional wet granulation method for preparing a standard immediate release dosage form. It has been adequately described. There are no critical steps or intermediate products other than the respecting proportion of excipients. The in-process controls are suitable to guarantee reproducible product quality. Process validation in line with the process validation guideline for this standard process and pharmaceutical form has been performed. The results of the process validation are sufficient to support the reliability of the manufacturing method.
Batch analysis results of two pilot scale batches of memantine hydrochloride 10mg film coated tablets and two pilot scale batches of 20 mg strength confirm consistency and uniformity of manufacture and indicate that the process is capable and under control.

Product specification

The finished product release specification includes appropriate tests for appearance (visual), uniformity of mass (Ph. Eur.), uniformity of dosage unit (Ph. Eur.), subdivision of tablets (Ph. Eur.), water content (Ph. Eur.), identification (memantine: HPLC, chlorides: Ph. Eur., colouring Ph. Eur.), assay (HPLC), related substances (HPLC), dissolution (Ph. Eur.) and microbiological quality (Ph. Eur.). Analytical methods have been well described and validated. The proposed limits for the impurities are in accordance with the ICHQ3B guideline.
Batch analysis results obtained from two batches for each strength manufactured with active substance from the proposed supplier have been provided. All batches complied with the proposed specification. Moreover there was no apparent difference between batches manufactured with active substance from either manufacturer.

Stability of the product

Studies under long term storage condition (25±2ºC/60±5%RH) and accelerated storage condition (40±2ºC/75±5%RH) were carried out in accordance with ICH Q1A guideline on two pilot scale batches of each strength with active substance by the proposed supplier in the proposed packaging.
Stability data in long term and accelerated conditions have been presented for up to 6 months for tablets manufactured with active substance by the proposed supplier.

In addition supportive stability studies under long term storage condition (25±2ºC/60±5%RH) and accelerated storage condition (40±2ºC/75±5%RH) were carried out in accordance with ICH Q1A guideline on two pilot scale batches of each strength in the proposed packaging with active substance by the second supplier used only during development.
Stability data in long term conditions have been presented for up to 24 months and for six months in accelerated conditions for tablets with active substance by the second supplier.

Analytical methods used are the same as for release and they have been suitably validated. The analytical procedures used were stability indicating. In addition to the tests established for the control of the finished product, in these stability studies disintegration and hardness tests were also performed. The specified limits were always met and moreover no significant trends were detectable under any condition.
Results from accelerated and long term conditions have not shown any significant change or trend in any tested parameter for any of the two tablet strengths, whichever active substance is used. Moreover, a variance study carried out with memantine and related substances results concludes that there is no linear relationship between these parameters and the elapsed time at 25 ± 2ºC / 60 ± 5 % RH.
The obtained results confirm that the drug products manufactured with drug substance by either manufacturer have the same behaviour.
In addition, a photostability study was carried out according to ICH Q1B Guideline on Photostability Testing of New Drug Substances and Products.Results demonstrate that the product is stable when fully exposed to light, since no physical or chemical changes have been observed.

In conclusion, the overall data support the proposed shelf life and storage conditions in the proposed packaging.

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 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 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 in the applicant's answers to the list of questions 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 was submitted. This was justified by the applicant as the introduction of Memantine LEK manufactured by Grupo Uriach S.A. 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.

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 Memantine LEK from a non-clinical point of view. The SmPC of Memantine LEK 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 tablet containing memantine. To support the marketing authorisation application, the applicant conducted a bioequivalence study with a cross-over design under fasting conditions with the 10 mg strength. This study was the pivotal study for the 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 Clinical trial was performed in accordance with GCP as claimed by the applicant.

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 strength 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 20 mg strength. The applicant provided 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 is dissolved within 15 minutes at all pH values tested. According to the SmPC of the originator, the pharmacokinetics of Memantine over the range from 10 mg to 40 mg is linear.

Based on these results, the CHMP concluded that the general biowaiver criteria were met. Therefore, one bioequivalence study with the dose of 10 mg and a biowaiver for the additional strengths was considered adequate.

Clinical studies

To support the application, the applicant submitted a bioequivalence study. Neither pharmacodynamic studies nor therapeutic equivalence studies were submitted.

The active substance of the product used in the bioequivalence study originated from a different manufacturer than in the product intended to be marketed. A full comparative dissolution study has been presented for both strengths between the batches with the active substance of both manufacturers. Dissolution results demonstrated that the quality of the drug product is not influenced by the source of the drug substance.

Based on the above and considering the high solubility of memantine, it can be concluded that the drug product dissolution is complete and independent from pH of the dissolution medium, strength or the manufacturer of the drug substance. The bioequivalence study can therefore be accepted.

Table 1. Tabular overview of clinical studies

Type of study	Study identifier	Location of study report	Objective(s) of the study	Study design and type of control	Test product; dosage regimen; route of administration	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status
BE	GE/09/MEM/2/10	5.3.1.2.	To assess bioequivalence of a new formulation of memantine 10 mg film-coated tablets with Axura 10 mg film-coated tablets	Randomized, crossover, single-dose, bioequivalence clinical study of two dosage forms of memantine 10 mg film-coated tablets	*Test:* Memantine 10 mg film-coated tablets single dose; oral use. *Reference:* Axura 10 mg film-coated tablets, single dose, oral use.	24	Healthy subjects.	1 day	Completed

2.4.2. Pharmacokinetics

Methods

Study design

Study GE/09/MEM/2/10 was a single dose (1x10 mg film-coated tablet), open, crossover (two sequences and two periods) and randomized study comprising 2 treatments periods leaving a minimum wash out period of 25 days between treatment. Blood sample were drawn at the following

times points (0 [predose] and 1h, 2h, 3h, 3.5h, 4h, 4.5h, 5h, 6h, 7h, 8h, 10h, 12h, 24h, 36h, 48h and 72h after dosing (17 blood samples/subject/treatment).

Memantine was analysed in plasma.

Test and reference products

Memantine LEK 10 mg manufactured by Grupo Uriach S.A (batch No. 1001 (same as D002), manufacturing date October 2010; exp. date October 2011) has been compared to Axura 10 mg manufactured by Merz Pharmaceuticals GmbH (Batch No: 849227., exp. date September 2012.).

Population studied

Based on literature data of studies using the same drug or drug group and on the sample size suggested by the bioequivalence guidelines, among others, it was considered that a sample size of 24 subjects was appropriate to meet the target set, covering possible losses both for the duration as possible problems with drug tolerability.

Thus, the study randomized 24 healthy volunteers, aged 19 to 41. All subjects included in the study met the predefined inclusion and exclusion criteria.

Eight protocol deviations were reported in total (6 reference group, 2 test group), all related to delay in the collection of the blood sample.

Analytical methods

Memantine hydrochloride plasma concentrations were determined using a LC/MS/MS method with a limit of quantification of 0.100 ng/mL.

The method was validated according to SOP ANI 33.12 and the Guidance for Industry entitled "Bioanalytical Method Validation" (May 2001) of the Food and Drug Administration, FDA., and it was partially validated. according to SOP ANE 24.02 entitled "Bioanalytical Method Validation".

Memantine was extracted from an aliquot of human EDTA plasma using a liquid-liquid extraction procedure with hexane: ethyl acetate (15:85) then injected into a liquid chromatograph equipped with tandem mass spectrometry detector. Quantitation was by peak area ratio method. A weighted linear regression was performed to determine the concentration of the analyte. All regressions and figures presented in this validation report were generated by MDS Sciex Analyst Version 1.4.2. Results obtained from this validation are presented in sections I to 10. This method demonstrates acceptable performance as outlined by Anapharm Europe SOPs and its suitability for the determination of Memantine in human EDTA plasma over the range 0.101 to 20.128 ng/mL.

The validation report 650300KI, original version and related raw data were inspected and verified for compliance to Good Laboratory Practice regulations and implemented internal Standard Operating Procedures by the Quality Assurance Unit. A partial validation was done to add anticoagulant effect and to extend and add stability using the method described in SOP ANI 9029.03 and according to SOP ANI 33.13 entitled "Bioanalytical Chromatographic Method Validation"

Pharmacokinetic variables

The primary variables evaluated were AUC_{0-72} and C_{max}. As secondary pharmacokinetic variable, t_{max}, was evaluated in a descriptive form using the Win Nolin-Pro program. Safety and tolerability of the

treatments were evaluated as secondary variables too by analyzing the clinical relevance of the changes observed in the ECG, biochemical and haematological parameters, vital signs values and the incidence of adverse events.

Statistical methods

The statistical analysis for bioavailability and bioequivalence was performed using WinNonlin Software, version 2.1 (8). The comparative study of the bioavailability parameters Ln($AUC_{0\ 72}$) and Ln(C_{max}) was performed by means of an analysis of variance (ANOVA), controlling for the sequence, the volunteers nested in the sequence, the period and the formulation; in order to obtain an estimation of residual variance and determine the role of these factors. The results obtained before and after the administration of each formulation in the clinical and laboratory parameters were tabulated applying a descriptive analysis (mean, standard deviation, minimum and maximum). All adverse events were described in detail.

Results

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

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-72h)}$	653.906	90.985	657.386	98.244
$AUC_{(0-\infty)}$	1009.343	189.663	1.016	215.215
C_{max}	15.783	3.064	16.060	3.269
T_{max}*	3.83 (1.00-8.00)	2.04	4.38 (1.00-10.00)	2.68

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 Statistical analysis for memantine (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	90% Confidence Intervals	CV%*
$AUC_{(0-72h)}$	0.99	0.97 - 1.01	-
C_{max}	0.98	0.95 - 1.01	-

* estimated from the Residual Mean Squares

Safety data

A total of 8 treatment emergent adverse events (AEs) were reported by 6 subjects (subject in the test group reported 4 AEs and 4 subjects in the reference group reported 4 AEs). Four adverse events were considered related after reference treatment and two were considered related after test treatment. The most frequent “related” adverse event was headache (62.5%), dysmenorrhea (25%) and pharyngitis (12.5%).All adverse events were tabulated as mild (62.5%) or moderate (37.5%). It was necessary to administer concomitant medication on two subjects due to appearance of adverse events (headache and pharyngitis).

No serious adverse events or death were recorded during the study. No clinically significant changes were observed in the laboratory parameters.

Conclusions

Based on the presented bioequivalence study Memantine LEK is considered bioequivalent with Axura.

The results of study GE/09/MEM/2/10 with the 10 mg formulation can be extrapolated to the 20 mg strength, 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 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 Memantine LEK. No new dose recommendations compared with the reference product have been made for this generic application.

According to the Guideline on the Investigation of Bioequivalence (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) bioequivalence studies should be performed with the highest strength. However, for products with linear pharmacokinetics and where the drug substance is highly soluble, as is the case for memantine, selection of a lower strength (10mg) is justified. Study design is acceptable and GCP and GLP conditions were assured. The Test and Reference product are appropriate. The study population chosen was considered acceptable. The protocol deviations reported were minor and not expected to impact on the results.

The analytical method met the acceptance criteria for all the validation parameters evaluated, demonstrating acceptable performance, and is suitable for the determination of memantine in human EDTA plasma over a concentration range 0.20 to 40.00 ng/mL using LC/MS/MS detection. The choice and performance of the pharmacokinetic variables are adequate. The statistical methods are standard.

For memantine hydrochloride, the 90% confidence intervals for AUC0-72 and Cmax lie within the acceptance interval of 80% - 125% for the ratio of the population means (test/reference). The bioequivalence in magnitude and the bioequivalence in rate of the two formulations were shown.

Based on the results obtained, it can be concluded that the test product (Memantine LEK 10 mg film-coated tablets) is bioequivalent to the reference product (Axura 10 mg film-coated tablets). The test and reference product are clinically comparable in their safety profile.

Since all requirements are met to waive the additional strengths, and bioequivalence was confirmed with the 10 mg tablet strength, it is considered justified to waive the bioequivalence study for the 20 mg strength.

2.4.6. Conclusions on clinical aspects

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

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.

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 Axura 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 forms the pivotal basis with a single dose, open, crossover (two sequences and two periods) and randomized design, 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 LEK met the protocol-defined criteria for bioequivalence when compared with Axura. The point estimates and their 90% confidence intervals for the parameters AUC_{0-72}, $AUC_{0-\infty}$, 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 by consensus that the benefit-risk balance of Memantine LEK 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

- **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 and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

Not applicable.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.