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EMA/228869/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nemdatine

International non-proprietary name: **Memantine**

Procedure No. EMEA/H/C/002680

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 Actavis Group PTC ehf. submitted on 31 May 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Nemdatine, 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 15 December 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 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 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 5 mg, 10 mg, 15 mg, 20 mg film-coated tablets
- Marketing authorisation holder: H. Lundbeck A/S
- Date of authorisation: 15/05/2002
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/02/219/001-003, EU/1/02/219/007-012, EU/1/02/219/014-021

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

- Product name, strength, pharmaceutical form: Ebixa 5 mg, 10mg, 15mg, 20mg 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/1/02/219/014-049

■ 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: EU/1/02/219/024
- Bioavailability study number /EudraCT number(s): 1985/09

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 Milena Stain

- The application was received by the EMA on 31 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 15 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 CHMP meeting on 14-17 January 2013, the CHMP agreed on a List of Outstanding Issues to be addressed in writing by the applicant. The final List of Outstanding Issues was sent to the applicant on 18 January 2013.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 23 January 2013.
- The Rapporteur circulated the updated Assessment Report on the applicant's responses to the List of Outstanding Issues 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 Nemdatine.

2. Scientific discussion

2.1. Introduction

Nemdatine 5 mg, 10 mg, 15 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 Nemdatine 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 Nemdatine is the same as authorized for the reference medicinal product.

Proposed pack sizes are consistent with the dosage regimen and duration of use. In comparison with the reference product where the 5 mg and 15 mg strengths are only marketed within the initiation pack, Nemdatine 5 mg and 15 mg tablets are in addition intended to me marketed separately as well. Considering the prescription status, the condition and the SmPC recommendation that treatment with Nemdatine should be initiated and supervised by physicians experienced in the diagnosis and treatment of Alzheimer's dementia, this is not expected to cause confusion and is therefore acceptable.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film coated tablets containing 5 mg, 10 mg, 15 or 20 mg memantine as active substance.

The composition is described in section 6.1 of the SmPC.

The product is available in blisters or in bottles in different pack sizes as described in section 6.5 of the SmPC.

2.2.2. Active substance

The active substance is a white or almost white, slightly hygroscopic, crystalline powder. The chemical name of memantine hydrochloride is 3,5-dimethyladamantan-1-amine hydrochloride, its chemical formula is $C_{12}H_{21}N{\cdot}HCl$ and its relative molecular mass 215.77 g/mol. It is highly soluble in water and its pK_a is 10.27. Memantine has a non-chiral molecular structure. Polymorphism has been discussed in a satisfactory manner. Consistent manufacture and stability of the manufactured crystalline form was confirmed by XRPD and DSC analyses even after the assigned retest period of the active substance.

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. There are two slightly different synthetic routes leading to the same intermediate with steps are well defined. Critical steps and intermediates are identified and are adequately controlled. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Adequate in–process and intermediates specifications ensure sufficient control of the manufacturing process. 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 (memantine: IR, chlorides: Ph. Eur.), water content (Ph. Eur.), sulphated ash (Ph. Eur.), heavy metals (Ph. Eur.), assay (HPLC) and related substances (GC).

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 for six full scale batches by the ASMF holder. 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

Stability data from three full scale older batches have been presented under long term (25° ± 2°C and 60% ± 5% RH) and accelerated (40° ± 2°C and 75% ± 5% RH) storage conditions. Data cover 5 year under long term and 6 months accelerated conditions.

Long term stability results from five new full scale batches were also provided covering for up to 5 years. The analytical methods used are the same for release testing and are stability indicating. The parameters tested were appearance, identification, water, impurities and assay. The results are well within the specifications.

Stability data under stress conditions (Acid/Base, Heat/Humidity, Oxidative and Light) were provided. The study demonstrated that memantine HCl is quite stable in all tested stressed conditions, except in the oxidized solutions, where the solutions show a strong degradation. In the alternative oxidating conditions a clear degradation pathway is observed, with the increase of an unknown impurity already observed in other degradation conditions and as degradation impurity in holding sample solutions.

In the light of the overall data the proposed retest period and storage conditions in the proposed packaging are accepted.

2.2.3. Finished medicinal product

Pharmaceutical development

The aim of the development was to develop a generic drug product that would be bioequivalent to the reference product Ebixa. Memantine hydrochloride is highly soluble in water. The polymorphic form of memantine has been monitored and confirmed that it remains unchanged during the manufacturing and stability of Nemdatine tablets. The excipients used in the formulation are well known and widely used; they are described in the European Pharmacopoeia except for iron oxides colourings which are compliant with Commission Directive 2008/128/EC.
The formulation was initially developed and optimised for one strength. The other strengths are weight proportional and manufactured from the same blend.
An in vivo bioequivalence study was performed successfully on the 20mg strength. Biowaivers for the other three tablet strengths (5 mg, 10 mg and 15 mg) have been requested and accepted as all the relevant biowaiver criteria according to Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr) are fulfilled.
Dissolution profiles for all strengths of the Actavis and reference product including the bioequivalence study test and reference batches were generated at three different pH values: pH 1.2, pH 4.5 and pH 6.8.
In summary, the dissolution profiles of these eight batches were compared at each of the pH values mentioned above. From the data presented it is clear that similar profiles are obtained at all three pH levels. Dissolution was very fast and complete and all profiles were similar.
Comparison of the levels of related substances in Nermdatine tablets (5 mg and 20 mg strengths) and the reference product stored at 40°C/75% RH were presented. The results presented show that the levels of impurities in the Actavis finished product are comparable to the levels in the reference product.

The manufacturing process is a conventional direct compression and coating process.

The suitability of these container closure systems has been demonstrated by means of stability studies.

Adventitious agents

Nemdatine tablets do not contain any material derived from human or animal origin apart from lactose monohydrate, which appears as a component of the film coating materials. 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 manufacture process consists of a of blending, compression, coating and packaging. It is well established standard process and is described in sufficient detail. Critical steps are defined and appropriate in-process controls and relevant limits are in place. Sufficient documentation and results of process validation studies are provided.
Batch analysis results confirm consistency and uniformity of manufacture and indicate that the process is under control.

Product specification

The finished product release specification includes appropriate tests for appearance (visual), identification (HPLC, GC), uniformity of mass (Ph. Eur.), average tablet mass (Ph. Eur.), assay (HPLC), related substances (GC), 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 pilot scale batches of each strength were presented. The results of all batches are in line with the specification.

Stability of the product

Stability studies on two pilot scale batches of each strength under long term storage conditions (25±2ºC/60±5%RH), intermediate (30±2°C / 75±5% RH) and accelerated conditions (40±2ºC/75±5%RH)were carried out in accordance with ICH Q1A guideline. The above batches were packaged in the proposed packaging. Results cover 24 months in long term and intermediate conditions and 6 months accelerated.
In-use stability
10 mg and 20 mg tablets are intended to be packaged in bottles. In-use stability testing has been done on the 5 mg and the 20 mg strengths and results show the proposed as per the SmPC in use-stability shelf life is considered acceptable however it is recommended that confirmatory results from in-use stability should be presented.
Photostability
A photostability study was carried out according to ICH Q1B guideline on Photostability on one batch of 20 mg. Results demonstrate that the product is photostable.

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. Stability of the product has been demonstrated and the proposed shelf life, storage conditions and in-use stability of tablets in bottles after first opening are supported. However, confirmatory results from in-use stabilityshould be presented.

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 for future quality development

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

- Confirmatory results from in-use stability should be presented.

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 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 Nemdatine manufactured by Actavis 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. 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 Nemdatine from a non-clinical point of view. The SmPC of Nemdatine is in line with 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. To support the marketing authorisation application the applicant conducted a bioequivalence study with the 20mg strength with a cross-over design under fasting conditions. 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 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 (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), if the pharmacokinetic of the active substance is linear and that the bioequivalence is demonstrated for one strength, *in vivo* bioequivalence studies for the other strengths could be waived. An exemption from the requirement to perform bioequivalence studies would be justified when the following conditions are met: the pharmaceutical products have the same manufacturer, same qualitative composition, same ratio between active substance and excipients and *in vitro* dissolution profile comparable to the reference product.

A biowaiver was applied for the 5 mg, 10 mg and 15 mg strengths. The applicant provided tabular listing of the composition of the four strengths (5 mg, 10 mg, 15 mg and 20 mg) and their dissolution curves at pH 1.2, 4.5 and 6.8. Finally, in answer to the List of Questions, the applicant provided literature data showing linear pharmacokinetics of memantine over the range from 5 mg to 40 mg (Liu M-Y., et al 2008 and Jarvis B., et al. 2003).

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 strengths were considered adequate.

Clinical studies

To support the application, the applicant submitted a bioequivalence study, neither pharmacodymanic studies, nor therapeutic equivalence studies.

Table 1. Tabular overview of clinical study

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	1985/09	Vol 5	BE versus reference product under fasting conditions	Crossover	Tablet, 20 mg, single dose, oral	24	Healthy Subjects	Single dose	Complete; Full

2.4.2. Pharmacokinetics

Methods

Study design

Study 1985/09 was a randomized, open label, two treatments, two periods, two sequences, single dose, crossover, bioequivalence study of Nemdatine 20 mg film-coated tablets and Ebixa 20 mg film-coated tablets, in healthy adult subjects, under fasting conditions.

The 0.00h blood samples for pharmacokinetic analysis were collected within 1 hour prior to dosing and the post-dose samples at 1.00, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 9.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours after dosing in each period. Treatment phases were separated by a washout period of 28 days.

Memantine was analysed in plasma, quantitated using validated LC-MS/MS method.

Test and reference products

Nemdatine 20mg manufactured by Actavis has been compared to Ebixa 20 mg manufactured by H. Lundbeck A/S.

Population studied

Determination of Sample Size: based on data from the literature an intra-subject variability of approximately 10-12% was assumed. Setting a = 0.05 and power = 90 the number of participants should be 20 if the difference between test and reference was 10%. Taking into account possible dropouts, the sample size should be 24.

Thus, twenty-four healthy adult male subjects, aged between 18 and 55 years, were enrolled. All subjects were dosed in period 01. One subject (subject No. 21) was withdrawn due to an adverse event in period 01 and 4 subjects (subjects No. 07, 12, 15 and 20) did not check in for period 02. Thus, 19 subjects completed the study and were included in the statistical analyses.

There was one late blood draw in both periods. Missing samples were reported for one subject in period I and 6 in period II. Four subjects received concomitant medications, none of which are known to have any interaction with memantine.

Analytical methods

The analytes memantine and its internal standard amantadine were extracted from human K_2EDTA plasma using liquid-phase extraction. Extracted samples were injected into a liquid chromatograph equipped with tandem mass spectrometry detector.

Pharmacokinetic variables

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

Secondary pharmacokinetic parameters: T_{max}

Statistical methods

The log-transformed pharmacokinetic parameters (AUC_{0-72} and C_{max}) were analysed using a GLM ANOVA model with the main effects of treatment, period and sequence as fixed effects and subjects nested within sequence as random effect. A separate ANOVA model was to be used to analyse each of the parameters. The sequence effect was to be tested at the 0.05 level of significance using the subjects nested within sequence mean square from the ANOVA as the error term. Main effects were to be tested at the 0.05 level of significance against the residual error (mean square error/MSE) from the ANOVA as the error term.

Each analysis of variance includes calculation of least-square means, the difference between the adjusted formulation means and the standard error associated with the difference. The above analyses were to be carried out using the appropriate SAS procedure.

The ratio of means (T/R) were to be expressed by taking the anti-log value of difference of Least Square Means (LSM) from the ANOVA of log-transformed C_{max} and AUC_{0-72} (difference = LSM of Test - LSM of Reference).

The 90% confidence intervals of the difference between the least square means (LSM) were calculated for the parameters AUC_{0-72} and C_{max} using log-transformed data, consistent with the two one-sided tests for bioequivalence. The 90% confidence intervals were to be expressed by taking the anti-log value.

Non-parametric analysis of T_{max} was performed on untransformed data, using the methods of Koch and Hauschke.

Results

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

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean geometric mean	SD CV%	arithmetic mean geometric mean	SD CV%
$AUC_{(0-72h)}$	1372.722 1367.751	117.287 8.54	1408.107 1403.861	112.669 8.00
$AUC_{(0-\infty)}$	-	-	-	-
C_{max}	29.574 29.472	2.519 8.52	30.307 30.199	2.506 8.27
T_{max}*	7.868 (2.500 – 10.000)	1.723 21.89	7.553 (3.000 – 12.000)	1.682 22.28
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%*
$AUC_{(0-72h)}$	0.98	0.96 – 1.00	3.75
C_{max}	0.98	0.95 – 1.01	4.90
* estimated from the Residual Mean Squares			

Safety data

A total of six adverse events (AEs) were reported during the study of which five were considered related and one unrelated to the investigational products. Four AEs were mild and two moderate in intensity, all resolved completely without sequelae.

End of study safety analysis was acceptable from a clinical safety point of view. There was no serious adverse event or death reported in the entire period of the study.

Conclusions

Based on the presented bioequivalence study Nemdatine is considered bioequivalent with Ebixa.

The results of study 1985/09 with 20mg formulation can be extrapolated to other strengths 5mg, 10mg, 15mg, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1/Corr **, 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 Nemdatine. No new dose recommendations compared with the reference product have been made for this generic application.

Bioequivalence study

According to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) the study design is appropriate for an immediate release product. As the pharmacokinetics of memantine over the therapeutic dose range is linear, one bioequivalence study (conducted at the highest strength of 20 mg) is sufficient to establish bioequivalence.

The trial was conducted as an open label study, which is considered appropriate for a bioequivalence study because of objective measurement of pharmacokinetic parameters. Bioanalytical analysts were blinded to the randomization during the course of the analysis and until the results were processed by the statistical department and reported. The administration of the study drug under fasting conditions is adequate as according to the SmPC of the originator (Ebixa) the tablets can be administered with or without food because there is no indication that food influences the absorption of memantine. The sampling period of 72 hours is appropriate as in accordance to the guideline a sampling period longer than 72 hours is not considered necessary for any immediate release formulation irrespective of the half-life of the drug. The sampling scheme is considered sufficient and adequate to the expected PK parameters (estimated T_{max} between 3 and 8 hours (SmPC of the originator)). A wash-out period of 28 days (672 hours) is adequate as this period exceeds more than 5-fold the half-life of memantine (the terminal half-life is 60 to 100 hours (SmPC of the originator)). The wash-out period is long enough to avoid any potential carry over effect to the second period. Evaluation of bioequivalence is based upon measured concentrations of the parent compound memantine.

The number of subjects included in the study is based on an appropriate sample size calculation. The selection of healthy volunteers as study population is in line with the BE Guideline and is considered ethical with regard to the study medication. The reported protocol deviations and the deviations in the blood sampling schedule are not considered relevant for the overall results.

The analytical method and its validation (between-run precision and accuracy and within-run accuracy) were described in detail. In the validation study the parameters' selectivity, linearity, accuracy and precision (6 QC concentrations, intra & inter batch), recovery and stability were evaluated. Matrix effects and carry-over were also investigated. All set acceptance criteria were in a plausible range and were fulfilled.

The statistics is described adequately, the statistical methods are acceptable. No changes were made in the conduct of the study or planned analyses for the statistical and clinical portions of the study. All concentration values below the limit of quantification (BLQ) were set to zero.

Use of a truncated AUC (AUC_{0-72h}) is justified due to the long half-life of the active substance. The 90% confidence intervals for AUC_{0-72h} and C_{max} are within the acceptance range of 80.00 and 125.00%. No statistically significant sequence, period or treatment effects have been detected for AUC_{0-72h} and C_{max} at the 0.05 level.

The safety of the formulations was assessed on the basis of clinical and laboratory examinations at the beginning and at the end of the study and registration of adverse events and/or adverse drug reactions. The test and reference product are clinically comparable in their safety profile.

Additional strengths biowaiver

The general biowaiver criteria are met and the pharmacokinetics over the therapeutic dose range is linear. Therefore, a biowaiver for the strengths 5 mg 10 mg and 15 mg is adequate.

2.4.6. Conclusions on clinical aspects

Based on the results obtained, Nemdatine 5 mg, 10 mg, 15 mg and 20 mg film-coated tablets of Actavis Group PTC ehf., and Ebixa 5 mg, 10 mg, 15 mg and 20 mg (Memantine Hydrochloride) film coated tablets of H. Lundbeck AIS are considered bioequivalent.

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system (version 5.03 dated 12 October 2009) 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 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 crossover, randomized, open label, two treatments, two periods, two sequences, single dose design under fasting conditions. 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 Nemdatine met the protocol-defined criteria for bioequivalence when compared with Ebixa. The point estimates and their 90% confidence intervals for the parameters AUC_{0-72} and C_{max} were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded. The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Nemdatine 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.