



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/610378/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Memantine Accord

International non-proprietary name: memantine

Procedure No. EMEA/H/C/002766

Note

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



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List of abbreviations

ASMF	Active Substance Master File
GC	Gas Chromatography
HDPE	High Density Polyethylene
HS-GC	Head Space Gas Chromatography
IR	Infrared
LDPE	Low Density Polyethylene
MS	Mass Spectrometry
NMR	Nuclear Magnetic Resonance
RH	Relative Humidity
UV	Ultraviolet
XRPD	X-Ray Powder Diffraction
HPLC	High Performance Liquid Chromatography

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare Limited submitted on 3 September 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Memantine Accord, 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 21 June 2012.

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

The applicant applied for the following indication.

Treatment of 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).

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 force for not less than 6/10 years in the EEA:
 - Product name, strength, pharmaceutical form: Axura 5 mg, 10 mg, 15 mg, 20 mg
 - Marketing authorisation holder: Merz Pharmaceuticals GmbH
 - Date of authorisation: 17-05-2002
 - Marketing authorisation granted by:
 - Community
 - Community Marketing authorisation number: EU/1/02/218
- Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:
 - Product name, strength, pharmaceutical form: Axura 5 mg, 10 mg, 15 mg, 20 mg
 - Marketing authorisation holder: Merz Pharmaceuticals GmbH
 - Date of authorisation: 17-05-2002
 - Marketing authorisation granted by:
 - Community
 - Community Marketing authorisation number: EU/1/02/218

Licensing status

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

1.2. Manufacturers

Manufacturer(s) responsible for batch release

Aegis Ltd
17 Athinon Street
Ergates Industrial Area
Nicosia
Cyprus
2643

Accord Healthcare Limited
Sage House
319 Pinner Road
North Harrow
HA1 4HF
United Kingdom

1.3. 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 3 September 2012.
- The procedure started on 19 September 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 7 December 2012.
- During the meeting on 17 January 2013, 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 18 January 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 25 March 2013.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 April 2013.
- During the CHMP meeting on 30 May 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 26 June 2013.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 02 July 2013.
- During the CHMP meeting on 25 July 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 18 August 2013.

- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 27 August 2013.
- PRAC RMP Advice and assessment overview were adopted by PRAC on 05 September 2013.
- During the meeting on 19 September 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 Accord.

2. Scientific discussion

2.1. Introduction

Memantine Accord 5 mg, 10 mg, 15 mg and 20 mg film coated tablets is a generic medicinal product of Axura, which has been authorised in the EU since 15 May 2002.

The active substance of Memantine Accord 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 Axura. 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 Axura, 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 biowaiver as they are considered not to have an impact on the bioavailability of memantine, therefore, a bioequivalence study versus the reference product Axura was not required.

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

The indication proposed for Memantine Accord is the same as authorized for the Reference medicinal product.

The proposed pack sizes are consistent with the dosage regimen and duration of use.

2.2. Quality aspects

2.2.1. Introduction

The product is presented as tablets film coated tablets containing 5 mg, 10 mg, 15 mg and 20 mg of memantine hydrochloride as active substance.

The ingredients of the film-coated tablets are: lactose monohydrate, microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate and croscopvidone. The film coating ingredients are hypromellose, polysorbate 80, macrogol, titanium dioxide and iron oxide.

The film coated tablets are available in PVC/PE/PVDC/Alu blisters as described in section 6.5 of the SmPC.

The Applicant also applied for oral drops, solution containing 10mg/g of memantine hydrochloride as active substance. However the application was withdrawn during the evaluation since the suitability of the delivery device was not demonstrated.

2.2.2. Active substance

The active substance is a white to off white crystalline powder, not hygroscopic, soluble in water, ethanol and methanol, practically insoluble in acetone and in ethyl acetate. 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) and XRPD (X-ray powder diffraction spectroscopy).

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

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

Manufacture

The Active Substance Master File (ASMF) procedure was followed for the active substance. Letter of access has been received from the ASMF Holder. Memantine is manufactured in four manufacturing sites.

Memantine is synthesized in 3 main steps using commercially available starting materials. The manufacturing process consists of both synthetic and recrystallisation steps.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

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

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 active substance specification includes tests for: appearance (visual examination), identity (IR, GC, reaction on chlorides), assay for memantine hydrochloride (HPLC), assay for chloride (potentiometric titration), pH (Ph Eur), impurities (GC), residual solvents (HS-GC), water content (Ph Eur), heavy metals (Ph Eur) and sulphated ash (Ph Eur).

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines.

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

Stability

Ten production scale batches of the active substance from one manufacturer and three production scale batches from the other three manufactures were put on stability testing as per ICH conditions: under long term (25°C/60%RH) for up to 30 months or 60 months, and accelerated (40°C/75%RH) for up to 6 months. Photostability test following ICH guidelines Q1B was performed on three batches.

The following parameters were tested: appearance, pH value, water, assay, and related substances. 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 suppliers 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 memantine Accord was designed to obtain an essentially similar product to the reference medicinal product, Axura film-coated tablets.

Memantine Accord film coated tablets are an immediate release oral solid dosage form, containing memantine (as hydrochloride) as the active ingredient.

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), colloidal anhydrous silica (glidant), magnesium stearate (lubricant) and crospovidone (disintegrant). The film coating components (hypromellose, polysorbate 80, macrogol, titanium dioxide, iron oxide) are of compendial quality. Compatibility studies between the excipients and active substance were conducted and no compatibility issue was observed.

During the pharmaceutical development important parameters such as polymorphism were monitored. Analysis of X-ray powder diffraction confirmed that the crystalline form remained unchanged during manufacture and storage.

The manufacturing process selected for the finished product was direct compression. The parameters evaluated during the pharmaceutical development were dissolution, hardness, friability, disintegration time, content uniformity as well as bulk density of blend.

The formulation development of memantine hydrochloride 5 mg, 15 mg and 20 mg film coated tablets were based on the formulation development of the 10 mg strength. There are quantitative differences between test and reference product in the composition of the tablet core.

A BCS-based biowaiver was applied for each strength of the product. It was considered that the qualitative and quantitative differences of excipients between the reference and the test product will have no impact on bioavailability.

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. In vitro dissolution studies performed at different media showed that the dissolution profiles were similar. Similarity factors were not calculated since more than 85% of memantine hydrochloride was dissolved within the first 15 minutes.

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

The finished product contains lactose as excipient. 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 five main steps: (1) mixing, (2) blending (3) compression, (4) film coating and (5) 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 (IR and GC), assay (HPLC), uniformity of dosage unit (PhEur), related substances (GC), subdivision of tablets for 10 mg and 20 mg strength (PhEur), dissolution (PhEur) and microbiological quality (PhEur). The 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 ten pilot scale batches and two commercial scale batches of memantine hydrochloride film coated tablets confirm consistency and uniformity of manufacture and indicate that the process is under control.

Stability of the product

Stability data of three pilot-scale batches of memantine hydrochloride film-coated tablets 5 mg; one pilot-scale batch and three product scale batches of memantine hydrochloride film-coated tablets 10 mg; three pilot-scale batches of memantine hydrochloride film-coated tablets 15 mg and three pilot-scale batches of memantine hydrochloride film-coated tablets 20 mg stored under long term conditions for 36 months at 25°C/60%RH and for up to 6 months under accelerated conditions at 40°C/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. In addition, supportive stability studies were performed on 5 pilot scale batches for the bulk tablets packed in the designated packaging material for bulk storage, i.e. two clear polyethylene bags packed in white HDPE buckets with desiccant and closed with HDPE lid. The bulk stability study testing was performed initially for up to 6 months.

Samples were tested for appearance, content of memantine hydrochloride, related substances, disintegration 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.

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.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided by the Applicant. Pharmacodynamic, pharmacokinetic and toxicological properties of memantine are well known. The non-clinical overview is based on appropriate scientific literature. It has been written by Raija Düsing, MD, 53859 Niederkassel, Germany and dated January 11, 2012. The overview refers to 22 publications up to year 2012.

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. It can be assumed that there will be no significant increase of the amount of the active substance on the market and, therefore, no significant increase of environmental exposure.

The proposed justification for omission of any further environmental risk assessment was considered acceptable by the CHMP.

2.3.3. Conclusion on the non-clinical aspects

There were no objections to approval of Memantine Accord from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

A clinical overview on human pharmacology, efficacy and safety was provided by the Marketing Authorisation Applicant. Human pharmacology, efficacy and safety of memantine are well known. The clinical overview was based on appropriate scientific literature. It refers to 44 publications up to year 2012 and was considered adequate by the CHMP.

GCP

N/A

Exemption

In the initially submitted dossier a BCS-based waiver was applied for the 10 mg tablets and an additional strength biowaiver for the 5 mg, 15 mg and 20 mg tablets. However this approach was

not considered approvable by the CHMP. Moreover, the presentation of the data was considered inconclusive and misleading.

In the d120 responses the applicant confirmed that a BCS-based biowaiver was claimed for each strength (5 mg, 10 mg, 15 mg and 20 mg) and the documents (biowaiver justification, dissolution study report) were revised with regard to a BCS-based biowaiver approach for each strength.

BCS-based biowaiver for the 5 mg, 10 mg, 15 mg and 20 mg tablets:

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 (NTIDs).

Drug Substance:

Solubility:

The results show that the solubility of Memantine hydrochloride is very high in all tested media.

Based on the data provided, it can be concluded that the highest strength, 20 mg, will be completely dissolved in 250 ml of each buffer.

Absorption:

The Applicant provided literature data of absolute bioavailability studies, conducted with Memantine (Study codes: MRZ 90001-8201; HUK-610/4; PAZ 1983) and in addition, data of a relative bioavailability study (MRZ 90001-9201) and an *in vitro* permeability study, performed on Caco-2 cells.

The oral dose administered in the absolute bioavailability studies ranged from 10 mg to 40 mg of Memantine hydrochloride and the intravenous dose was 20 mg of Memantine hydrochloride.

In all studies high variability in absolute bioavailability was observed with absolute bioavailability results greater than 100%.

However, the EPAR on Axura® reports the absolute bioavailability being approximately 100 % and based on the innovator's data in the public assessment report on Memantine absorption/permeability characteristics, complete drug absorption (defined as extent of absorption is ≥ 85 %) of Memantine hydrochloride is considered established.

BCS classification:

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

Based on data on solubility and absorption/permeability characteristics of the drug substance, classification of Memantine hydrochloride as a BCS-class I compound (high soluble and high permeable) is justified and considered established.

Therefore, further requirements on the drug product regarding *in vitro* dissolution and excipients for BCS-class I drugs are applicable.

Drug product:

In vitro dissolution:

The Applicant provided dissolution profiles for all strengths of the test and the reference product.

Evaluation of *in vitro* dissolution results:

In vitro dissolution results of all batches tested were provided.

Dissolution of test and reference product is very rapid in all investigated dissolution media as more than 85 % of the labeled amount of Memantine hydrochloride is dissolved within 15 min.

Hence, similarity of dissolution profiles can be accepted as demonstrated without any further mathematical calculation.

Excipients:

All excipients used in the test product are commonly used, in the European Pharmacopoeia described substances with well-established action.

According to the Guideline on the Investigation of Bioequivalence (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, Appendix III), the impact of excipients in immediate release dosage forms on bioavailability of highly soluble and completely absorbable drug substances (i.e., BCS-class I) is considered rather unlikely. Similar amounts of the same excipients in the composition of test like in the reference product are preferred.

None of the excipients is expected or known to impact bioavailability; further the composition of both formulations is qualitatively similar.

In the test product lactose monohydrate is used as filler. As a water soluble excipient it will have no impact on dissolution or bioavailability and is also not known to have any impact on the above properties.

The other difference is the presence of Polysorbate 80 in the film coating of the test product.

Film coating does not impact any properties of dissolution or bioavailability, also the coating is not functional. The disintegrants used although are different; both act by swelling mechanism and, looking at the dissolution values, produce a similar effect.

The dissolution of both the reference and the test product is very rapid. Furthermore, the reference product uses a functional polymer in the film coating, which is known for enteric properties, but it appears that the concentration in which it is used does not impact any enteric properties and it acts as only a non-functional film former. Other differences are triacetin, sodium lauryl sulfate and simethicone emulsion, all in the film coating and are known to impact bioavailability.

No interactions of the drug substance with the excipients have been found during compatibility studies. No impact on gastrointestinal motility, on drug permeability or interaction with membrane transporters as well as interaction with the active substance is expected. Also the

dissolution profiles show no evidence of an impact of any of the excipients on the dissolution rate.

Discussion and Conclusion:

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).

Additionally, Memantine is not considered to be a narrow therapeutic index drug.

The applicant was requested to provide a description of the solubility experiments as part of the dissolution study report, a study protocol, a validation report of the experimental methods and Certificate of Analysis of all tested batches as recommended in the Guideline on the Investigation of Bioequivalence (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, Appendix III). As the submitted study protocol was dated 13-03-2013 and thus later than the revised study report, which was dated 15-02-2013, the document could only serve as additional information on the study conditions but not as a predefined protocol. However, the documentation of method description was considered sufficient.

The applicant provided detailed information of the batches of the reference product and the test product used in the BCS-based biowaiver studies (such as batch number, country of origin, expiry date, and actual strength).

It was clarified that the identical Lot numbers for the different strengths of the reference product were due to the use of starter packs containing all four strengths, for dissolution testing.

Confirmation that the test product was identical to the formulation intended to be marketed is provided.

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

There were quantitative differences between test and reference product in the composition of the tablet core concerning croscarmellose sodium, magnesium stearate and colloidal anhydrous silica and qualitative differences concerning crospovidone in the core and polysorbate 80 in the film coating.

As outlined in Appendix III of the Guideline on the investigation of bioequivalence (CPMP/QWP/EWP/1401/98 Rev. 1/corr**): "Even in the case of class I drugs it is advisable to use similar amounts of the same excipients in the composition of test like in the reference product." The weight of the core tablet of the test product differed in all strengths compared to the reference product (see table below):

	Average tablet weight reference product (Axura)	Average tablet weight test product (PMS Memantine)
5mg	75 mg	102 mg

	Average tablet weight reference product (Axura)	Average tablet weight test product (PMS Memantine)
10mg	251,3 mg (previous formulation with lactose)	251,3 mg
15 mg	225 mg	306 mg
20 mg	306 mg	408 mg

The Applicant provided a discussion of the qualitative and quantitative differences between the reference and the test product, based on assumed amounts of excipients in the reference product which was considered sufficient to conclude that there would be no impact of excipients on bioavailability.

As the applicant applied for a BCS-based biowaiver for each strength, proportionality of the strengths of the test product was not a requirement any longer.

The applicant provided literature data to show linear pharmacokinetics over the range from 5 mg to 40 mg. However, as the applicant applies for a BCS-based biowaiver for all strengths, linear pharmacokinetics is not a requirement.

In vitro dissolution was very rapid in all pH values tested. Similarity of test and reference product was shown under physiologically relevant pH conditions (range of pH 1.2 – 6.8) in all strengths.

2.4.2. Pharmacokinetics

To support the application, the applicant submitted no bioequivalence study, no pharmacodynamic studies, no therapeutic equivalence studies.

Film-coated tablets (5 mg, 10 mg, 15 mg, 20 mg):

As a BCS-based biowaiver was applied for all strengths (5 mg, 10 mg 15 mg and 20 mg tablets) to establish bioequivalence between test and reference product, a bioequivalence study was not required.

Oral solution, 10 mg/g:

The applicant decided to withdraw the application for the oral solution.

Pharmacokinetics - conclusion

Based on the presented documentation supporting the justification of the BCS-based biowaiver approach Memantine Accord film-coated tablets (5mg, 10mg, 15mg and 20mg) were considered bioequivalent with the reference product Axura® film-coated tablets.

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

Film-coated tablets (5 mg, 10 mg, 15 mg, 20 mg):

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).

Additionally, Memantine is not considered to be a narrow therapeutic index drug.

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

There were quantitative differences between test and reference product in the composition of the tablet core concerning croscarmellose sodium, magnesium stearate and colloidal anhydrous silica and qualitative differences concerning crospovidone in the core and polysorbate 80 in the film coating.

The Applicant provided a sufficient discussion of the qualitative and quantitative differences between the reference and the test product, based on assumed amounts of excipients in the reference product to conclude that there will be no impact of excipients on bioavailability.

In vitro dissolution is very rapid in all pH values tested. Similarity of test and reference product is shown under physiologically relevant pH conditions (range of pH 1.2 – 6.8) for all strengths.

Oral solution, 10 mg/g:

The applicant decided to withdraw the application for the oral solution.

2.4.6. Conclusions on clinical aspects

Film-coated tablets (5 mg, 10 mg, 15 mg, 20 mg):

Based on the presented documentation Memantine Accord film-coated tablets were considered bioequivalent with the reference product Axura[®] film-coated tablets.

Oral solution, 10 mg/g:

The applicant decided to withdraw the application for the oral solution.

This was done in the process of assessment when the CHMP raised concern due to a potential risk of medication error and requested that other administration devices, e.g. a spoon, measuring cup or syringe that could minimize the risk of administration errors, should be considered instead of the proposed dropper device. The MAH was asked to thoroughly discuss the benefits of the dropper device proposed versus the pump device used by the originator and potential risks that might result from the impracticable handling of the product, especially within the scope of long-term treatment in the daily routine of a large number of patients in care homes. Moreover, the risk of under- and overdosing due to miscounting of drops should have been addressed.

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 received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 4.0, the PRAC considers by consensus that the risk management system for memantine (Memantine Accord) in the treatment of moderate to severe Alzheimer's disease is acceptable.

Pharmacovigilance plans

The applicant did not propose any pharmacovigilance activities in addition to routine activities.

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine pharmacovigilance is sufficient to monitor the effectiveness of the risk minimisation measures.

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 and published on the European medicines web-portal.

User consultation

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

3. Benefit-risk balance

This application concerns a generic version of memantine film-coated tablets.

The reference product Axura® film-coated tablets is indicated for the 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. A benefit/risk ratio comparable to the reference product can therefore be concluded based on the presented information.

Memantine Accord oral solution, 10 mg/g:

The application for Memantine Accord oral solution, 10mg/g was withdrawn.

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 Accord in the treatment of patients with moderate to severe Alzheimer's disease is favourable and therefore recommends the granting of the marketing authorisation.

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other 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)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

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

Not applicable.