Public Assessment Report

UKPAR

Memantine Hydrochloride 10 mg and 20 mg Film-coated Tablets

(memantine hydrochloride)

UK Licence No: PL 20416/0260-0261

Crescent Pharma Ltd
LAY SUMMARY
Memantine Hydrochloride 10 mg and 20 mg Film-coated Tablets
(memantine hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Memantine Hydrochloride 10 mg and 20 mg Film-coated Tablets (PL 20416/0260-0261). These medicinal products will be referred to as Memantine Hydrochloride Tablets in the remainder of this summary, for ease of reading.

This summary explains how Memantine Hydrochloride Tablets were assessed and their authorisations recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

For practical information about using Memantine Hydrochloride Tablets, patients should read the package leaflets or contact their doctor or pharmacist.

What are Memantine Hydrochloride Tablets and what are they used for?
Memantine Hydrochloride Tablets are ‘generic medicines’. This means that Memantine Hydrochloride Tablets are similar to ‘reference medicines’ authorised in the European Union (EU) called Ebixa 10 mg and 20 mg film-coated tablets (H. Lundbeck A/S).

Memantine Hydrochloride Tablets are used for the treatment of patients with moderate to severe Alzheimer’s disease.

How do Memantine Hydrochloride Tablets work?
The active substance in Memantine Hydrochloride Tablets, memantine hydrochloride, is an anti-dementia medicine. Memory loss in Alzheimer’s disease is due to a disturbance of message signals in the brain. The brain contains so-called N-methyl-D-aspartate (NMDA)-receptors that are involved in transmitting nerve signals important in learning and memory. Memantine belongs to a group of medicines called NMDA-receptor antagonists. These medicinal products act on these NMDA-receptors improving the transmission of nerve signals and the memory.

How are Memantine Hydrochloride Tablets used?
Memantine Hydrochloride Tablets are taken orally once a day. The tablet should be swallowed with some water and can be taken with or without food every day at the same time of the day. The film-coated tablets can be divided into equal doses.

The recommended dose of Memantine Tablets for adults and elderly patients is 20 mg once a day. In order to reduce the risk of side effects, this dose is achieved gradually by the following daily treatment scheme:

<table>
<thead>
<tr>
<th>Week</th>
<th>Dose</th>
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<tr>
<td>Week 1</td>
<td>half a 10 mg tablet</td>
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<tr>
<td>Week 2</td>
<td>one 10 mg tablet</td>
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<tr>
<td>Week 3</td>
<td>One and a half 10 mg tablet</td>
</tr>
<tr>
<td>Week 4 and beyond</td>
<td>two 10 mg tablets</td>
</tr>
</tbody>
</table>

The usual starting dose is half a tablet once a day (1×5 mg) for the first week. This is increased to one tablet once a day (1×10 mg) in the second week and to 1 and a half tablets once a day (1×15 mg) in the third week. From the fourth week on, the usual dose is 2 tablets once a day (1×20 mg).

These medicinal products can only be obtained on prescription from a doctor.
For further information on how Memantine Hydrochloride Tablets are used, refer to the Summaries of Product Characteristics or package leaflets available on the MHRA website.

What benefits of Memantine Hydrochloride Tablets have been shown in studies?
As Memantine Hydrochloride Tablets are generic medicines, studies have been limited to tests to determine that they are bioequivalent to Ebixa 10 mg and 20 mg film-coated tablets (H. Lundbeck A/S). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Memantine Hydrochloride Tablets?
Because Memantine Hydrochloride Tablets are generic medicines and are bioequivalent to Ebixa 10 mg and 20 mg film-coated tablets, their benefits and possible side effects are taken as being the same as those of the reference medicines.

For the full list of all side effects reported with Ebixa 10 mg and 20 mg film-coated tablets, see section 4 of the package leaflets available on the MHRA website.

Why was Memantine Hydrochloride Tablets approved?
It was concluded that, in accordance with EU requirements, Memantine Hydrochloride Tablets have been shown to have comparable quality and to be bioequivalent to Ebixa 10 mg and 20 mg film-coated tablets. Therefore, the MHRA decided that, as for Ebixa 10 mg and 20 mg film-coated tablets, the benefits of Memantine Hydrochloride Tablets are greater than their risks and recommended that they can be approved for use.

What measures are being taken to ensure the safe and effective use of Memantine Hydrochloride Tablets?
A risk management plan has been developed to ensure that Memantine Hydrochloride Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflets for Memantine Hydrochloride Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

Other information about Memantine Hydrochloride Tablets
Marketing Authorisations were granted in the UK on 23rd July 2015.

The full PAR for Memantine Hydrochloride Tablets follows this summary.

For more information about treatment with Memantine Hydrochloride Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in September 2015.
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I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Crescent Pharma Ltd, Marketing Authorisations for the medicinal products for Memantine Hydrochloride 10 mg and 20 mg Film-coated Tablets (PL 20416/0260-0261) on 23rd July 2015. The products are prescription-only medicines (POM) indicated for the treatment of adult patients with moderate to severe Alzheimer’s disease.

These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, cross-referring to Ebixa 10 mg and 20 mg film-coated tablets, which were originally authorised to H. Lundbeck A/S in May 2002 via the Centralised procedures.

Memantine is a voltage-dependent, moderate-affinity uncompetitive NMDA-receptor antagonist. It modulates the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction.

A bioequivalence study was submitted to support these applications comparing the applicant’s test product Memantine Hydrochloride 20 mg Film-coated Tablets (Pharmaceutical Works Polpharma S.A) with the reference product, Ebixa® 20 mg film-coated tablets (H. Lundbeck A/S) in healthy volunteers under fasting conditions. The applicant has stated that the bioequivalence study was conducted in compliance with Good Clinical Practice (GCP) requirements.

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that these applications were based on being generic medicinal products of the originator products that have been in clinical use for over 10 years.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Memantine Hydrochloride 10 mg and 20 mg Film-coated Tablets outweigh the risks and Marketing Authorisations were granted.
II QUALITY ASPECTS

II.1 Introduction

Each film-coated tablet contains 10 mg or 20 mg of memantine hydrochloride equivalent to 8.31 mg and 16.62 mg memantine respectively, as active ingredient. The excipients present are lactose monohydrate, microcrystalline cellulose, crospovidone type B, colloidal anhydrous silica, magnesium stearate making up the tablet core, and the tablet coat consists of Advantia™ Prime 190100BA01 white (hypromellose 6 cP, titanium dioxide [E171], macrocol 400) for the 10 mg strength and Advantia™ Prime 171996BA01 pink (hypromellose 6 cP, titanium dioxide [E171], red iron oxide [E172], macrocol 400) for the 20 mg strength.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of Advantia™ Prime 190100BA01 white and Advantia™ Prime 171996BA01 pink which comply with in-house specifications. Satisfactory Certificates of Analysis have been provided for these excipients.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. In addition, the supplier has confirmed that no ruminant material other than calf rennet is used during the production of lactose monohydrate. Confirmation has also been given that the magnesium stearate used in the tablets is of vegetable origin.

The finished product is packed in polyvinylchloride (PVC)/polyvinylidenechloride (PVdC) aluminium blisters containing 14, 28, 42, 56, 98 and 112 film-coated tablets, in a carton box. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2. Drug Substance

INN: Memantine hydrochloride
Chemical name(s): 1-Amino-3,5-dimethyladamantane hydrochloride (or) 3,5-Dimethyl-1-adamantanamine hydrochloride

Structural formula:

![Memantine Hydrochloride Structural Formula](image)

Molecular formula: C_{12}H_{21}N, HCl
Molecular mass: 215.76 g/mol
Appearance: Memantine hydrochloride is a white to off white crystalline powder.
Solubility: Memantine hydrochloride is soluble in water and methanol, practically insoluble in petroleum ether.

Memantine hydrochloride is the subject of an active substance master file (ASMF).
Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis for all working standards have been provided.

Batch analyses data are provided that comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been provided, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious, film-coated tablets containing memantine hydrochloride that are bioequivalent to Ebixa 10 mg and 20 mg film-coated tablets (H. Lundbeck A/S).

A satisfactory account of the pharmaceutical development has been provided.

Comparative impurity and in-vitro dissolution profiles have been provided for the proposed and originator products.

Manufacture of the products
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing processes. The manufacturing processes have been validated on pilot scale batches, of each strength, and have shown satisfactory results. A commitment is given that process validation studies will be performed on the first three consecutive commercial scale batches of each strength and the process validation protocol is satisfactory.

Finished Product Specifications
The finished product specifications are acceptable. The test methods have been described and have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Products
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years with a storage condition ‘This medicinal product does not require any special temperature storage conditions. Keep blisters in the outer carton in order to protect from light’. These are satisfactory.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.
II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of these applications from a pharmaceutical point of view.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of memantine hydrochloride are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Environmental Risk Assessment (ERA)
Since these products are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

There are no objections to the approval of these applications from a non-clinical point of view.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology of memantine hydrochloride is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamic or pharmacokinetic data are provided and none are required for these applications.

No new efficacy or safety studies have been performed and none are required for this type of applications. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of memantine hydrochloride.

IV.2 Pharmacokinetics
In support of these applications, the applicant has submitted a single dose bioequivalence study under fasting conditions comparing the test product with the reference product.

This was an open label, single dose, randomised, two period, cross-over bioequivalence study comparing the pharmacokinetics of the applicant’s test product Memantine 20 mg film-coated tablets (Pharmaceutical Works Polpharma S.A) versus the reference product, Ebixa® 20 mg film-coated tablets (H. Lundbeck A/S), in 24 healthy adult subjects under fasting conditions.
Serial blood sampling pre-dose and at 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 12.0, 14.0, 16.0, 24.0, 32.0, 48.0 and 72.0 hours post-dose was carried out in each period. The washout period between treatments was 21 days.

**Results**

Ratio and 90% Confidence Intervals of Test versus Reference for memantine hydrochloride (N=24)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Geometric Least Squares Means</th>
<th>Ratio (%)</th>
<th>90% Confidence Limits (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;(ng/ml)</td>
<td>24.40</td>
<td>24.33</td>
<td>100.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>98.18 - 102.42</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt;(ng.h/ml)</td>
<td>1105.28</td>
<td>1077.50</td>
<td>102.58</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100.24 - 104.97</td>
</tr>
</tbody>
</table>

**Conclusion**

The 90% confidence intervals for C<sub>max</sub> and AUC<sub>0-t</sub> were within the acceptance criteria of 80.00-125.00%. Bioequivalence has been shown for the test formulation (Memantine 20 mg film-coated tablets) and the reference formulation (Ebixa® 20 mg film-coated tablets) under fasting conditions.

As the 10 mg and 20 mg strength products meet all the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev.1 Corr**), the results of the study for 20 mg tablets can be extrapolated to the other strength i.e. 10 mg Film-coated Tablets. Therefore, bioequivalence has been shown between the 10 and 20 mg strengths of the test products and their respective reference products.

**IV.3 Pharmacodynamics**

No new pharmacodynamic data were submitted and none were required for applications of this type.

**IV.4 Clinical efficacy**

No new efficacy data were submitted and none were required for applications of this type.

**IV.5 Clinical safety**

Nine subjects experienced a total of fifteen mild and two moderate adverse events over the course of the study. In total, there were eight adverse events considered related to the oral administration of Memantine 20 mg Film-Coated Tablets and nine adverse events considered related to the oral administration of Ebixa® 20 mg Film-Coated Tablets. No serious adverse events were recorded.

**IV.6 Risk Management Plan (RMP)**

The Marketing Authorisation Holder (MAH) has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Memantine Hydrochloride 10 mg and 20 mg Film-coated Tablets.
A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

<table>
<thead>
<tr>
<th>Important identified risks</th>
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<tbody>
<tr>
<td><strong>Safety concern</strong></td>
</tr>
<tr>
<td>Hepatic disorders</td>
</tr>
<tr>
<td>Overdose/drug administration error with pump device</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Important potential risks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Safety concern(s):</strong></td>
</tr>
<tr>
<td>Prostate cancer</td>
</tr>
</tbody>
</table>

IV.7  Discussion on the clinical aspects

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

Bioequivalence has been demonstrated between the applicant’s product Memantine 20 mg film-coated tablets and the reference product, Ebixa® 20 mg film-coated tablets (H. Lundbeck A/S), under fasting conditions. As the 10 mg and 20 mg strength products meet all the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev.1 Corr**), the results of the study for 20 mg tablets can be extrapolated to the other strength i.e. 10 mg Film-coated Tablets. Therefore, bioequivalence has been shown between the 10 and 20 mg strengths of the test products and their respective reference products.

The grant of Marketing Authorisations is recommended for these applications.

V  User consultation

For Memantine 10 mg and 20 mg film-coated tablets a user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Ebixa (H. Lundbeck A/S). The bridging report submitted by the applicant is acceptable.

VI  Overall conclusion, benefit/risk assessment and recommendation

The quality of the products is acceptable, and no new non-clinical or clinical concerns have been identified. Bioequivalence has been demonstrated between the applicant’s products and the reference products. Extensive clinical experience with memantine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit / risk assessment is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Memantine Hydrochloride 10 mg and 20 mg Film-coated Tablets is presented below:
## Table of content of the PAR update
Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitment)

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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