Amantadine Hydrochloride 100 mg Capsules

(Amantadine Hydrochloride)

PL 20620/0085

UKPAR

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LAY SUMMARY
Amantadine Hydrochloride 100 mg Capsules
(Amantadine hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Amantadine Hydrochloride 100 mg Capsules (PL 20620/0085). It explains how Amantadine Hydrochloride 100 mg Capsules were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Amantadine Hydrochloride 100 mg Capsules.

For practical information about using Amantadine Hydrochloride 100 mg Capsules, patients should read the package leaflet or contact their doctor or pharmacist.

What are Amantadine Hydrochloride 100 mg Capsules and what are they used for?
Amantadine Hydrochloride 100 mg Capsules is a generic medicine. This means Amantadine Hydrochloride 100 mg Capsules are similar to ‘reference medicine’ already authorised in the UK called Symmetrel 100 mg Capsules (PL 16853/0015; Alliance Pharmaceuticals Limited).

Amantadine Hydrochloride 100 mg capsules is used:

- To treat Parkinson’s disease by improving muscle control and reducing stiffness, shakiness and shuffling
- In the treatment of shingles (herpes zoster), to reduce pain
- To prevent or treat a certain type of flu infection (influenza A).

How are Amantadine Hydrochloride 100 mg Capsules used?
Amantadine Hydrochloride 100 mg Capsules are taken by mouth. This medicine can only be obtained on prescription from the doctor. A whole capsule should be swallowed with a glass of water.

The dosage depends on the condition being treated. Details of the correct dose to be given are included in the package leaflet.

How do Amantadine Hydrochloride 100 mg Capsules work?
Amantadine hydrochloride is a dopaminergic drug (chemical that allows communication between nerve cells). Amantadine Hydrochloride 100 mg Capsules increase the levels of certain chemicals which transmit impulses in the nervous system, including the brain.

How have Amantadine Hydrochloride 100 mg Capsules been studied?
Because Amantadine Hydrochloride 100 mg Capsules is a generic medicine, studies in patients have been limited to tests to determine that this is bioequivalent to the reference medicine, Symmetrel 100 mg Capsules (PL 16853/0015; Alliance Pharmaceuticals Limited). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.
What are the benefits and risks of Amantadine Hydrochloride 100 mg Capsules?
As Amantadine Hydrochloride 100 mg Capsules is a generic medicine that is bioequivalent to the reference medicine, its benefits and risks are taken as being the same as the reference medicine.

Why are Amantadine Hydrochloride 100 mg Capsules approved?
It was concluded that, in accordance with EU requirements, Amantadine Hydrochloride 100 mg Capsules has been shown to have comparable quality and to be bioequivalent to Symmetrel 100 mg Capsules. Therefore, the view was that, as for Symmetrel 100 mg Capsules the benefit outweighs the identified risk.

What measures are being taken to ensure the safe and effective use of Amantadine Hydrochloride 100 mg Capsules?
A risk management plan has been developed to ensure that Amantadine Hydrochloride 100 mg Capsules are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Amantadine Hydrochloride 100 mg Capsules, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Amantadine Hydrochloride 100 mg Capsules
A Marketing Authorisation for Amantadine Hydrochloride 100 mg Capsules was granted on 26th February 2014.

The full PAR for Amantadine Hydrochloride 100 mg Capsules follows this summary.

For more information about treatment with Amantadine Hydrochloride 100 mg Capsules, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in April 2014.
Amantadine Hydrochloride 100 mg Capsules

PL 20620/0085

SCIENTIFIC DISCUSSION

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INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation for the medicinal product Amantadine Hydrochloride 100 mg Capsules (PL 20620/0085) on 26th February 2014. This is a prescription-only medicine (POM) used in the treatment of Parkinson's disease, herpes zoster and prophylaxis and treatment of signs and symptoms of infection caused by influenza A virus.

This application was submitted as a national abridged application according to Article 10(1) of Directive 2001/83/EC, as amended. The applicant has cross-referred to Symmetrel 100 mg Capsules (PL 00101/0452), which was originally granted to Novartis Pharmaceuticals UK Limited on 24th June 1997. The reference product has undergone a Change of Ownership (CoA) procedure and was authorised to the current Marketing Authorisation Holder, Alliance Pharmaceuticals Limited (PL 16853/0015), on 25th June 1998.

The mechanisms of action of amantadine

Parkinson's Disease: Amantadine has been shown to be a low affinity antagonist at the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors. Overactivity of glutamatergic neurotransmission has been implicated in the generation of parkinsonian symptoms. The clinical efficacy of amantadine is thought to be mediated through its antagonism at the NMDA subtype of glutamate receptors. In addition, amantadine may also exert some anticholinergic activity.

Herpes zoster: The mechanism of action of amantadine in herpes zoster has not been fully characterised.

Influenza A Virus: Amantadine specifically inhibits the replication of influenza A viruses at low concentrations. If using a sensitive plaque-reduction assay, human influenza viruses, including H1N1, H2N2 and H3N2 subtypes, are inhibited by ≤0.4µg/ml of amantadine. Amantadine inhibits an early stage in viral replication by blocking the proton pump of the M2 protein in the virus. This has two actions; it stops the virus uncoating and inactivates newly synthesised viral haemagglutinin. Effects on late replicative steps have been found for representative avian influenza viruses.

Data from tests with representative strains of influenza A virus indicate that Amantadine hydrochloride is likely to be active against previously unknown strains, and could be used in the early stages of an epidemic, before a vaccine against the causative strain is generally available.

A summary of the pharmacovigilance system and detailed Risk Management Plan have been provided with this application and are satisfactory.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Nomenclature
rINN: Amantadine hydrochloride

Chemical name: Tricyclo[3.3.1.1^{3,7}]decan-1-amine hydrochloride

Structure:

\[
\begin{array}{c}
\text{NH}_2 \\
\text{HCl}
\end{array}
\]

Molecular Formula: C_{10}H_{17}N, HCl

Molecular Weight: 187.7 g/mol

Solubility: White or almost white crystalline powder.

Amantadine hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance amantadine hydrochloride are covered by a European Directorate for the Quality of Medicines Healthcare (EDQM) Certificate of Suitability.

DRUG PRODUCT

Other ingredients

Other ingredients consist of the pharmaceutical excipients lactose monohydrate, povidone K30, magnesium stearate and the capsule shell consists of gelatin, titanium dioxide (E171) and red iron oxide (E172).

All excipients used comply with their respective European Pharmacopoeia monographs, with the exception of gelatin that complies with an in-house specification and red iron oxide which complies with a National formulary. Satisfactory Certificates of Analysis have been provided for all excipients.

The excipients used that contain materials of animal or human origin are lactose monohydrate and gelatin. 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. EDQM Certificates of Suitability have been provided by each supplier of gelatine, showing that it is in compliance with
current European regulations concerning the minimisation of transmission of TSE/BSE. Confirmation has also been given that the magnesium stearate used in the capsules is of vegetable origin.

**Pharmaceutical development**
The objective of the development programme was to formulate robust, stable, capsules containing amantadine hydrochloride that could be considered as a generic medicinal product of Symmetrel 100 mg Capsules (Alliance Pharmaceuticals Limited).

Comparable dissolution and impurity profiles are provided for this product versus the originator product.

**Manufacture**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated on a pilot scale batches and has shown satisfactory results. A Process validation scheme for the full scale batches has been provided. This is satisfactory.

**Finished product specification**
The finished product specification is satisfactory. Test methods have been described and adequately validated. Batch data have been provided that complies with the release specification. Certificates of Analysis have been provided for any working standards used.

**Container Closure System**
The product is supplied in a polyvinylchloride (PVC)/polyvinylidichloride (PVdC) foiled aluminium blister. The pack sizes are 5, 14, 28 and 56 capsules.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 24 months with no special storage conditions are set. These are satisfactory.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**
The SmPC, PIL and labelling are pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the package leaflet contains.
Marketing Authorisation Application (MAA) Form
The MAA form is pharmaceutically satisfactory.

Expert Report/Quality Overall Summary
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There are no objections to the approval of this product from a pharmaceutical point of view.
NON-CLINICAL ASSESSMENT

The pharmacodynamic, pharmacokinetic and toxicological properties of amantadine hydrochloride are well-known. Thus, the applicant has not provided additional studies and further studies are not required.

A non-clinical overview has been provided, written by an appropriately qualified person. This is satisfactory.

A suitable justification has been provided for not submitting an environmental risk assessment.

There are no objections to the approval of this product from a non-clinical point of view.
**CLINICAL ASSESSMENT**

In support of this application, the Marketing Authorisation Holder has submitted a single bioequivalence study under fasting conditions.

This was a single blind, balanced, randomised, 2-period, 2-sequence, single-dose crossover oral pilot study comparing the pharmacokinetics of the test product Amantadine Hydrochloride 100 mg capsules (Lime Pharma Limited) with the reference product, Symmetrel® 100 mg capsules (Alliance Pharmaceuticals Limited) in healthy adult male subjects, under fasting conditions.

Blood samples were collected at pre-dose and at 0.50, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00, 72.00 hours post dose. The washout period was 7 days.

**Geometric Least Square Mean, Ratios and 90% Confidence Interval for amantadine hydrochloride**

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<tr>
<th>PK Parameter</th>
<th>Geometric Least Square Mean</th>
<th>90% Confidence Interval</th>
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<tbody>
<tr>
<td>Test (T)</td>
<td>Reference (R)</td>
<td>Ratio (T/R)%</td>
</tr>
<tr>
<td>C\text{max} (ng/ml)</td>
<td>423.39</td>
<td>417.47</td>
</tr>
<tr>
<td>AUC\text{0-72} (ng.h/ml)</td>
<td>6541.36</td>
<td>6569.68</td>
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The 90% confidence intervals for C\text{max} and AUC\text{0-72} were within the pre-defined limits acceptance criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**). Bioequivalence has been shown for the test formulation (Amantadine Hydrochloride 100 mg capsules) and the reference formulation (Symmetrel® 100 mg capsules) under fasting conditions.

**Pharmacodynamics**

No new data have been submitted and none are required for applications of this type.

**Clinical efficacy**

No new data have been submitted and none are required for applications of this type.

**Clinical safety**

No new safety data have been submitted and none are required for applications of this type.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling**

The SmPC, PIL and labelling are satisfactory from a clinical perspective and consistent with those for the reference product.
Clinical Expert Report
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Marketing Authorisation Application (MAA) Form
The MAA form is satisfactory from a clinical perspective.

Clinical Conclusion
There are no objections to the approval of this product from a clinical point of view.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Amantadine Hydrochloride 100 mg Capsules are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s product and the reference product.

No new or unexpected safety concerns arose from this application.

The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with amantadine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit risk assessment is therefore considered to be positive.
Amantadine Hydrochloride 100 mg Capsules

PL 20620/0085

**STEPS TAKEN FOR ASSESSMENT**

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<td>1</td>
<td>The MHRA received the Marketing Authorisation application on 1st November 2013.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 12th November 2013.</td>
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<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information relating to the quality dossier on 14th January 2014.</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information to the quality section on 22nd January 2014.</td>
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<tr>
<td>5</td>
<td>The application was determined on 26th February 2014.</td>
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SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
LABELLING
UKPAR Amantadine Hydrochloride 100 mg Capsules

Amantadine hydrochloride 100 mg Capsules

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