Medicines & Healthcare products Regulatory Agency

MHRA

# Public Assessment Report

# National Procedure

# AMANTADINE HYDROCHLORIDE 100 MG CAPSULES, HARD

## Amantadine hydrochloride

## PL 42765/0010

## Renata (UK) Limited

# LAY SUMMARY

## Amantadine hydrochloride 100 mg Capsules, hard
## Amantadine hydrochloride

This is a summary of the Public Assessment Report (PAR) for Amantadine hydrochloride 100 mg Capsules, hard. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Amantadine hydrochloride Capsules in this lay summary for ease of reading.

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

**What are Amantadine hydrochloride Capsules and what are they used for?**
This application is for a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised in the European Union (EU) called Symmetrel capsules 100 mg.

Amantadine hydrochloride Capsules are used in the treatment of Parkinson's disease by improving muscle control and reducing stiffness, shakiness and shuffling. They are also used in the treatment of shingles (herpes zoster), to reduce pain.

**How do Amantadine hydrochloride Capsules work?**
This medicine contains the active ingredient amantadine hydrochloride. Amantadine is a dopaminergic drug which means it can increase the levels of certain chemicals which transmit impulses in the nervous system, including the brain.

**How are Amantadine hydrochloride Capsules used?**
The pharmaceutical form of this medicine is a hard capsule and the route of administration is oral.

The capsules should be swallowed whole with a drink of water.

The recommended dose for the treatment of Parkinson's disease is as follows:
Adults: 1 capsule (100mg) a day for the first week. A doctor will increase this to 2 capsules a day (200 mg). Higher doses, up to 4 capsules (400 mg) a day may be given in some cases.
Adults over 65 years: 1 capsule (100mg) once a day.

The recommended dose for the treatment of Shingles (herpes zoster) is as follows:
The dose is 2 capsules (200 mg) a day for 14 days. If pain continues a doctor may give the patient another 14 days treatment.
If the patient has kidney problems, a doctor may give them a lower dose.

For further information on how Amantadine hydrochloride Capsules are used, refer to the package leaflet and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

**What benefits of Amantadine hydrochloride Capsules have been shown in studies?**
Because Amantadine hydrochloride Capsules are a generic medicine, studies in healthy volunteers have been limited to tests to determine that they are bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Amantadine hydrochloride Capsules?**
Because Amantadine hydrochloride Capsules are a generic medicine and are bioequivalent to the reference medicine, their benefits and possible side effects are considered to be the same as the reference medicine.

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflet or the SmPC available on the MHRA website.

**Why were Amantadine hydrochloride Capsules approved?**
It was concluded that, in accordance with EU requirements, Amantadine hydrochloride Capsules have been shown to be comparable to and to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that they can be approved for use.

**What measures are being taken to ensure the safe and effective use of Amantadine hydrochloride Capsules?**
A Risk Management Plan (RMP) has been developed to ensure that Amantadine hydrochloride Capsules are used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet, 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 and reviewed continuously.

**Other information about Amantadine hydrochloride Capsules**
A Marketing Authorisation for Amantadine hydrochloride Capsules was granted in the UK on 09 September 2019.

The full PAR for Amantadine hydrochloride Capsules follows this summary.

This summary was last updated in September 2019.

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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) considered that the application for Amantadine hydrochloride 100 mg Capsules, hard (PL 42765/0010) could be approved.

The product is approved for the following indications:

- Parkinson's disease.
- Herpes zoster: It is recommended that Amantadine be given to elderly or debilitated patients in whom the physician suspects that a severe and painful rash could occur. Amantadine can significantly reduce the proportion of patients experiencing pain of long duration.

Amantadine hydrochloride is an anti-Parkinson drug. 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. The mechanism of action of Amantadine in herpes zoster has not been fully clarified.

This application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic medicine of a suitable originator medicinal product, Symmetrel capsules 100 mg, that has been licensed within the EU for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is based on being a generic medicinal product of a reference product that has been licensed for over 10 years.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is based on being a generic medicinal product of a reference product that has been in clinical use for over 10 years. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A Marketing authorisation was granted for this product on 09 September 2019.

# II QUALITY ASPECTS

## II.1 Introduction

This product consists of hard gelatin capsules, each containing 100 mg Amantadine hydrochloride.

In addition to amantadine hydrochloride, this product also contains the following excipients:
Capsule Powder
Lactose monohydrate
Povidone
Magnesium stearate

Capsule shell
Gelatin
Iron oxide black (E172)
Iron oxide red (E172)
Titanium dioxide (E171)

Printing Ink
Shellac
Black iron oxide (E172)
Potassium hydroxide (E525)

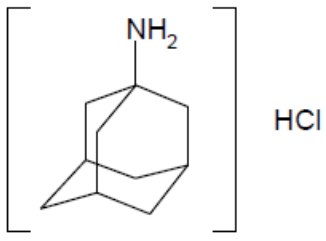
The finished product is packaged in polyvinyl chloride/polyvinylidene chloride - aluminium blisters in pack sizes of 12, 14, 24, 28 and 56 capsules. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

## II.2 ACTIVE SUBSTANCE

**rINN: Amantadine hydrochloride**

Chemical Name: tricyclo [3.3.1.1$^{3,7}$] decan-1-amine, hydrochloride
Molecular Formula: $C_{10}H_{17}N$. HCl
Chemical Structure:




Molecular Weight: 187.7
Appearance: White or almost white, crystalline powder
Solubility: At room temperature amantadine hydrochloride is freely soluble in water, ethanol and methanol; soluble in chloroform; sparingly soluble in methylene chloride; and practically insoluble in ether.

Amantadine hydrochloride is the subject of a European Pharmacopoeia monograph.

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

## II.3 DRUG PRODUCT

### Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution profiles have been provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of gelatin and lactose monohydrate, no excipients of animal or human origin are used in the final products. EDQM Certificates of Suitability have been provided for the gelatin.

The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

This product does not contain or consist of genetically modified organisms (GMO).

### Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

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 and has shown satisfactory results.

### Finished Product Specification

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

### Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years, with no special storage conditions, is acceptable.

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

The grant of a marketing authorisation is recommended.

# III NON-CLINICAL ASPECTS

## III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of Amantadine 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.

### III.2 Pharmacology
No new pharmacology data were provided and none were required for this application.

### III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for this application.

### III.4 Toxicology
No new toxicology data were provided and none were required for this application.

### III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of an already authorised product, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisation for the proposed product.

### III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisation is recommended.

## IV CLINICAL ASPECTS

### IV.1 Introduction
The clinical pharmacology, efficacy and safety of Amantadine hydrochloride are well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

### IV. 2 Pharmacokinetics
In support of the application, the applicant conducted the following study:

**Bioequivalence Study 1**
This study was an open label, balanced, randomised, two-treatment, two-period, two-sequence, single oral dose, crossover bioequivalence study comparing the test product Amantadine hydrochloride 100 mg Capsules, hard, versus the reference product Symmetrel capsules 100 mg (PL 16853/0015 now PL 00289/2249) in subjects under fasted conditions.

After an overnight fast of at least 10 hours, a single oral dose (100 mg) of either the test product or the reference product was administered with 240 mL of drinking water. Blood samples were taken pre-dose and up to 72 hours post dose, with a washout period of 12 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

| Parameters | Geometric least square mean | | % Ratio | 90% Confidence Interval for ln-transformed data | | Intra Subject CV (%) | Power (%) |
|---|---|---|---|---|---|---|---|
| | Test (T) | Reference (R) | T/R | Lower Limit | Upper Limit | | |
| $\ln C_{max}$ | 295.269 | 285.461 | 103.4 | 96.69 | 110.65 | 13.3 | 100.0 |
| $\ln AUC_{0-t}$ | 6092.214 | 5971.435 | 102.0 | 97.85 | 106.37 | 8.2 | 100.0 |

In line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

### IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for this application and none were required.

### IV.4 Clinical efficacy

No new efficacy data were submitted with this application and none were required.

### IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with this application.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

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

The applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

### IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application.

## V USER CONSULTATION

The Patient Information Leaflet (PIL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the PIL 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.

## VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with amantadine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The product is bioequivalent to the reference product and its benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

The following text is the currently approved label text. No label mock-ups have been provided for this product. In accordance with medicines legislation, this product shall not be marketed in the UK until approval of the label mock-ups has been obtained.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Amantadine hydrochloride 100 mg Capsules, hard.

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each capsule contains 100 mg Amantadine hydrochloride.

**3. LIST OF EXCIPIENTS**

Contains lactose monohydrate

**4. PHARMACEUTICAL FORM AND CONTENTS**

Capsule, hard

24 capsules.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.

For oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP:

**9. SPECIAL STORAGE CONDITIONS**

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

**MA Holder:**
Renata (UK) Limited
Greenway Business Centre,
Harlow Business Park,
Harlow, CM19 5QE,
United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

PL 42765/0010

## 13. BATCH NUMBER

Lot:

## 14. GENERAL CLASSIFICATION FOR SUPPLY

POM

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Amantadine hydrochloride 100 mg capsules, hard

## 17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

## 18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOIL**

**1. NAME OF THE MEDICINAL PRODUCT**

Amantadine hydrochloride 100 mg Capsules, hard.

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Renata (UK) Limited

**3. EXPIRY DATE**

EXP:

**4. BATCH NUMBER**

Lot:

**5. OTHER**

# TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

| **Application type** | **Scope** | **Product information affected** | **Date of grant** | **Outcome** | **Assessment report attached Y/N** |
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