IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Amantadine hydrochloride Renata 100 mg Capsules, hard
AMANTADINE HYDROCHLORIDE
PA22865/005/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Amantadine hydrochloride Renata 100 mg Capsules, hard, from Renata Pharmaceuticals (Ireland) Limited on 25th February 2022 for the symptomatic treatment of Parkinson's disease. Amantadine can be given as monotherapy at the start of treatment for Parkinson's disease or in combination with levodopa.

With Ireland as the Reference Member State, marketing authorisations were applied for in IE and MT. This decentralised application was submitted as a generic application according to Article 10(1) of Directive 2001/83/EC. The active substance, amantadine hydrochloride, is not considered a new active substance.

Amantadine hydrochloride Renata 100 mg Capsules, hard will be subject to prescription.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie.

Name of the product	Amantadine hydrochloride Renata 100 mg Capsules, hard
Name(s) of the active substance(s) (INN)	AMANTADINE HYDROCHLORIDE
Pharmacotherapeutic classification (ATC code)	N04BB01
Pharmaceutical form and strength(s)	100 mg Capsules, hard
Marketing Authorisation Number(s) in Ireland (PA)	PA 22865/005/001
Marketing Authorisation Holder	Renata Pharmaceuticals (Ireland) Limited
MRP/DCP No.	IE/H/1146/001/DC
Reference Member State	IE
Concerned Member State	MT

II. QUALITY ASPECTS

II.1. Introduction

This application is for Amantadine hydrochloride Renata 100 mg Capsules, hard

II.2 Drug substance

The active substance is Amantadine hydrochloride, an established active substance described in the European/ Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur. / EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

Adventitious Agent Safety

Certificates of suitability issued by EDQM have been provided Amantadine hydrochloride Renata 100 mg Capsules, hard and compliance with the *Note For Guidance on Minimising the Risk if Transmitting Animal Spongiform Encephalopathy Agents* via Medicinal Products has been satisfactorily demonstrated

Adventitious viruses
N/A

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Amantadine hydrochloride Renata 100 mg Capsules, hard.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Symmetrel 100 mg capsules Novartis Pharma B.V. (Netherlands) on the European market. No new preclinical data have been submitted. This is acceptable for this type of application.

III.2 Pharmacology

Although its precise mechanism of action is uncertain, Amantadine is known to function as a low affinity, non-competitive antagonist at the phencyclidine (PCP) site within the N-methyl-D-aspartate (NMDA)-subtype of glutamate receptors at therapeutic concentrations. It also binds to the sigma site of the NMDA receptor, binding to both sites with Ki values in the µM range. Amantadine has been reported to exhibit neuroprotective properties against glutamate related toxicity in in-vitro experiments. Amantadine activity at noradrenaline and dopamine transporters as well as general anti-inflammatory effects have also been suggested to play a role in the mechanism of action of amantadine in parkinson's disease

III.3 Pharmacokinetics

Amantadine is reported as well absorbed following oral administration to non-clinical species with the unchanged amantadine the major eliminated component primarily via urine. Amantadine crosses the blood brain barrier via a saturable active transport mechanism.

III.4 Toxicology

Only very limited information in the published literature on the general toxicity of Amantadine in laboratory animal studies. Data are often old, sparse and not performed according to current guidelines. Data currently included in the SmPC adequately summarise the available data.

III.5 Ecotoxicity/environmental risk assessment

Since Amantadine 100 mg Capsules Hard is 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

Pharmacodynamic, pharmacokinetic and toxicological properties of amantadine are well known. As amantadine is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate and there are no outstanding non-clinical issues precluding the authorisation of this product.

IV. CLINICAL ASPECTS

IV.1 Introduction

Amantadine hydrochloride is a well known active substance with established efficacy and tolerability.
The European Reference Product (ERP) is Symmetrel 100 mg capsules Novartis Pharma B.V. (Netherlands) registered since 08-Jan-1969.
The content of the SmPC approved during the decentralised procedure is overall in accordance with that accepted for the ERP. However the applicant has applied for a reduced indication for this generic medicinal product and this is acceptable, the approved indication is for the symptomatic treatment of Parkinson's disease.

For this generic application, the applicant has submitted one bioequivalence study.

The reference medicinal product to which bioequivalence has been demonstrated is Symmetrel capsules 100 mg [Current MAH: Teva UK Ltd, PL 00289/2249). This UK reference product (PL00289/2249) is considered as part of the same Global Marketing Authorisation as the ERP and is therefore acceptable.

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Amantadine hydrochloride Renata 100 mg Capsule, manufactured by Rajendrapur General Facility, Renata Limited hard was compared to the reference product , Symmetrel capsules 100 mg , manufactured by Alliance Pharmaceuticals Ltd, United Kingdom (current MAH: Teva UK Ltd, PL 00289/2249). Based on the pharmacokinetic parameters of active substance and metabolite, the reference tablet and test tablet are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

No new pharmacokinetics studies were presented and no such studies are required for this application. The applicant has provided a clinical overview outlining the pharmacokinetics of Amantadine hydrochloride based on literature; this is considered acceptable.

IV.3 Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application**.** The applicant has provided a clinical overview outlining the pharmacodynamics of Amantadine hydrochloride based on literature; this is considered acceptable.

IV.4 Clinical Efficacy

No new efficacy data were submitted with this generic application and none were required for a generic application according to Article 10(1) of Directive 2001/83/EC.

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. No new or unexpected safety data were raised from the bioequivalence study.

Risk Management Plan

The 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 Amantadine hydrochloride 100 mg capsules.

Safety specification

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

Based on the submitted bioequivalence study Amantadine 100 mg Capsules manufactured by Rajendrapur General Facility, Renata Limited is considered bioequivalent with the Reference Product (R): Symmetrel 100 mg Capsule manufactured by Alliance Pharmaceuticals Ltd, United Kingdom in terms of rate (as measured by Cmax) and extent (as measured by AUC) of absorption under fasting conditions**.**

In addition, comparative dissolution profiles of the test product batches manufactured and reference product over the physiological pH ranges have been demonstrated.

It can be concluded that bioequivalence has been shown.

The product information for Amantadine hydrochloride Renata 100 mg Capsules, hard has been aligned with the ERP Symmetrel 100 mg capsules Novartis Pharma B.V. (Netherlands) however a reduced indication has been applied for: the symptomatic treatment of Parkinson's disease. Amantadine can be given as monotherapy at the start of treatment for Parkinson's disease or in combination with levodopa.

V. OVERALL CONCLUSIONS

Amantadine hydrochloride Renata 100 mg Capsules, hard is a generic form of Symmetrel 100 mg capsules Novartis Pharma B.V. (Netherlands).

Symmetrel 100 mg capsules Novartis Pharma B.V. (Netherlands) is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents.

The SmPC is consistent with that of the reference product apart from the reduced indication which the applicant has applied for.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Amantadine hydrochloride Renata 100 mg Capsule, hard demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

16.12.2026