COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Amantadine Ethypharm 10 mg/ml oral solution

(amantadine hydrochloride)

NL/H/4493/001/DC

Date: 18 May 2020

This module reflects the scientific discussion for the approval of Amantadine Ethypharm 10 mg/ml oral solution. The procedure was finalised at 11 March 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Amantadine Ethypharm 10 mg/ml oral solution, from Ethypharm.

The product is indicated for symptomatic treatment of Parkinson's disease. Amantadine can be given as monotherapy at the start of treatment of the Parkinson's disease or in combination with levodopa.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Symmetrel 10 mg/ml syrup which has been registered in the Netherlands by Novartis Pharma B.V. since 8 January 1969. Symmetrel has been withdrawn during this application procedure on 1 December 2019.

The concerned member states (CMS) involved in this procedure were Austria, Germany, Italy, Spain and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Amantadine Ethypharm is a clear and colourless liquid with a slightly sweet taste and lemon flavour. Each ml of oral solution contains 10 mg of amantadine hydrochloride.

The oral solution is packed in amber glass bottles with child resistant tamper evident cap containing 150 ml with a polypropylene dosing cup of 15 ml. The dosing cup is marked in ml (millilitres).

The excipients are: methyl parahydroxy benzoate (E218), propyl parahydroxy benzoate (E216), sorbitol 70% (E420), sodium citrate dihydrate, lemon flavour, propylene glycol and purified water.

II.2 Drug Substance

The active substance is amantadine hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or

practically white crystalline powder and is freely soluble in water, soluble in alcohol and chloroform. The active substance also sublimes on heating. Amantadine hydrochloride does not have a chiral centre and is not optically active.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with an additional test for residual solvents in accordance with the CEP. Batch analytical data demonstrating compliance with this specification have been provided for one batch.

Stability of drug substance

The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The choices of the packaging and manufacturing process are justified in relation to the innovator. An active pharmaceutical ingredient compatibility study was conducted. According to the analysis methods and the results obtained no incompatibility was detected. A protocol on the preservative efficacy test has been submitted and data as per this protocol was presented to support current preservative levels. The dose accuracy of the accompanying measuring cup has been shown for the recommended doses of 5 ml and 10 ml. A biowaiver has been requested of *in vivo* testing based on the guideline on the investigation of bioequivalence regarding oral solutions. Overall, the pharmaceutical development is considered acceptable.

Manufacturing process

The manufacturing process consists of preparation of the drug solution, preparation of the additive solution and preparation of the final oral solution, filling and sealing. The

manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full-scaled batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with the Ph.Eur. and/or British Pharmacopoeia requirements. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity, pH at 25°C, deliverable volume, weight/ml at 25°C, clarity of solution, assay, assay of preservatives, related substances, uniformity of mass of delivered doses from multi-dose containers and microbial limits. The test for efficacy of antimicrobial preservatives has also been included in the specifications. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three pilot scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three exhibit batches stored at 25°C/60% (24 months) and 40 °C/75% (6 months). The conditions used are in accordance with applicable European guidelines. The batches were stored (inverted) in amber coloured type III glass bottles. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 30 months without any special precautions for storage. Stability data have been provided demonstrating that the product remains stable for 140 days following first opening of the bottle.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Amantadine Ethypharm has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Amantadine Ethypharm 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.2 Discussion on the non-clinical aspects

This product is a generic formulation of Symmetrel which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Amantadine hydrochloride is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Biowaiver

The MAH has requested a biowaiver for Amantadine Ethypharm 10 mg/ml oral solution based on a comparison of the qualitative and quantitative composition of the test product and the reference product Symmetrel. The excipients are essentially similar except for sodium citrate dihydrate and propylene glycol. The MAH has sufficiently shown that these ingredients do not affect bioavailability. Additionally, the quantitative concentration of the excipient sorbitol is markedly different in the test product compared to the reference product. The MAH sufficiently showed that in this case sorbitol is not expected to influence amantadine absorption as amantadine is well and fast absorbed from the gastrointestinal tract and can be considered highly permeable. A biowaiver is therefore granted.

IV.3 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 Ethypharm.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Symmetrel. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

Amantadine Ethypharm 10 mg/ml oral solution has a proven chemical-pharmaceutical quality and is a generic form of Symmetrel 10 mg/ml syrup. Symmetrel is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are oral solutions, no bioequivalence study is deemed necessary. A biowaiver has been granted.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Amantadine Ethypharm with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 March 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse