CBG MEB

Public Assessment Report

Scientific discussion

Mantomed 5 mg, 10 mg, 15 mg and 20 mg, film-coated tablets

(memantine hydrochloride)

NL/H/3001/001-004/DC

Date: 26 February 2015

This module reflects the scientific discussion for the approval of Mantomed 5 mg, 10 mg, 15 mg and 20 mg, film-coated tablets. The procedure was finalised on 11 September 2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Mantomed 5 mg, 10 mg, 15 mg and 20 mg, film-coated tablets from Medochemie Limited.

The product is indicated for treatment of patients with moderate to severe Alzheimer's disease.

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 products Ebixa 5 mg, 10 mg, 15 mg and 20 mg, film-coated tablets which have been registered in the EEA through a centralised procedure (EU/1/02/219) since 15 May 2002 by H. Lundbeck A/S.

The concerned member states (CMS) involved in this procedure were Croatia, Cyprus, Czech Republic, Estonia, Greece, Lithuania, Romania and Slovakia.

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

II. QUALITY ASPECTS

II.1 Introduction

Mantomed 5 mg is a yellow, round, biconvex film-coated tablet. It contains 5 mg of memantine hydrochloride equivalent to 4.15 mg memantine.
Mantomed 10 mg is a yellow, oblong, biconvex, scored on both side film-coated tablet. The tablet can be divided into equal doses. It contains 10 mg of memantine hydrochloride equivalent to 8.31 mg memantine.
Mantomed 15 mg is a pink, round, biconvex film-coated tablet. It contains 15 mg of memantine hydrochloride equivalent to 12.46 mg memantine.
Mantomed 20 mg is a yellow, round, biconvex film-coated tablet. It contains 20 mg of memantine hydrochloride equivalent to 16.62 mg memantine.

The film-coated tablets are packed in PVC/PE/PVDC-Alu transparent blisters or PA/Al/PVC-Al blisters.

The excipients are:
Tablet cores - cellulose microcrystalline, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate
Tablet coat for 5/10/20 mg – hypromellose, titanium dioxide (E171), macrogol 400, iron oxide yellow (E172).
Tablet coat for 15 mg – hypromellose, titanium dioxide (E171), macrogol 400, iron oxide red (E172)

The composition of the different strengths is quantitatively proportional.

II.2 Drug Substance

The active substance is memantine hydrochloride, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). The active substance is a fine white to off- white solid and is soluble in water and freely soluble in methanol. Memantine hydrochloride does not exhibit optical isomerism, but does exhibit polymorphism. The anhydrous form is consistently produced.

The Active Substance Master File (ASMF) procedure is used for the three manufacturers of the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product,

the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing processes of the ASMF-holders have been adequately described. The active substance has been adequately characterized. Specifications of raw materials in the synthesis are acceptable. The starting material in the synthesis is acceptable and no class-1 solvents are used. Sufficient information on presence, carry-over and control of impurities has been provided.

Quality control of drug substance
The specification of the drug substance of the MAH is acceptable in view of the route of synthesis and the various European guidelines. General tests are performed as per Ph.Eur. and the methods for assay, related substances and residual solvents are developed and validated in-house. Batch analytical data demonstrating compliance with the drug substance specification have been provided for one production scale batch of each ASMF-holder.

Stability of drug substance
The first ASMF-holder has provided stability data on the active substance for 24 months long-term (30°C/65% RH) and 6 months accelerated (40°C/75% RH) storage conditions. No clear trends could be observed and all results were well within limits. The claimed retest period of 30 months and 'store below 30 °C' are deemed justified.
The second manufacturer has provided stability data on the active substance for 36 months long-term (25°C/60% RH) and 6 months accelerated (40°C/75% RH) storage conditions. No clear trends could be observed and all results were well within limits. The claimed retest period of 60 months is deemed justified and no specific storage conditions are required.
The third ASMF-holder has provided stability data on the active substance for 60 months long-term (25°C/60% RH) and 6 months accelerated (40°C/75% RH) storage conditions. No clear trends could be observed and all results were well within limits. The claimed retest period of 60 months is deemed justified and no specific storage conditions are required.
The MAH has claimed a re-test period of 24 months, when stored below 25°C. The packaging system of the ASMF-holders is used. This is acceptable.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The formulation development has been adequately described. The manufacturing process development has been described adequately. The MAH applied for a biowaiver based on the BSC class I of memantine HCl. The drug substance is highly soluble. Comparative dissolution testing was performed with the test products against the innovator products Ebixa. The profiles can be considered similar with more than 85% dissolved after 15 minutes. The products have the same qualitative composition with the reference Ebixa, the excipients are well-established and in usual amounts and it is considered that there are no interactions affecting drug bioavailability. Therefore from chemical-pharmaceutical point of view all requirements for a biowaiver as listed in the 'Note for Guidance on the investigation of bioavailability and bioequivalence' have been met (solubility, dissolution, excipients) and a biowaiver is considered to be acceptable, The choice of manufacturing process and packaging material is justified. The 10 mg tablets bear a score line. The functionality was demonstrated in compliance with Ph.Eur. and EMA Q&A requirements. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The drug product is manufactured by blending, direct compression and film-coating. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three pilot scaled batches, one commercial scale blend as used for the 5 mg, 10 mg and 15 mg tablets, and one commercial scale blend as used for the 20 mg tablets. The product is manufactured using conventional manufacturing techniques. Additional validation on larger scale production batches will be performed post-approval.

Control of excipients

The excipients comply with the Ph.Eur or in-house specifications (iron oxide yellow and iron oxide red). These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, average weight, disintegration, uniformity of dosage units (content uniformity), dissolution, identification of colouring, identification of memantine, memantine HCl content, related substances and microbiological quality. The release and shelf-life specifications are identical.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two pilot-scale batches and one commercial-scale batch of each strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the products has been provided for two pilot-scale batches of each strength and one commercial-scale batch of each strength. The drug product was stored at 25°C/60%RH (12 months) and 40°C/75% RH (6 month). The pilot-scale batches were of a slightly different formulation (without colourant iron oxide yellow). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in transparent two types of PVC/PE/PVdC-Aluminium blisters and Aluminium-Aluminium blisters.
All results remain within limits at all storage conditions although fluctuations in hardness, water content and disintegration time were observed. A shelf-life period of 24 months can be granted based on the provided data. The claimed storage condition “No special storage conditions” is justified, and the drug product is not sensitive to light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Magnesium stearate is the only material of animal origin. A valid TSE certificate has been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Mantomed 5 mg, 10 mg, 15 mg and 20 mg, film-coated tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. From chemical-pharmaceutical point of view all requirements for a biowaiver have been met.

The following post-approval commitments were made:
- The MAH committed to continue the ongoing stability studies of the drug product.
- The MAH committed to include the first 3 production scale batches in the stability studies.
- The MAH committed to perform comparative dissolution profile testing (in three media) on the first three production batches.
- The MAH committed to perform validation of the manufacturing processon three batches of the common blend, for two batch sizes.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Mantomed 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 Ebixa, 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

Memantine 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
In order to obtain a biowaiver, a report was submitted to support this application. Reference is made to the 'Note for Guidance on the investigation of bioavailability and bioequivalence'. The RMS considers it possible to grant a full biowaiver for memantine since this substance is very soluble with complete absorption, high permeability (BCS class I) and is not considered to be a narrow-therapeutic drug.
The same excipients as in the innovator product are used in the generic formulation in similar amounts. The differences in the quantitative composition are acceptable. Memantine can be considered BCS class I drug substance.

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 Mantomed.

- Summary table of safety concerns as approved in RMP

Important identified risks	Hepatic disorders
Important potential risks	Prostate cancer
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 Ebixa. No new clinical studies were conducted. The MAH demonstrated equivalence to the innovator on quality and *in vitro* tests. The argumentation for a biowaiver is acceptable and no bioequivalence study is required. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The MAH applied for an exemption to perform a readability test on the package leaflet (PL) of Mantomed. A bridging report is provided in which the differences and similarities in the key messages compared to the reference PL are discussed. The MAH stated that the proposed package leaflet is identical to the centrally authorised package leaflet of Ebixa (EMEA/H/C/000463). Furthermore, a successfully tested layout is used. The bridging report has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Mantomed 5 mg, 10 mg, 15 mg and 20 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Ebixa 5 mg, 10 mg, 15 mg and 20 mg, film-coated tablets. Ebixa is a well-known medicinal product with an established favourable efficacy and safety profile.

No comparative bioavailability or bioequivalence study was carried out. Instead, reference was made to fulfilling all requirements for a biowaiver. This has been sufficiently justified.

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 Mantomed 5 mg, 10 mg, 15 mg and 20 mg, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 September 2014.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached