

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Memantine CF 10 mg and 20 mg, film-coated tablets
Memantine CF 5 mg + 10 mg + 15 mg + 20 mg film-coated tablets
Centrafarm B.V., the Netherlands**

memantine (as hydrochloride)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

**EU-procedure number: NL/H/2727/001-003/DC
Registration number in the Netherlands: RVG 112196, 112198, 112199**

27 November 2013

Pharmacotherapeutic group:	psychoanaleptics, anti-dementia drugs
ATC code:	N06DX01
Route of administration:	oral
Therapeutic indication:	treatment of patients with moderate to severe Alzheimer's disease
Prescription status:	prescription only
Date of authorisation in NL:	11 November 2013
Concerned Member States:	Decentralised procedure with: 10 mg – AT, BE, BG, CZ, DE, ES, FR, HU, IE, LU, PT, SL 20 mg – AT, BE, DE, ES, FR, LU, PT, SK 5/10/15/20 mg – AT, DE, ES, PT
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Memantine CF 10 mg and 20 mg, film-coated tablets and Memantine CF 5 mg + 10 mg + 15 mg + 20 mg, film-coated tablets from Centrafarm B.V. The date of authorisation was on 11 November 2013 in the Netherlands.

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 SPC.

There is increasing evidence that malfunctioning of glutamatergic neurotransmission, in particular at NMDA-receptors, contributes to both expression of symptoms and disease progression in neurodegenerative dementia.

Memantine is a voltage-dependent, moderate-affinity uncompetitive NMDA-receptor antagonist. It modulates the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Axura 10 mg and 20 mg, film-coated tablets (EU/1/02/218), which have been registered in the EEA through a centralised procedure since 17 May 2002 by Merz Pharmaceuticals GmbH. A starter pack of Axura 5 mg +10 mg +15 mg + 20 mg film-coated tablets has also been registered through this procedure.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. The current application does not include a comparative bioavailability or bioequivalence study, but reference is made to fulfilling all requirements for a biowaiver. See paragraph II.3 "Clinical Aspects". This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance

The active substance is memantine hydrochloride, an established active substance not described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white or almost white crystalline powder, which is freely soluble in methanol and in ethanol, soluble in water and practically insoluble in acetone. Memantine hydrochloride does not exhibit optical isomerism, but does exhibit polymorphism (solvates). The anhydrous form is consistently produced

The Active Substance Master File (ASMF) procedure is used for both 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

Memantine hydrochloride from the first supplier is produced in two production steps. The second manufacturer uses three steps. Sufficient details have been provided.

Quality control of drug substance

In general, the drug substance specification is acceptable in view of the route of synthesis and the various European guidelines. The substance is tested for appearance, identification, water, pH, assay, sulphated ash, heavy metals, particle size, microbial contamination, related substances and residual solvents. Sufficient batch analytical data demonstrating compliance with the drug substance specification have been provided for both manufacturers.

Stability of drug substance

The first ASMF has provided stability data on the active substance stored at long-term conditions (25°C/60% RH; up to 60 months), intermediate conditions (30°C/65% RH; up to 60 months) and accelerated conditions (40°C/75% RH; 6 months). Based on the results a re-test period of 60 months is acceptable.

The second supplier has provided stability data on the active substance stored at long-term conditions (30°C/65% RH; 12 months for lab-scale batches and 12 months for pilot batches) and accelerated conditions (40°C/75%; 6 months for lab-scale batches and 3 months for pilot batches). For all studied parameters no real trends or out of specification results have been observed. On the basis of the provided data the proposed re-test date of 12 months can be assigned.

The applicant has adopted a re-test periods of 3 years and 1 year for the two manufacturers, respectively.

* *Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition

Memantine CF 10 mg is a white, slim through the middle, biconvex, film-coated tablet with breaking lines on both sides and engraving '1 0' on one side. The tablet can be divided into equal doses.

Memantine CF 20 mg is a pink, oval, biconvex, film-coated tablet.

Memantine CF 5 mg included in the starter pack is a white, oval, biconvex, film-coated tablet embossed on one side with '5'.

Memantine CF 15 mg included in the starter pack is a light brown, oval, biconvex, film-coated tablet.

The film-coated tablets are packed in PVC/PE/PVDC-Aluminium blister packs. One treatment initiation pack contains 28 tablets with 7 tablets of Memantine CF 5 mg, 7 tablets of Memantine CF 10 mg, 7 tablets of Memantine CF 15 mg and 7 tablets of Memantine CF 20 mg.

The excipients are:

Tablet core - microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate

Tablet coat - polyvinyl alcohol, titanium dioxide (E 171), macrogol (3350), talc; 20 mg only - iron oxide yellow and red (E172); 15 mg only – iron oxide yellow, red and black.

The composition of the different strengths is quantitatively proportional.

Pharmaceutical development

In general the development of the product has been adequately described, the choice of excipients is justified and their functions explained. Memantine HCl tablets are a generic form of the marketed tablet named Axura®. The qualitative composition (with exception of the colouring agents) of the test product is the same as the reference product. Subdivision of the 10 mg tablets in compliance with the general Ph.Eur. monograph on tablets has been demonstrated.

The MAH applied for a BCS-based biowaiver. From chemical-pharmaceutical point of view there is no objection. Comparative dissolution profiles have been provided for test and reference product at three different pH values. For both test and reference product in all three media, more than 85% of the labelled amount is dissolved within 15 minutes. Profiles can be considered similar. The choice of manufacturing process is justified.

Manufacturing process

The manufacturing process is a standard, straightforward manufacturing process: mixing of the excipients followed by direct compression, coating and packaging, which are regarded as conventional manufacturing techniques.

The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three pilot-scale batches of each strength. Additional validation on larger scale production batches will be performed post-approval.

Control of excipients

With the exception of the coating material, all excipients comply with the European Pharmacopoeia. For the coating material, separate specifications are provided. Information on functionality-related characteristics has been included where relevant. The specifications are acceptable.

Quality control of drug product

The drug product specification includes tests for appearance, dimensions, identification, mean tablet weight, uniformity of mass, uniformity of mass in subdivided tablets (for the 10 mg tablets only), hardness, friability, assay, dissolution, uniformity of dosage units, impurities, water content, disintegration, titanium dioxide identification, iron oxide identification (15 and 20 mg tablets only) and microbial contamination. Release and shelf-life limits are identical, except for water content. The higher shelf-life limit is justified in view of the provided stability data.

The analytical methods were adequately described and validated. Batch analytical data were provided for three validation batches of each tablet strength using active substance from both manufacturers, demonstrating compliance with the proposed release specification.

Stability of drug product

Stability data on the drug product were provided on three pilot scale batches of each strength, for both tablets manufactured with active substance from both manufacturers. The batches were stored at 25°C/60% (24 months/12 months), 30°C/65% (24 months/12 months) and 40°C/75% RH (6 months). The batches were stored in the proposed commercial packaging (PVC/PE/PVdC-aluminium blisters).

The conditions used in the stability studies are according to the ICH stability guideline. Furthermore, a photostability study has been carried out on the 20 mg tablets. The study was performed in line with the Photostability Guideline. All stability indicating parameters remain stable for all batches tested. A shelf-life period of 36 months can be granted based on the provided data. No special storage conditions are required.

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

No material derived from or exposed to animals infected by TSE/BSE has been used in the manufacture of Memantine HCl tablets. Memantine HCl tablets are thus free from potential risks associated with the transmission of TSE/BSE.

II.2 Non-clinical aspects

This product is a generic formulation of Axura, which is available on the European market. 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.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of memantine released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

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.

In order to obtain a biowaiver, a report was submitted to support this application. Reference is made to 'Relating issues' in 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. There is a slight difference in the quantitative composition between the test and reference product, but the potential effect on the bioavailability has been adequately addressed and the lack of any effect has been justified.

Risk management plan

Memantine was first approved in 2002, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of memantine can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. The MAH committed to monitor and specifically report on, as appropriate, the following issue: systematic and continuous capture and follow-up of all prostate cancer ADRs.

Product information

SPC

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Axura.

Readability test

The package leaflet 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 package leaflet 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. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Memantine CF 10 mg and 20 mg, film-coated tablets and Memantine CF 5 mg + 10 mg + 15 mg + 20 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Axura 10 mg and 20 mg, film-coated tablets. Axura 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 demonstrated.

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

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

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 Memantine CF 10 mg and 20 mg and Memantine CF 5 mg + 10 mg + 15 mg + 20 mg, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 1 August 2013. Memantine CF 10 mg and 20 mg, film-coated tablets Memantine CF 5 mg + 10 mg + 15 mg + 20 mg, film-coated tablets were authorised in the Netherlands on 11 November 2013.

The date for the first renewal will be: 1 August 2018.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to perform manufacturing process validation on the first three consecutive commercial-scale batches of each strength.
- The MAH committed to continue and complete the stability studies on pilot batches in order to firmly establish the shelf-life of the product.
- The MAH committed to place the first three production batches on stability studies.
- The MAH committed to determine comparative dissolution profiles when the first three batches of commercial size production are available.

List of abbreviations

ADR	Adverse Drug Reaction
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
t _{1/2}	Half-life
t _{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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