CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Memantine CF 10 mg/ml oral solution
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/2693/001/DC
Registration number in the Netherlands: RVG 112073

20 March 2014

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:	12 November 2013
Concerned Member States:	Decentralised procedure with CZ, DE, ES, IE, 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/ml oral solution from Centrafarm B.V. The date of authorisation was on 12 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 product Ebixa 5 mg/pump actuation, oral solution (initially registered as Ebixa 10 mg/g oral drops, solution), which has been registered in the EEA since 15 May 2002 by H. Lundbeck A/S through centralised procedure EMEA/H/C/000463.

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. A biowaiver was applied for. This is acceptable, as essential similarity was sufficiently demonstrated on quality grounds for this oral solution. For the argumentation in support of the biowaiver, refer to section II.3 of this report: ‘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.*). It is a white crystalline powder, which is soluble in hot water; slightly soluble in diluted hydrochloric acid (15%) and freely soluble in methanol. Memantine HCl polymorphism is reported in literature and the most stable polymorph is Form I, which is used in the drug product. Two asymmetric atoms of carbon are present in the molecule. Since there is a plane of symmetry between the two chiral centres, memantine is not a chiral molecule.

The Active Substance Master File (ASMF) procedure is used for 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 step of the drug substance consists of six steps. A flow chart is provided in the dossier as is a reaction scheme. The starting materials are considered acceptable.

Quality control of drug substance
The specification of the drug substance has been provided and the methods and limits have been justified. Batch analytical data on three production-scale batches have been provided demonstrating compliance with the specification. The analytical methods have been described and validated.

Stability of drug substance
Stability data have been provided for 5 batches at 25°C/ 60% (three for 60 months; one for 18 months and one for 9 months) and at 40°C/75% RH (6 months). The stability results demonstrate that the drug substance is stable at long term and accelerated stability studies. Based on the submitted data in the dossier, the proposed retest period of 60 months without special storage conditions was granted.

** 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/ml is a clear to colourless to light yellowish solution with pH 5-8. Each activation of the pump (one downward pump) delivers 0.5 ml of solution containing 5 mg of memantine hydrochloride equivalent to 4.16 mg of memantine.

The oral solution is packed in amber glass bottles (Type III) containing either 50 ml, 100 ml or 10 x 50 ml solution with a screw cap(PP) and either a pump (PP and LDPE) or dosing pipette (LDPE and Polystyrol). The dosing pipette is printed in 0.5 ml graduations.

The excipients are: potassium sorbate E202, sorbitol E420, purified water.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The excipients in the generic formulation are the same as the reference product excipients. The quantity of potassium sorbate in the formulation was based on information retrieved from public literature determining the quantity in the innovator product. A series of studies such as physical similarity, taste, pH, density and filter studies were conducted.. Efficacy of microbial preservation was sufficiently demonstrated.
The pharmaceutical development of the product has been adequately performed. An adequate risk assessment concerning potential dosing errors due to the different dosing devices within the product is provided. Pump studies adequately demonstrated that the mass of the delivered dose from the multidose container of the test and reference product are similar and that the dose delivered by the pump is accurate and reproducible. The requested biowaiver is acceptable from a chemical-pharmaceutical point of view.

Manufacturing process
The manufacturing process chosen for the oral solution is a standard mixing process followed by filtration. From the trial formulations leading up to the final formulation, it is clear that the most critical parameter for the product is to achieve a clear solution with suitable pH of the final product. The product is then filtered and meets the proposed specifications. The manufacturing process has been adequately validated according to relevant European guidelines.

Control of excipients
All excipients are tested against individual Ph.Eur. monographs. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, condition of the packaging, pH, assay of the active, identity, assay of the preservative, uniformity of mass of delivered doses from multidose container, fill volume and microbiological quality. The analytical methods have been adequately described and validated. A forced degradation study has been performed demonstrating that the drug product is very stable and that the drug product is photostable.
Batch analytical data from the proposed production site have been provided on two production-scale batches demonstrating compliance with the release specification.

Stability of drug product
Stability data have been provided for three batches stored at 25°C/60% RH (18 months) and stored at 40°C/75% RH (6 months). No trends or out-of-specification results were observed in the stability studies at accelerated, long term and in-use conditions.
An in-use stability study with the dosing pump was performed on one batch for 12 weeks. No trends or out of specification results were observed. The in-use study has been performed with the dose pump attached to the vial and a daily dose has been removed from the drug. Additional in-use stability studies that include the mass of the delivered dose are initiated. With respect to the dosing pipette an in-use study is being performed and the results will be submitted post-authorisation. Photostability has been demonstrated.
Based on the submitted data the shelf life of 30 months and the in-use shelf life of 12 weeks for the dosing pump without special storage conditions can be granted. For the dosing pipette additional data or a justification is needed before an in-use shelf-life can be granted.

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.2 Non-clinical aspects

This product is a generic formulation of Ebixa 5 mg/pump actuation, oral solution, 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.

Biowaiver
In accordance with the guideline, since both test (memantine 10 mg/ml) and reference products (Ebixa 5 mg/pump actuation) are aqueous oral solutions, the MAH applied for a biowaiver.
The test product of memantine 10 mg/ml contains the same excipients as the reference product. Compared with the composition of the reference product, the quantity of each excipient is identical. The amount of sorbitol, an excipient which may affect gastrointestinal transit, is similar to the amount in Ebixa.
Moreover, all physical-chemical properties are essentially similar between the two products. Therefore, a biowaiver has been granted.

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. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

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

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. Fifteen questions were asked about all parts of the leaflet. After the pilot round or between tests rounds, no amendments of the PIL were considered necessary. Overall, each and every question met the criterion of 81% correct answers. The report is of good quality and the results show that the PL fulfils the criteria as set in the readability guideline.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Memantine CF 10 mg/ml oral solution has a proven chemical-pharmaceutical quality and is a generic form of Ebixa 5 mg/pump actuation, oral solution. Ebixa is a well-known medicinal product with an established favourable efficacy and safety profile.

The requested biowaiver is considered acceptable. The test product of memantine 10 mg/ml oral solution contains the same excipients as the reference products; the quantity of the excipients is identical. All physical-chemical properties are essentially similar between the two products.

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/ml oral solution with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 13 June 2013. Memantine CF 10 mg/ml oral solution was authorised in the Netherlands on 12 November 2013.

The date for the first renewal will be: 13 June 2018.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to provide the results of the in-use stability study on the dosing pipette which is currently running and additional in-use stability studies that include the mass of the delivered dose.

List of abbreviations

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
$t_{½}$	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