CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Rivastigmine DEMO 2 mg/ml oral solution
Demo SA Pharmaceutical Industry, Greece

rivastigmine (as hydrogen tartrate)

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/1523/001/DC
Registration number in the Netherlands: RVG 103057

19 July 2010

Pharmacotherapeutic group:	anti-dementia drugs; anticholinesterases
ATC code:	N06DA03
Route of administration:	oral
Therapeutic indication:	mild to moderately severe Alzheimer's dementia; mild to moderately severe dementia in patients with idiopathic Parkinson's disease
Prescription status:	prescription only
Date of authorisation in NL:	28 April 2010
Concerned Member States:	Decentralised procedure with EL
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 Rivastigmine DEMO 2 mg/ml oral solution, from Demo SA Pharmaceutical Industry. The date of authorisation was on 28 April 2010 in the Netherlands. The product is indicated for:

- symptomatic treatment of mild to moderately severe Alzheimer's dementia,
- symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease.

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

Rivastigmine is an acetyl- and butyrylcholinesterase inhibitor of the carbamate type, thought to facilitate cholinergic neurotransmission by slowing the degradation of acetylcholine released by functionally intact cholinergic neurones. Thus, rivastigmine may have an ameliorative effect on cholinergic-mediated cognitive deficits in dementia associated with Alzheimer's disease and Parkinson's disease.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Exelon 2 mg/ml (EU License EU/1/98/066/018) which has been registered through a centralised procedure by Novartis Europharm Limited since 1998.

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. The 2 mg/ml rivastigmine oral solution is a watery solution with the same qualitative composition as Exelon 2 mg/ml oral solution. In accordance with the *NfG on The Investigation of Bioavailability and Bioequivalence* no bioequivalence studies are deemed necessary. 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 generic medicinal products.

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 rivastigmine hydrogen tartrate, an established active substance not described in the European (Ph.Eur.*), or anu other Pharmacopoeia. The active substance is a white to almost white powder and is soluble in methanol, ethanol, acetonitrile and water and partly soluble in acetone. Rivastigmine hydrogentartrate is manufactured as the S-enantiomer. 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/EMEA 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.

Manufacture
For both drug substance manufacturers, the manufacturing process consists of three main reaction steps and a purification step. The starting materials and solvents have been described sufficiently. No metal catalysts are used. The active substance has been adequately characterized and the specifications that have been adopted for the starting material, solvents and reagents are acceptable.

Quality control of drug substance
The drug substance specification has been established in-house by the MAH. The specification is considered acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 full-scale batches.

Stability of drug substance.
First manufacturer - stability data on the active substance have been provided for 3 full-scale batches stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). The batches were adequately stored. No changes are seen during the tested period for both storage conditions. The proposed re-test period of 24 months without any additional storage requirements is justified.
Second manufacturer - stability data on the active substance have been provided for 3 full-scale batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). The batches were adequately stored. No changes are seen during the tested period for both storage conditions. The proposed re-test period of 30 months is justified when stored in the original container is justified.
The MAH has committed to continue long term testing for up to 3 years to cover the desired re-test period of 3 years.

** 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
Rivastigmine DEMO 2 mg/ml is a clear, yellow, oral solution,with a pH value of 3.5 - 4.5. Each ml of the solution contains 2 mg of rivastigmine.

The excipients are: citric acid, anhydrous (E330), sodium benzoate (E211), sodium citrate (E331), quinoline yellow (E104), and purified water.

The oral solution is packaged in a Type III amber coloured glass bottle (although the product was found not to be light sensitive, amber coloured glass is used in line with the originator product) containing 120 ml of rivastigmine 2 mg/ml oral solution. The bottle is equipped with a syringe adaptor (LDPE) in the bottle throat and a (HDPE) child resistant closure packed together with a 3 ml oral dosing syringe (LDPE). Calibrations of the oral dosing syringe are marked at 0.5 mg increments from 1.5 mg to 6 mg.
The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. During pharmaceutical development, studies were performed with respect to the characterisation of the originator product, the robustness of the drug product with regard to pH changes and preservative content, antimicrobial efficacy and compatibility of the drug product with the plastic packaging materials. No bioequivalence studies have been performed. This is acceptable in view of the nature of the drug product. The pharmaceutical development of the product has been adequately performed.

Excipients
The excipients comply with the Ph.Eur. requirements or with the requirements of Directive 95/45/EC for quinoline yellow. These specifications are acceptable.

Manufacturing process
The main steps of the manufacturing process are dissolving of the components, filtering the solution and filling the drug product into bottles. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three production-scale batches. The product is manufactured using conventional manufacturing techniques.

Container closure system
The specifications and certificates of analyses for each packaging component are included in the dossier. Also drawings of each component are provided. The following packaging for rivastigmine 2 mg / ml oral solution is described:

125 ml Ph.Eur. type III, amber coloured screw neck glass bottles
A certificate of analyses of 100 ml bottles is included. The quality of the glass is Ph.Eur. type III hydrolytic resistance and complies with Ph.Eur. 3.2.1 (Glass containers for pharmaceutical use).
According to Ph.Eur. monograph 3.2.1 type III glass containers are in general suitable for non-aqueous preparations for parenteral use, powders for parental use and for preparations not for parenteral use. For this drug product, type III glass is therefore acceptable.

28 mm Child resistant and tamper evident HDPE closure
White opaque HDPE outer cap with a PE inlay and tamper evident ring. It has a translucent polypropylene (PP) inner cap. The materials have been described in sufficient detail and comply with Ph.Eur. 3.1.3 (polyolefines), 3.1.6 (polypropylene PP) and 3.2.2 and Directive 2002/72/EC.

LDPE adaptor plug and separately supplied 3 ml LDPE dosing pipette (syringe)
The dosing device consists of three LDPE components that come into contact with the drug product: plunger, barrel and adaptor. All components comply with Directive 2002/72/EC. The materials have been

described in sufficient detail. The dosing scale printed on the dosing pipette has specific markings for 1.5, 3, 4.5 and 6 mg. This is acceptable in view of the posology of the drug product.

Quality control of drug product
The product specification includes tests for appearance, uniformity of mass, identification, assay, impurities, efficacy of antimicrobial preservation and microbial contamination. Except for total impurities, the shelf-life requirements are identical to the release requirements. The requirements are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production sites have been provided on three production batches, demonstrating compliance with the release specification.

Compatibility
A compatibility study of the drug product with the dosage device and closure was performed for rivastigmine oral solution. Bottles were stored in inverted position for two weeks at 40°C/75% RH. No changes were observed in assay purity and appearance.
As it is not unthinkable at all that the drug product will be kept in an inverted or horizontal position during storage throughout its shelf-life, the MAH has also demonstrated the compatibility of the drug product with the bottle closure by storing one batch in inverted position for 12 months at accelerated conditions (40°C/75% RH). After 12 months no changes in the physical and chemical characteristics of the Rivastigmine 2 mg/ml oral solution were observed.

Microbiological attributes
Microbial tests on total viable aerobic count (fungi and aerobic bacteria) and *Escherichia coli* were performed in accordance with the Ph.Eur. 5.1.4 requirement.

Stability tests on the finished product
Stability data on the product has been provided three production batches stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in 100 ml amber glass bottles, with the same specification as for the 120 ml bottles intended for marketing. No changes are seen under both storage conditions. The claimed shelf-life of 24 months with no special storage conditions is justified.

In-use stability
Stability data has been provided demonstrating that the product remains stable for 1 month following first opening of the container, when stored at 30°C/65% RH.

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 Exelon, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

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 rivastigmine 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

Rivastigmine is a well-known active substance with established efficacy and tolerability. No new clinical data have been provided or are required, in accordance with the *NfG on The Investigation of Bioavailability and Bioequivalence*, as the 2 mg/ml rivastigmine oral solution is a watery solution with the same qualitative composition as Exelon 2 mg/ml oral solution. The pharmacology, pharmacokinetics and toxicology of the active substance is well known. This generic product can be used instead of its reference product.

Risk management plan

For the innovator product Exelon, a RMP has been constituted which has been updated based on post-marketing safety information. The MAH has committed to follow the RMP of the innovator, where appropriate. The MAH has therefore committed to the following issues:

- the following issues will be monitored and specifically reported upon in the PSURs: Gastro-intestinal symptoms (nausea, vomiting and diarrhoea); worsening of symptoms associated with Parkinson's disease; increased amylase, lipase and pancreatitis; cardiac arrhythmia; exacerbation of asthma and COPD; liver disorders including hepatitis; severe skin reactions (bullous reactions); cardiac disorders (myocardial infarction); haematuria; hypertension; cerebrovascular accidents; urinary tract obstruction; seizures (convulsions); gastrointestinal ulceration; and pulmonary infections.
- The SPC for the product will follow and be kept in line with that of the innovator.

The MAH has committed to follow, where appropriate, the risk minimisation activities of the innovator, e.g. participate in DHPCs where needed, produce and distribute educational material for patients and physicians when applicable, etc.

Product information

Readability test

The MAH has submitted a bridging statement. In this statement it is concluded that the results of the usertest for Rivastigmine capsules (procedures NL/H/1504-1514/001-004/DC) can be extended to the PIL of Rivastigmine oral solution. This is considered acceptable, taking into account the comparability of both PILs.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Rivastigmine DEMO 2 mg/ml oral solution has a proven chemical-pharmaceutical quality and is a generic form of Exelon 2 mg/ml oral solution. Exelon is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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 Rivastigmine DEMO 2 mg/ml oral solution with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 16 July 2009. Rivastigmine DEMO 2 mg/ml oral solution is authorised in the Netherlands on 28 April 2010.

The PSUR submission cycle should be aligned with the PSUR submissions of the innovator product Exelon with the first data lock point of 31 July 2010. Currently (at the time of writing), a 6-monthly PSUR cycle is applicable for the innovator product and depending on the content of these PSURs this may change in the future.

The date for the first renewal will be: 16 July 2014. The MAH has the possibility to apply for an early renewal should this be more convenient to align the renewal application with the PSUR submissions in the future.

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

Quality - active substance
- The MAH has committed to continue long term testing for up to 3 years to cover the desired retest period of 3 years.

Quality - medicinal product
- The MAH has confirmed that all studies will continue according to the stability study schedule as provided in the dossier.

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