CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Rivastigmine Peseri 1.5/3/4.5/6 mg hard capsules Peseri Trading, Cyprus

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/1923/001- 004/DC
Registration number in the Netherlands: RVG 106763,106775,106778,106779

30 March 2011

Pharmacotherapeutic group:	anticholinesterases
ATC code:	N06DA03
Route of administration:	oral
Therapeutic indication:	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.
Prescription status:	prescription only
Date of authorisation in NL:	13 December 2010
Concerned Member States:	Decentralised procedure with DE
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 Peseri 1.5 mg, 3 mg, 4.5 mg, and 6 mg hard capsules, from Peseri Trading. The date of authorisation was on 13 December 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.

Rivastigmine interacts with its target enzymes by forming a covalently bound complex that temporarily inactivates the enzymes. In healthy young men, an oral 3 mg dose decreases acetylcholinesterase (AChE) activity in CSF by approximately 40% within the first 1.5 hours after administration. Activity of the enzyme returns to baseline levels about 9 hours after the maximum inhibitory effect has been achieved. In patients with Alzheimer's disease, inhibition of AChE in CSF by rivastigmine was dose-dependent up to 6 mg given twice daily, the highest dose tested. Inhibition of butyrylcholinesterase activity in CSF of 14 Alzheimer patients treated by rivastigmine was similar to that of AChE.

This decentralised procedure concerns a generic application claiming essential similarity with Exelon® 1.5/ 3 / 4.5 / 6 mg capsules (EU License EU/1/98/001-012) which have been registered through a centralised procedure by Novartis Europharm since 12 May 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. 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. To this end the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference products Exelon 1.5 mg and 6 mg hard capsules, registered in France. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. 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 in rivastigmine capsules is rivastigmine hydrogen tartrate, an established active substance not described in the European, British or US Pharmacopoeia*. The active substance is a white to almost white powder, very hygroscopic and is very soluble in water and soluble in methanol. 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
The manufacturing process consists of four steps. The used solvents have been described. No class 1 solvents or metal catalysts are used. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

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
Stability data on the active substance have been provided for 6 production-scale batches stored at 25°C/60% RH (up to maximally 60 months) and for 3 production scale batches at 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 and no additional storage requirements are justified.

** Pharmacopoeia official handbooks in which methods of analysis with specifications for substances are laid down by the authorities.*

Medicinal Product

Composition
Rivastigmine Peseri 1.5 mg – are yellow/yellow hard gelatine capsules imprinted with "*RIVA 1.5mg*" on body with black ink containing white to off-white granular powder of 1.5 mg of rivastigmine.
Rivastigmine Peseri 3 mg – are light orange/ light orange hard gelatine capsule imprinted with "*RIVA 3mg*" on body with black ink containing white to off-white granular powder of 3.0 mg of rivastigmine
Rivastigmine Peseri 4.5 mg – are caramel/caramel hard gelatine capsule imprinted with "*RIVA 4.5mg*" on body with black ink containing white to off-white granular powder of 4.5 mg of rivastigmine.
Rivastigmine Peseri 6 mg – are light orange/caramel hard gelatine capsule imprinted with "*RIVA 6mg*" on body with black ink containing white to off-white granular powder of 6.0 mg of rivastigmine.

The excipients are:
Capsule content - microcrystalline cellulose E460, hypromellose E464, colloidal anhydrous silica E551, magnesium stearate E572.
Capsule shell - yellow iron oxide E172, titanium dioxide E171, gelatin E441, iron oxide red, E172 (only for the 3.0, 4.5 & 6.0 mg capsule shells).
Printing ink - shellac, propylene glycol, concentrated ammonia solution, iron oxide black, potassium hydroxide.

The quantitative composition of the capsules is not dose proportional, but the ratio between the amounts of excipients is similar. The amount of microcrystalline cellulose differs marginally to compensate the differences in active substance. This is in line with the *NfG on the Investigation of Bioavailability and Bioequivalence* for preparations containing a low concentration of the active substance.
The capsules are packed into transparant PVC/Aluminium blisters.

The excipients and packaging are usual for this type of dosage form.

Container closure system
The capsules are packed into clear PVC/Al-blisters for commercial use. After final mix/lubrication the bulk granule or the capsules prior to blistering, might be stored in double transparent LDPE bags.

PVC/Aluminium-blisters
Certificates of analysis from both the supplier and the MAH, of the Aluminium and PVC blister material, are included in the dossier. Both materials comply with the specifications. The 250 µm PVC foil complies with Directive 2002/72/EC and with Ph.Eur. 3.1.11 requirements. The heat seal lacquer of the aluminium foil complies with Directive 2002/72/EC.

Bulk packaging
The LDPE bags meet the specification of Directive 2002/72/EC and Ph.Eur. 3.1.3 (polyolefines).
The compatibility and suitability of the packaging material with the drug product was verified with the in process holding time studies.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies were the investigation of the originator product Exelon for composition and dissolution profiles. The choices of the packaging and manufacturing process are justified. The different strengths of the drug product show a similar dissolution profile in media of pH 1.2, 6.8 and in water. A fast dissolution of more than 85 % in 15 minutes is shown for all capsule strengths. The composition of the biobatch is similar to the final product. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of pre-mixing, wet granulation, drying, sizing, final mixing and capsule filling. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 3 pilot scaled batches for the 3,

4.5 and 6 mg strengths and 3 production scale batches of the 1.5 mg strength. Process validation for full-scale batches of the 3, 4.5 and 6 mg strengths will be performed post authorisation.

Excipients

The excipients comply with Ph.Eur requirements. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identification, water content, disintegration, dissolution, average weight, uniformity of dosage units, assay, related substances and microbiological quality. The shelf-life requirements are not identical to the release requirements in respect to water content, dissolution and average weight. The proposed specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data have been provided on 3 pilot scale batches for the 3, 4.5 and 6 mg strengths and 3 full scale batches for the 1.5 mg strength, demonstrating compliance with the proposed release specification.

Microbiological attributes

The test for microbial contamination is included as a part of finished product specification to check the microbiological quality of the drug product, since some excipients may tend to support microbial growth. The drug product complies with the requirements for oral administration of Ph.Eur. 5.1.4 monograph (category 3a) on Microbiological Quality of Pharmaceutical Preparations (NMT 103 bacteria and NMT 102 fungi per g and absence of *E. coli* in 1 g).

Stability of drug product

Stability data on the product has been provided 3 pilot scale batches for the 3, 4.5 and 6 mg strengths and 3 full scale batches of the 1.5 mg strength, stored at 25°C/60% RH (24 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 transparent PVC/Al-blisters. At long-term conditions no clear trends or changes are observed. At accelerated conditions a decrease in assay and increase in total impurities is seen, an increase in disintegration time and a slight decrease in dissolution percentage. All tested parameters remain within the specified limits. The proposed shelf life of 36 months without additional storage requirements is justified.

The MAH has committed to continue the stability studies of the submitted batches according to the stability protocol up to 60 months. In addition, the first three production scale batches of each strength of drug product will be tested for their stability under both long term and accelerated conditions. Results at least up to the proposed shelf life are awaited as soon as available.

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

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

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.

For this generic application, the MAH has submitted two bioequivalence studies under fed conditions in which the pharmacokinetic profile of the test products Rivastigmine Peseri 1.5 mg and 6 mg hard capsules (Peseri Trading, Cyprus) is compared with the pharmacokinetic profile of the reference product Exelon 1.5 mg and 6 mg capsules (Novartis Europharm Limited, France). The fed conditions of the BE study are justified as the product is recommended to be taken with food, to improve bioavailability.

The choice of the reference product
Exelon tablets are registered via the centralised procedure and hence are presumed to be identical in all member states of the EEA.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study 1 – 1.5 mg capsules, single dose, fed conditions
A single centre, randomised, single-dose, open-label, 2-way crossover bioequivalence study was carried out under fed conditions in 36 healthy (12 male, 24 female) volunteers, aged 31 ± 9 years, race: 2 Black, 34 White, all non-Hispanic. After a supervised overnight fast of at least 10 hours, and 30 minutes before drug administration, subjects were served a standard breakfast. The breakfast consisted of one individual cereal box of Kellogg's Corn Flakes (27 g), one sugar packet, one carton of 2% M.F. milk (200 mL), 2 slices of toasted white bread, one Petit Quebec cheese (individual package, 21 g), two pats of butter, and one box of orange juice (200 mL). The pre-dose meal is considered a standardized non high-fat meal. The calorie content is for about 30% derived from fat. Subjects were required to consume this breakfast completely prior to drug administration.
Subjects were administered the test or reference medication as a single oral dose (1.5 mg) with 240 mL of water and subsequently fasted for a period of at least 4 hours. The treatment phases were separated by a washout period of 7 days.

Blood samples were collected prior to drug administration and at 0.333, 0.667, 1.00, 1.33, 1.67, 2.00, 2.25, 2.50, 2.75, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 6.00, 8.00, and 10.0 hours after administration of the products. The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
There were 4 drop-outs and 1 withdrawal before dosing, who was replaced. Thirty-two subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of rivastigmin under fed conditions.

Treatment N = 34	AUC_{0-t} pg.h/ml	$AUC_{0-\infty}$ pg.h/ml	C_{max} pg/ml	t_{max} h	$t_{1/2}$ h
Test	5673.36 ± 3182.90	5777.62 ± 3208.86	2570.98 ± 1331.50	2.00 (0.33 – 3.67)	0.91 ± 0.15
Reference	5561.05 ± 3280.76	5652.45 ± 3296.56	2447.74 ± 1238.39	2.00 (1.00 – 3.33)	0.91 ± 0.16
***Ratio (90% CI)**	1.03 (0.97 – 1.09)	1.03 (0.98 -1.09)	1.03 (0.96 -1.11)	---	---
CV (%)	12.5	12.0	17.2	---	---

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of rivastigmin under fed conditions, it can be concluded that Rivastigmine Peseri 1.5 mg hard capsules and the Exelon 1.5 mg capsules are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Bioequivalence study 2 – 6 mg capsules, single dose, fed conditions
A single centre, randomised, single-dose, open-label, 2-way crossover bioequivalence study was carried out under fed conditions in 36 healthy (21 male, 15 female) volunteers, aged 31 ± 9 years. After a supervised overnight fast of at least 10 hours, subjects were served breakfast. The breakfast consisted of: Kellogg's corn flakes, sugar, 2% milk, slices of bread, light cheddar cheese, butter, strawberry jam, orange juice (250 mL). The pre-dose meal is considered a standardized non high-fat meal. The calorie content is for about 30% derived from fat. Subjects were required to completely consume this breakfast within 30 minutes prior to drug administration. Subjects were administered the test or reference medication as a single oral dose of 1 capsule (6 mg rivastigmine) with 240 mL of water and subsequently fasted for a period of at least 4 hours. The treatment phases were separated by a washout period of at least 7 days.

In this study, dimenhydrinate was administered as a co-medication to alleviate or avoid nausea and vomiting associated with high dose of rivastigmine. Dimenhydrinate was administered as 75 mg (1.5 mL) by intra-muscular injection within 5 minutes after dosing and 3 hours after dosing.

Blood samples were collected prior to drug administration and at 0.333, 0.667, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 6.00, 8.00, 10.0, and 12.0 hours after administration of the products. The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
There were 4 drop-outs and 8 withdrawals. The withdrawals are equally distributed over Test and Reference product. The reason for withdrawals were mentioned in the study report, mostly because of vomiting or other side effects of the study medication. Twenty-four subjects aged 31 ± 9 years, race: 5 Black, 13 White, 2 Asian, and 4 other (7 Hispanic and 17 non-Hispanic) completed the study and were included in PK- and statistical analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of rivastigmin under fed conditions.

Treatment N = 24	**AUC_{0-t}** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	58568.12 ± 36179.10	59309.02 ± 36440.64	20293.78 ± 12234.23	2.00 (0.67 – 3.00)	1.34 ± 0.25
Reference	57966.72 ± 33129.24	58872.84 ± 33308.70	20359.67 ± 9717.83	2.00 (1.00 – 3.33)	1.38 ± 0.28
***Ratio (90% CI)**	0.99 (0.92-1.06)	0.98 (0.92-1.05)	0.96 (0.87 -1.05)	---	---
CV (%)	14.3	14.0	19.7	---	---

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of rivastigmin under fed conditions, it can be concluded that Rivastigmine Peseri 6 mg hard capsules and the Exelon 6 mg capsules are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Extrapolation of results to other strengths
The MAH claimed a biowaiver to the 3 mg and 4.5 mg strengths based on the following reasoning:
- All strengths are manufactured by the same process and manufacturer
- All strengths possess the same qualitative composition and the ratio between the excipients is considered similar (hard capsules have the same weight and the active substance comprises less than 5% of the total weight)
- All 4 strengths have similar dissolution profiles (all tested products release more than 85% in 15 minutes).
- Rivastigmine has linear pharmacokinetics up to 3 mg twice daily but is non-linear at higher doses. However, the BE studies have been performed with the lowest and the highest strength, which is the most sensitive approach to detect differences in the rate and extent of absorption between formulations.

The biowaiver is considered acceptable.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan
For the innovator product Exelon, a risk Management Plan has been constituted in which several safety issues have been identified.
The MAH commits to monitoring and reporting upon the following issues in the PSURS in line with the innovator's RMP:
- gastrointestinal symptoms (nausea, vomiting and diarrhoea),
- worsening of symptoms associated with Parkinson's disease (tremor, muscle rigidity, bradykinesia and falls),
- increased amylase, lipase and pancreatitis, cardiac arrhythmias, and exacerbation of asthma and chronic obstructive pulmonary disease (COPD),

- liver disorders including hepatitis,
- severe skin reactions (bullous, reactions),
- cardiac disorders (myocardial, infarction),
- hematuria,
- hypertension,
- cerebrovascular accident,
- urinary tract obstruction,
- seizures,
- gastrointestinal ulceration,
- pulmonary infections,
- death.

The MAH also commits to following, where appropriate, the risk minimisation activities of the innovator, e.g. participate in Direct Healthcare Professional Communications (DHPCs) where needed, produce and distribute educational material for patients and physicians when applicable, etc.

SPC
At the time of writing, the SPC submitted by the MAH is in line with that of the innovator. The MAH commits to update their SPC when safety variations are proposed by the authorities and also to propose safety variations on own initiative to keep it's SPC up-to-date, i.e. in line with that of the innovator.

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.

Setup
The test was conducted in 3 rounds: a pilot round involving 3 professionals, a first test round involving 10 participants, and a second Test round involving 10 participants. The recruitment method is clearly described in the report. A total of 20 participants were recruited by placing advertisements in the local press, contacts in local community groups and through random approaches to members of the public in the targeted age groups. All participants were potential users and could imagine their need to use or supervise the use of the medication. Health care personnel, persons employed in media or advertising, persons not fluent in the language being tested, persons refusing to take prescription medicines on principle and persons who had participated in user tests in the preceding 12 months were excluded. The age of the participants (11 females, 9 males) was >35 years (with 6 of the participants being > 65 years). A total number of 26 questions were asked. The first question solely served to let the participants feel more at ease during the interview. Eighteen questions specifically addressed the key safety messages of the leaflet in a randomised order; most of the other questions were meant to obtain a general impression of the package leaflet, including aspects as design and lay-out. It was determined whether the respondents were able to find the information and whether they understood the information and could act upon it. Both for locating the information and understanding the information, four categories (Very Easy, Easy, Slight Difficulty, Lots of Difficulty) were defined. Clear criteria for each of these categories were set. The participant's response to each question was scored according to these criteria. The criteria set for the categories Very Easy and Easy (understanding) do not exclude that an answer will be assigned to one of these categories (considered positive) if a participant reads out the correct text without hesitation, but does not understand it.

Results
Data are presented in clear figures and tables. The correct answers to the questions addressing the key elements of the leaflet are provided in the questionnaire; individual answers to these questions have not been provided. Individual answers to the questions regarding the general impression of the leaflet as well notes from the interviewers regarding each of the participants are included in the report. The package leaflet included in the report seems not be a mock-up of the tested leaflet. The mock-up of the leaflet submitted is of plain white text with no lay-out. Apart from the size of the leaflet no technical details of the leaflet have been provided.

The overall impression of the leaflet was positive. Five out of 20 participants indicated to prefer a bigger print size . However, this negative finding is not reflected in the scoring obtained for print size (only 2 out of 20 participants gave a score below 6) and the print size did not result in a failure to find and understand information. No weaknesses of the PL were identified from the questions specifically addressing the key safety issues or from the open questions aiming to identify positive and negative impressions of the PL (including lay-out). Nevertheless, the MAH proposed to replace "*somnolence*" by "*drowsiness*" in the section on driving and using machines. The proposal is deemed acceptable.

Conclusion
The results of the user testing are acceptable according to the guideline on the readability, because the criterion "*90% of literate adults are able to find the information requested within the package leaflet, of whom 90% can show that they understand it*" is fulfilled. The main objective of the readability testing has been examined, i.e. well-finding and well understanding. The key messages for the safe use of Rivastigmine capsules were identified and they were included in the questionnaire.

In summary, the package leaflet seems to be in line with the current readability requirements. The results show that the leaflet is easy to read and understandable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Rivastigmine Peseri 1.5 mg, 3 mg, 4.5 mg, and 6 mg hard capsules have a proven chemical-pharmaceutical quality and are generic forms of Exelon® 1.5 mg, 3 mg, 4.5 mg and 6 mg capsules. 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. Several commitments were made with regard to pharmacovigilance.

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 Peseri 1.5 mg, 3 mg, 4.5 mg, and 6 mg hard capsules with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 4 November 2010. Rivastigmine Peseri 1.5 mg, 3 mg, 4.5 mg, and 6 mg hard capsules are authorised in the Netherlands on 13 December 2010.

A European harmonised birth date has been allocated 12 May 1998 and subsequently the first data lock point for rivastigmine is 31 January 2011. The first PSUR will cover the period from approval to 31 January 2011, after which the PSUR submission cycle will be 6 monthly.

The date for the first renewal will be 1 October 2015.

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

Quality - medicinal product

- The MAH has committed to continue the stability studies of the submitted batches according to the stability protocol up to 60 months. In addition, the first three production scale batches of each strength of drug product will be tested for their stability under both long term and accelerated conditions. Results at least up to the proposed shelf life are awaited as soon as available.

List of abbreviations

AchE	Acetylcholesterase
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
CSF	CerebralSpinal Fluid
CV	Coefficient of Variation
DHPCs	Direct Healthcare Professional Communications
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