European Medicines Agency
Evaluation of Medicines for Human Use

ASSESSMENT REPORT
FOR

Rivastigmine Teva

International Non proprietary Name: rivastigmine

Procedure No. EMEA/H/C/001044

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Teva Pharma B.V submitted on 03 July 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Rivastigmine Teva, in accordance with the centralised procedure falling within the scope of the Annex to Regulation (EC) 726/2004 under Article 3 (3) – 'Generic of a Centrally authorised product'.

The application legal basis refers to Article 10(1) at the time of the opinion.

The chosen reference product is:

■ Reference medicinal product which is or has been authorised in accordance with the community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: **Exelon 1.5mg hard capsules, Exelon 3mg hard capsules, Exelon 4.5mg hard capsules, Exelon 6mg hard capsules**
- Marketing authorisation holder: **Novartis Europharm Limited**
- First authorisation: 12/05/98
- Member State (EEA)/Community: EU registration

■ Reference medicinal product authorised in the Community/Member State where the application is made:

- Product name, strength, pharmaceutical form: **Exelon 1.5mg hard capsules, Exelon 3mg hard capsules, Exelon 4.5mg hard capsules, Exelon 6mg hard capsules**
- Marketing authorisation holder: **Novartis Europharm Limited**
- Marketing authorisation number(s): **EU/1/98/066/001-3, EU/1/98/066/004-6, EU/1/98/066/007-9, EU/1/98/066/010-12, EU/1/98/066/014-16, EU/1/98/066/017.**

■ Medicinal Product used for bioequivalence study (where applicable)

- Product name, strength, pharmaceutical form: **Exelon 1.5 mg hard capsules, Exelon 6 mg hard capsules**
- Marketing authorisation holder: **Novartis Europharm Limited**
- Member State of source: UK

Rapporteur : Dr. Broich
Pharmacovigilance Rapporteur : Dr. Demolis

Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

Licensing status:

The product was not licensed in any country at the time of submission of the application.

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 03 July 2008.
- The procedure started on 23 July 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 October 2008.
- During the meeting on 17 - 20 November 2008, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 November 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 December 2008.
- The Rapporteur circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 January 2009.
- During the meeting on 16 – 19 February 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Rivastigmine Teva on 19 February 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 10 February 2009.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Rivastigmine Teva 1.5 mg, 3 mg, 4.5 mg, 6 mg hard capsules is a generic medicinal product containing rivastigmine hydrogen tartrate as the active substance. The reference product Exelon 1.5 mg, 3 mg, 4.5 mg and 6 mg hard capsules has been centrally authorised on 12 May 1998.

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.

The safety and efficacy of rivastigmine has been demonstrated in randomised, placebo-controlled trials in patients with Alzheimer's disease. A summary of these studies may be found in the EPAR of Exelon.

The indication proposed for Rivastigmine Teva is the same as for the authorized Reference medicinal product Exelon.

Rivastigmine Teva is indicated for the treatment of mild to moderately severe Alzheimer's dementia and treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease.

Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's dementia or dementia associated with Parkinson's disease.
Diagnosis should be made according to current guidelines. Therapy with rivastigmine should only be started if a caregiver is available who will regularly monitor intake of the medicinal product by the patient.

2.2 Quality aspects

Introduction

Rivastigmine Teva is presented as hard gelatin capsules containing 2.4 mg, 4.8 mg, 7.2 mg and 9.6 mg of rivastigmine hydrogen tartrate as active substance, corresponding respectively to 1.5 mg, 3 mg, 4.5 mg and 6 mg of rivastigmine. The other ingredients are microcrystalline cellulose, hydroxypropyl methyl cellulose, colloidal silicon dioxide, magnesium stearate, purified water, gelatin capsules and Imprinting Inks (shellac glaze-45% in ethanol, iron oxide black, N-butyl alcohol, Isopropyl alcohol, propylene glycol, ammonium hydroxide). The hard gelatin capsules are marketed in blister (PVC/alu) packed in cartons or in bottles (HDPE) with a white polypropylene cap. It was verified that the pack sizes are consistent with the posology and treatment duration as approved in the summary of product characteristics.

Active substance

The drug substance is Rivastigmine hydrogen tartrate and its chemical name is (S)-N-ethyl-3- [1-(dimethyl amino) ethyl] - N-methyl phenyl carbamate hydrogen tartrate according to the IUPAC nomenclature.
Rivastigmine hydrogen tartrate white to off-white fine crystalline powder, very hygroscopic and deliquescent. According the information described in the literature this active substance is very soluble in water, in ethanol and acetonitrile, slightly soluble in n-octanol and slightly soluble in ethyl acetate. It was noticed that rivastigmine hydrogen tartrate has one chiral centre. Therefore, it is optically active.

- **Manufacture**

Rivastigmine hydrogen tartrate is synthesised in three reactions steps. The manufacturing process has been adequately described. Critical parameters have been identified and adequate in-process controls included. Specifications for starting materials, reagents, and solvents have been provided. Adequate control of critical steps and intermediates has been presented. The active substance is purified by filtration. The purified active substance is finally packed in a double polythene bag enclosed within a triple laminated high barrier bag, which is placed in a fibre drum. Silica gel desiccant bags are at the top of the triple laminated high barrier bag. It was confirmed that the polythene bags comply with EU Directive 2002/72/EC and Ph.Eur. monograph 3.1.3 Polyolefines.
Structure elucidation has been performed by infrared absorption spectroscopy, ultraviolet spectroscopy, ^{1}H-NMR spectroscopy and mass spectroscopy. The molecular weight was determined by elemental analysis. Taking into account that the active substance has one chiral centre it was established that the specific optical rotation should be between +4.00 and +6.5 when calculated on dried basis.

- **Specification**

The active substance specifications include tests for appearance (white to off-white fine crystalline powder, very hydroscopic and deliquescent), identification (IR/ complies with the requirements of test for tartrate), water content (KF), sulphated ash (Ph.Eur.) assay (HPLC), release potency, heavy metals (Ph.Eur.), impurities (HPLC), residual solvents (GC) and particle size.
All specifications reflect the relevant quality attributes of the active substance. The analytical methods, which were used in the routine controls, were well described and their validations are in accordance with the relevant ICH Guidelines.
Impurities were described, classified as process related impurities and possible degradation products, and specified. Residual solvents were satisfactorily controlled in the active substance according to the relevant ICH requirements. Certificates of analyses for the active substances were provided and all batch analysis results comply with the specifications and show a good uniformity from batch to batch.

- **Stability**

The stability results from long-term and accelerated studies were completed according to ICH guidelines demonstrated adequate stability of the active substance. The following parameters were monitored during the stability studies: identification (IR), melting point, specific optical rotation, water content, assay (HPLC) and impurities (HPLC). It is important to underline that the test methods applied are those used for release of the drug substance. Following stress studies, which performed under heat, acidic and alkaline conditions, oxidizing conditions as well as under light stress conditions, it was concluded that no major changes occurred in the assay and chromatographic purity. Furthermore, the photatsability study that was performed in accordance with the note for guidance on photostability testing of new active substances and medicinal products (CPMP/ICH/279/95) confirmed that the active substance is not photosensitive since no degradation of the active substance has been observed. In can be concluded that the proposed re-test period is justified based on the stability results when the active substance is stored in the original packing material.

Medicinal Product

- **Pharmaceutical Development**

All information regarding the choice of the drug substance and the excipients are sufficiently justified.
The main aim of the applicant was to develop an oral immediate release capsule formulation bioequivalent to the reference product (Exelon). Due to the very low concentration of the active substance in the hard capsules, wet granulation was chosen as the method of manufacture for the proposed hard capsules in order to achieve the required content uniformity.
the EU submission batches were compared to the European Reference product (Exelon). The comparative dissolution profiles shows that there is a closely match in the 0.1 N HCl dissolution media. Furthermore, it was verified that the physical characteristics of the two innovators products are very similar.

All the excipients used are well known and commonly used in the pharmaceutical industry.

- **Adventitious Agents**

Neither the excipients nor the active substance is derived from human or animal origin. Certificates of suitability have been provided for the gelatine capsule which is of ruminant origin.

- **Manufacture of the Product**

The proposed commercial manufacturing process involves standard technology using standard manufacturing processes such as granulation, drying, milling, blending, final blend, encapsulation and packaging. Furthermore, the equipment used is commonly available in the pharmaceutical industry. It was verified that the critical steps of this manufacturing site have been identified and characterised. Furthermore, the manufacturing process has been adequately validated for two commercial scale batches (1.5mg and 6 mg) and for common granulation (3 mg, 4.5 mg and 6 mg) and the results of the manufacturing validation reports were considered satisfactory.

- **Product Specification**

The drug product specifications were established according the ICH guidelines and include the following tests: appearance, identification (UV/HPLC), identification of colorants, identification of tartaric acid, uniformity of weigh (Ph. Eur.), dissolution, assay, impurities and microbial limits (Ph Eur).
No new impurities have been arising compared to the active substance and the specifications have been justified.
All analytical procedures that were used for testing the drug product were properly described. Moreover, all relevant methods were satisfactorily validated in accordance with the relevant ICH guidelines.
The batch analysis data for two batches of each strength confirm that the hard capsules can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of the finished product.

- **Stability of the Product**

The stability studies were conducted according to the relevant ICH guidelines.
Two batches of each strength have been stored at long term, intermediate and accelerated conditions. The following parameters were controlled: description, appearance of capsule content, assay, dissolution, related substances and microbial limits.
Following the stress testing on the finished product it was concluded that the medicinal product is relatively stable under ultraviolet light irradiation, sonication, humidity and acid hydrolysis, somewhat susceptible to dry heat and base hydrolysis, and sensitive towards oxidation. The results of the photostability study that was conducted under ICH conditions demonstrated that the finished product is not affected by the exposure to the light.
Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture, control of the active substance and the finished product have been presented in a satisfactory manner and justified in accordance with relevant CHMP and ICH guidelines. The results of tests carried out indicate satisfactory consistency and uniformity of the finished product. Therefore, this medicinal product should have a satisfactory and uniform performance in the clinic. The bioequivalence studies indicate bioequivalence with the reference product (Exelon). At the time of the CHMP opinion, there was an unresolved quality issue, which will not have an impact on the benefit/risk ratio of the medicinal product. Therefore, it can be concluded that the quality characteristics of the finished product are adequate and should have a satisfactory and uniform performance in the clinic.

2.3 Non-Clinical aspects

This generic application is made in accordance with Article 10(1) of Directive 2001/83/EC. The applicant did not provide further non-clinical studies. However based on published pharmacological, toxicological and pharmacokinetic data, the properties of the active substance have been sufficiently described by the applicant in the non-clinical overview.
All impurities contained in the formulation of Rivastigmine Teva are below levels which would require any further qualification. Therefore additional non-clinical studies are not necessary. The SmPC is in line with that of the reference medicinal product.
No environmental risk assessment is required as the use of Rivastigmine Teva is unlikely to result in any significant increase in the combined sales volumes for all rivastigmine containing products.

2.4 Clinical Aspects

Introduction

This generic application concerns a medicinal product that contains the strengths of 1.5 mg, 3 mg, 4.5 mg and 6 mg rivastigmine in hard capsules. The proposed SmPC of the generic product is in line with the one of the reference medicinal product.
To support this application two single-dose, comparative bioequivalence studies (study: 2007-1526/ 1.5 mg strength and study: 2007-1527/ 6 mg strength) were submitted. Study: 2007-1527/ 6 mg strength being the pivotal study of this assessment. Bioequivalence determined at the 6 mg dose was extrapolated to the 3 mg and 4.5 mg strength. Furthermore a bioequivalence study with the 1.5 mg dose rivastigmine was conducted as it contains a separate granulation formulation

Scientific advice was not sought for the development programme. For the clinical assessment the Note for Guidance on Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) in its current version as well as the Questions & Answers on the Bioavailability and Bioequivalence Guidelines (EMEA/CHMP/EWP/40326/2006) are relevant.
GCP

The bioequivalence studies were complying with GCP, as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials 2007-1526 and 2007-1527 were conducted outside the community and were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Clinical studies

To support the application, the applicant has submitted two single-dose, comparative bioequivalence studies (study: 2007-1526 for the lowest 1.5 mg strength and study: 2007-1527 for the highest 6 mg strength). The objective of these studies was to evaluate the comparative bioavailability between Rivastigmine Teva and the originator Exelon from Novartis.

Since this is a generic application, no further clinical studies were required and the applicant provided none. The clinical overview provided an adequate summary of the clinical data of rivastigmine. It consists of an overview of the published literature regarding clinical pharmacodynamics, pharmacokinetics, safety and efficacy aspects of orally administered rivastigmine.

Pharmacokinetics

- Methods

STUDY DESIGN

Study: 2007-1526 (1.5 mg hard capsule) and Study: 2007-1527 (6 mg hard capsule)
In the two bioequivalence studies the 1.5 mg and 6 mg Rivastigmine Teva hard capsules were chosen for comparison to the originator (1.5 mg and 6 mg respectively Exelon hard capsules) in 40 healthy male subjects. A randomized crossover design in an open-label, single dose, two periods, two sequence bioavailability studies under standardized fed conditions was employed. The hard capsules (one capsule each) were administered with 240 ml of water after a standardized high fat, high calorie breakfast. Meals (xanthine-free) and beverages (caffeine-free) during further study conduct were also standardized
In each period, 19 blood samples from 18 time points were obtained from an arm vein of each subject by direct venipuncture or from an indwelling cannula. All blood samples were collected (prior to drug administration and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 5, 6, 8, 10 and 12 hours after dosing following drug administration) in pre-chilled, labelled 6 ml blood collection tubes containing K2EDTA as the anticoagulant.
All samples were stored at -20ºC ± 5ºC or colder pending shipment. The stored samples were then transferred to the analytical facility.

The washout interval between successive drug administrations was 7 days.

Concomitant treatment in study: 2007-1527 (6 mg hard capsule) only:
Subjects received two 75 mg doses of Gravol (dimenhydrinate, 50 mg/ml; Church & Dwight Canada Corp., Canada; Lot No.: KK6 3046) as intra muscular injections, in order to avoid vomiting at 10 minutes prior to rivastigmine dosing and at 3 hours post dosing.

The clinical part of the study as well as the analytical and statistical analysis was performed by a contract research organisation in Ontario, Canada.

TEST AND ORIGINATOR

Study: 2007-1526 (1.5 mg hard capsule)
Test Product: Rivastigmine 1.5 mg Capsules (Novopharm Limited, Canada);
Lot No.:35300619;
Manufacturing Date: 26/07/2007
Originator: Exelon 1.5 mg Capsules (Novartis Europharm Limited, United Kingdom);
Lot No.: B5070;
Expiration Date: 10/2011

Study: 2007-1527 (6 mg hard capsule)
Test: Rivastigmine Teva 6 mg hard capsules (Novopharm Limited, Canada);
Lot No.: 35300656
Originator: EXELON 6 mg hard capsules (Novartis Europharm Limited, United Kingdom);
Lot No.: B8018

POPULATIONS STUDIED

Study: 2007-1526 (1.5 mg hard capsule)
40 healthy male non-smoking subjects were enrolled and received either test or originator. One subject (subject 19) voluntarily withdrew from the study prior to period 2 due to personal reasons. The plasma samples from 39 subjects were assayed for rivastigmine. Of the 39 subjects who completed the study, 19 were Caucasian, 6 were Black, 7 were Asian and 7 were Hispanic. The demographics of the subjects are summarised in table 1.
Inclusion and exclusion criteria were presented and were acceptable for the product and for this type of study.

Table 1: Demographics of participants in study 2007-1526

Subject No.	Age (years)	Height (cm)	Height (in)	Weight (kg)	Weight (lb)	BMI
All Subjects (N = 40)						
Mean	34	174.9	68.9	78.6	173.2	25.7
+/- SD	10	7.3	2.9	9.5	20.9	2.5
Median	35	176	69.3	79.4	175	25.6
Range	20-54	160-187.5	63-73.8	56.4-95.8	124.3-211.2	20.5-29.8
Subjects Completed (included in the data analysis) (N = 39)						
Mean	34	174.7	68.8	78.6	173	25.7
+/- SD	10	7.3	2.9	9.5	21.1	2.5
Median	35	176	69.3	79.4	176.6	25.6
Range	20-54	160-187.5	63-73.8	56.4-95.8	124.3-211.2	20.5-29.8

Study: 2007-1527 (6 mg hard capsule)
40 healthy male non-smoking subjects were enrolled and received either test or originator.
Five subjects withdrew from the study, three of them due to adverse events (AE) and two due to protocol non-compliance.
The plasma samples from 35 subjects were assayed for rivastigmine.
Of the 35 subjects who completed the study, 24 were Caucasian, 6 were Black, 4 were Asian and 1 was Hispanic. The demographics of the subjects are summarised in table 2.
Inclusion and exclusion criteria were presented and were acceptable for the product and for this type of study.

Table 2: Demographics of participants in study 2007-1527

Subject No.	Age (years)	Height (cm)	Height (in)	Weight (kg)	Weight (lb)	BMI
All Subjects (N = 40)						
Mean	38	177.9	70	84.1	185.4	26.5
+/- SD	9	7.2	2.8	9.6	21.1	2.2
Median	38	178.3	70.2	83.3	183.6	27
Range	19-54	157-192	61.8-75.6	64.3-102.9	141.8-226.9	21.5-29.6
Subjects Completed (included in the data analysis) (N = 35)						
Mean	37	178.3	70.2	84.4	186	26.5
+/- SD	9	7.2	2.9	10	22.1	2.2
Median	37	178.5	70.3	83.4	183.9	26.9
Range	19-54	157-192	61.8-75.6	64.3-102.9	141.8-226.9	21.5-29.6

ANALYTICAL METHODS

Study: 2007-1526 (1.5 mg hard capsule) and Study: 2007-1527 (6 mg hard capsule)
The bioanalytical procedure for the determination of Rivastigmine from human plasma treated with K2EDTA anticoagulant was as follows:
Subject plasma concentrations of Rivastigmine were measured according to a liquid chromatographic (LC) tandem mass spectrometric detection (MSMS) method. The method involved liquid-liquid extraction.

PHARMACOKINETIC VARIABLES

Study: 2007-1526 (1.5 mg hard capsule) and Study: 2007-1527 (6 mg hard capsule)
The pharmacokinetic parameters AUC_t, AUC_{inf}, C_{max}, T_{max}, K_{el} and $T_{1/2}$ were estimated based on rivastigmine plasma levels for each subject included in the statistical analysis.

STATISTICAL METHODS

Study: 2007-1526 (1.5 mg hard capsule) and Study: 2007-1527 (6 mg hard capsule)

Pharmacokinetics:
Statistical analysis was applied to quality assured data from all subjects in the final data set. The PROC GLM procedure from SAS was used.
Analysis of variance (ANOVA) was applied to log-transformed AUC_t, AUC_{inf}, C_{max} and to untransformed K_{el} and $T_{1/2}$ parameters. The significance of the sequence, period, treatment and subject (within sequence) random effects were tested. Using the same statistical model, the least square means, the differences between the treatments least square means, and the corresponding standard errors of these differences were estimated for log-transformed AUC_t, AUC_{inf} and C_{max} parameters. Based on these statistics the ratios of the geometric means for treatments and their 90% confidence intervals were calculated. Values for the Tmax parameter were analyzed by a non-parametric approach. Based on the log-transformed parameters, the following criteria were used to evaluate the bioequivalence between the test and originator:

- The 90% confidence intervals of the relative mean AUC_t, AUC_{inf} and C_{max} of the test to originator should be between 80% and 125%.

Sample size determination:
Taking into account an intra-subject variability for rivastigmine Cmax of approximately 27% under fed conditions. Assuming a 30% intra-subject variability and a difference between the treatment means of 5% or less (true ratio of treatment means between 95 and 105), the necessary sample size for a 75% probability of the 90% confidence interval of the treatment means ratio to be within the 80-125% range was estimated to be 34 subjects.

The statistical methods were deemed adequate for the analysis of the data.

- Results

Study No.: 2007-1526 (rivastigmine 1.5 mg)

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD)

Treatment	**AUC_{0-t}** ng/ml*h	**$AUC_{0-\infty}$** ng/ml*h	**C_{max}** ng/ml	**t_{max}** h	**$T_{1/2}$** h
Test	5.73	5.99	2.18	2.62	0.98
Reference	5.55	5.78	2.08	2.67	0.88
***Ratio (90% CI)**	103.32 (98.21 - 108.70)	103.62 (98.66 - 108.82)	104.83 (97.56 - 112.64)		
CV (%)	13%	13%	19%		

$AUC_{0-\infty}$	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

**lg-transformed values*

The 90% confidence intervals of the relative mean rivastigmine AUC_t, AUC_{inf} and C_{max} of the test to originator are within the 80-125% range.
Therefore, Rivastigmine 1.5 mg Capsules (Novopharm Limited, Canada) exhibited equivalent rate and extent of absorption to Exelon 1.5 mg Capsules (Novartis Europharm Limited, United Kingdom) in healthy subjects after an oral single-dose, under fed conditions.

Study No.: 2007-1527 (rivastigmine 6 mg)

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD)

Treatment	**AUC_{0-t}** ng/ml*h	**$AUC_{0-\infty}$** ng/ml*h	**C_{max}** ng/ml	**t_{max}** h	**$T_{1/2}$** h
Test	68.53	69.32	18.74	2.66	1.44
Reference	64.01	64.93	18.26	2.74	1.46
***Ratio (90% CI)**	107.06 (101.21 - 113.25)	106.75 (101.00 - 112.83)	102.61 (97.34 - 108.17)		
CV (%)	14%	14%	13%		

$AUC_{0-\infty}$	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

**lg-transformed values*

A statistically significant difference (α= 0.05) was detected between the two periods of the study in the analysis of K_{el} (p=0.0465) and T_{half} (p=0.0227). All clinical procedures were under strict control and were kept the same between the two periods of the study. Hence, it is possible that the observed effect is due solely to chance. The least-squares means of the treatment effect were adjusted for the period effect. Therefore, the final results are not influenced by the statistically significant period effect noticed for K_{el} and T_{half} parameters.

A significant treatment effect was detected by ANOVA for AUC_t parameter (p=0.0480). However it is considered that the statistically significant difference has no clinical importance since the 90% confidence intervals for the relative mean $AUC_{0-t,}$ $AUC_{0-\infty}$ and C_{max} are contained within the 80 – 125% range.

Therefore, Rivastigmine 6 mg capsules (Novopharm Limited, Canada) exhibited equivalent rate and extent of absorption to Exelon 6 mg capsules (Novartis Europharm Limited, United Kingdom) in healthy subjects after an oral single-dose, under fed conditions.

Systemic concomitant medication has been applied to all subjects (2x 75 mg dimenhydrinate intra muscular) however no interaction of rivastigmine and dimenhydrinate in regard to PK is expected.
Cytochrome P450 isozymes are minimally involved in rivastigmine metabolism and no drug interactions related to cytochrome P450 have been observed in humans. Dimenhydrinate on the other hand is metabolized by the liver primarily by the cytochrome P450 isozymes. Additionally the absorption of the rivastigmine tables would not have been affected by the intra muscular co-administration of the antiemetic, since the dimenhydrinate would not have interfered with oral absorption. Furthermore there is no published data indicating that there is a pharmacokinetic interaction between rivastigmine and dimenhydrinate.

Protocol deviations

Study No.: 2007-1527 (rivastigmine 6 mg)
None of the protocol deviations had a significant impact on the safety of the subjects or on the integrity of the study results.

Safety

Study: 2007-1526 (1.5 mg hard capsule)
There were 43 adverse events (AE) in 27 subjects from the test and originator treatment groups. The most commonly reported adverse event was increased creatinine levels. The AE did not require any intervention; all of them were graded as mild.
No relevant difference between number and severity of AE was found between the tested drug (Rivastigmine Teva) and the originator (EXELON).

Study: 2007-1527 (6 mg hard capsule)
There were 226 adverse events (AE) involving 39 subjects from the test and originator treatment groups. The most commonly reported AE were pain at injection site, somnolence (might have been caused by dimenhydrinate or rivastigmine), edema at injection site and increased creatinine levels. All of them were graded as mild and none of the AEs had a significant impact on the safety of the subjects or on the integrity of the study results.
Three subjects (subject 07, 40 and 02) withdrew from the study due to adverse events (AE):

- Subject 07 prior to Period 2 check-in due to AE (body ache, burning sensation and pain in the throat)
- Subject 40 after Period 1 dosing due to AE (vomiting)
- Subject 02 after Period 2 dosing due to AE (vomiting)

No relevant difference between number and severity of AE was found between the tested drug (Rivastigmine Teva) and the originator (EXELON).

Transferability of study results to other strengths

The Applicant claims that the bioequivalence studies with rivastigmine 1.5 mg and 6 mg hard capsules also prove bioequivalence for the 3 mg and 4.5 mg strengths hard capsules.
Rivastigmine exhibits non linear kinetics with more than proportional increase in AUC and C_{max} with the dose without dose accumulation. Therefore a bioequivalence study with the highest dose of 6 mg rivastigmine is submitted in accordance with the Questions and Answers on the Bioavailability and Bioequivalence Guideline EMEA/CHMP/EWP/40326/2006, Section 9.
The 1.5 mg strength is a separate granulation formulated to be proportional to the 3 mg strength. The 3 mg, 4.5 mg and 6 mg is formulated as an all strength granulation (common/geometric granulation). Therefore a bioequivalence study with the 1.5 mg dose rivastigmine was submitted in addition.
All the strengths are manufactured by the same manufacturer and process. The qualitative composition of all strengths is the same. The ratio between the amounts of excipients is similar.
Dissolution tests with release medium (0.1 N HCL), pH 6.8 phosphate buffer and pH 4.5 acetate buffer showed comparable dissolution profiles to the originator Exelon from Novartis and the rapid drug release from Rivastigmine Teva hard capsules in all three media could be confirmed.
In conclusion extrapolation of the results obtained for the 1.5 mg and 6 mg rivastigmine hard gelatine capsules to the 3 mg and 4.5 mg capsules was deemed acceptable.

- Conclusions

Based on the two presented bioequivalence studies Rivastigmine Teva 1.5 mg and 6 mg hard capsules are considered bioequivalent with Exelon 1.5 mg and 6 mg hard capsules.

The results of study 2007-1527 with the 6 mg strength can be extrapolated to the 3 mg and 4.5 mg strengths, according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4.

Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.5 Pharmacovigilance

- **Description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements. The company must ensure that this system is in place and functioning before the product is placed on the market. The company should ensure that the pharmacovigilance activities are in line with the current safety measures applied to the reference medicinal product.

- **Risk Management Plan**

A Risk Management Plan was not submitted. Since the application concerns a generic of a reference medicinal product for which no safety concerns requiring additional risk minimisation activities have been identified, a Risk Management Plan was not required.

- **PSUR**

The PSUR submission schedule for Rivastigmine Teva hard capsules should follow the PSUR schedule for the reference medicinal product (Exelon).

- **User consultation**

The results of user consultation provided indicates that the package leaflet is well structured and organised, easy to understand and written in a comprehensible manner. The test shows that the leaflet is readable in patients /users are able to act upon the information that it contains.

Discussion on Clinical aspects

Two single doses two periods, two sequences cross over bioequivalence studies under fed conditions were conducted to support the marketing authorisation application for four generic products containing 1.5 mg, 3 mg, 4.5 mg and 6 mg rivastigmine.

The study was conducted under fed conditions and the SmPC of the originator recommends drug intake with food twice a day (in the morning and evening). The starting dose in adults is 1.5 mg and can be gradually increased, depending on how the patient responds to the treatment. The recommended maximum daily dose is 6 mg.
Rivastigmine exhibits non linear kinetics with more than proportional increase in AUC and C_{max} with the dose without dose accumulation. Therefore the highest dose of 6 mg was tested. Furthermore a bioequivalence study with the 1.5 mg dose rivastigmine was conducted as it contains a separate granulation formulation.

In the 1.5 mg rivastigmine bioequivalence study the 90% confidence intervals of the relative mean rivastigmine AUC_t, AUC_{inf} and C_{max} of the test to originator are within the 80-125% range. In the 6 mg rivastigmine bioequivalence study a significant treatment effect was detected by ANOVA for AUC_t parameter (p=0.0480). It is considered that the statistically significant difference has no clinical importance since the 90% confidence intervals for the relative mean $AUC_{0-t,}$ $AUC_{0-\infty}$ and C_{max} are contained within the 80 – 125% range.

In the 1.5 mg bioequivalence study 39 out of 40 subjects were included in the data analysis due to withdrawal of one subject for personal reasons.
In the 6 mg bioequivalence study 35 out of 40 subjects were included in the data analysis due to withdrawal of five subjects for occurrence of adverse events (three subjects) and protocol non-compliance (two subjects). Subject 09 who did not reveal any rivastigmine in his plasma throughout period two was still included in the data analysis but his pharmacokinetic values were set to missing.
The CHMP agreed to this approach.

The adverse events in both studies were graded mild and comparable to the reference medicinal product. In the higher dose bioequivalence study (6 mg) concomitant medication with dimenhydrinate has been applied intra muscular to all subjects and a pharmacokinetic interaction between rivastigmine and dimenhydrinate was deemed unlikely.

Based on the available data it is concluded that bioequivalence of the product containing 1.5 mg and 6 mg rivastigmine has been demonstrated. On the grounds of the non linear pharmacokinetics of rivastigmine and the separate granulation formulation of the 1.5 mg dose the selected doses for the bioequivalence studies are acceptable and the 6mg strength can be extrapolated to the 3 mg and 4.5 mg strength.

2.6 Overall conclusions, benefit/risk assessment and recommendation

Overall conclusion and Benefit/risk assessment

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. At the time of the CHMP opinion, there were a few minor unresolved quality issues, which do not have any

impact on the benefit/risk ratio of the medicinal product. These will be addressed as part of the follow-up measures post-authorisation.

The application contains adequate non clinical and clinical data and the bioequivalence has been shown. A benefit/risk ratio comparable to the originator can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

Recommendation

Based on the CHMP review of available data, the CHMP considered by consensus that the benefit/risk ratio of Rivastigmine Teva (1.5 mg, 3 mg, 4 mg and 6 mg strengths hard capsules) in the treatment of mild to moderately severe Alzheimer's dementia, mild to moderately severe dementia in patients with idiopathic Parkinson's disease was favourable and therefore recommended the granting of the marketing authorisation.