MINISTERIO
DE SANIDAD, CONSUMO
Y BIENESTAR SOCIAL

agencia española de
medicamentos y
productos sanitarios

# Public Assessment Report
# Scientific discussion

# Rivastigmine Brill Pharma 1.5 mg, 3 mg, 4.5 mg and 6 mg hard capsules

## Rivastigmine hydrogen tartrate

## ES/H/0310/001-004/DC

## Applicant: BRILL PHARMA S.L.

This module reflects the scientific discussion for the approval of **Rivastigmine Brill Pharma 1.5 mg, 3 mg, 4.5 mg and 6 mg hard capsules.** The procedure was finalised on May 2016. For information on changes after this date please refer to the module 'Update'.

(1) El nombre del medicamento y el titular de la autorización de comercialización pueden haber sufrido cambios después de la autorización.

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## INTRODUCTION

This decentralised procedure concerns a generic application of rivastigmine hydrogen tartrate, under Rivastigmine Brill Pharma 1.5 mg, 3 mg, 4.5 mg and 6 mg hard capsules trade names, according to Article 10(1) of Directive 2001/83/EC. In this Assessment Report, the name Rivastigmine is used. Rivastigmine Brill Pharma 1.5 mg, 3 mg, 4.5 mg and 6 mg hard capsules have the same qualitative and quantitative composition in active substance (rivastigmine hydrogen tartrate) and same pharmaceutical form as the reference product Exelon 1.5, 3, 4.5 and 6 mg hard capsules (Novartis Europharm Limited).

The originator product Exelon 1.5, 3, 4.5 and 6 mg hard capsules, by Novartis Europharm Limited, United Kingdom, was approved through the centralised procedure on May 12th, 1998.

With Spain as Reference Member State in this Decentralised Procedure, Brill Pharma, S.L. is applying for the Marketing Authorisations of Rivastigmine Brill Pharma 1.5 mg, 3 mg, 4.5 mg and 6 mg hard capsules in DE and UK.

Rivastigmine is a second generation cholinesterase inhibitor. Rivastigmine is an acetyl- and butyryl-cholinesterase inhibitor (dual action inhibitor) of the carbamate type which is thought to facilitate cholinergic neurotransmission by slowing the degradation of acetylcholine released by functionally intact cholinergic neurones. Rivastigmine interacts with its target enzymes by forming a covalent complex that temporarily inactivates the enzymes.
Rivastigmine is indicated in symptomatic treatment of mild to moderately severe Alzheimer's dementia and in symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease.

The starting dose is 1.5 mg twice a day. The recommended maximum daily dose is 6 mg twice a day.
A comprehensive description of the product information is given in the SmPC.

## RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Member States have granted a marketing authorisation for **Rivastigmine Brill Pharma 1.5 mg, 3 mg, 4.5 mg and 6 mg hard capsules** for Brill Pharma, S.L.

## I. SCIENTIFIC OVERVIEW AND DISCUSSION

### II-1 Quality aspects

### ACTIVE SUBSTANCE

The active substance is Rivastigmine hydrogen tartrate and it is described in the Ph.Eur. The applicant has used the ASMF procedure.

Description of the manufacturing process is adequate. Elucidation and characterization of the drug substance are sufficient. The control tests and specifications for the drug substance are adequately drawn up. Analytical methods are correctly described and their validation is performed according to ICH. Certificates of analysis of the drug substance complying with Rivastigmine hydrogen tartrate Ph.Eur, monograph, have been presented.

The material used for the container closure system complies with European legislation on plastic materials and articles intended to come into contact with food and with Ph.Eur. This container closure system is similar to the one used in the stability studies.

Stability studies have been performed according to ICH/CPMP guidelines and guarantee the proposed retest period and storage conditions.

**FINISHED PRODUCT**

**Description of the product**
Capsule, Hard (capsules):

1.5 mg: Yellow/yellow hard gelatin capsule (with a closed length of 18 mm ±0.5 mm) of size "2" imprinted with "RIVA 1.5mg" on body with black ink.

3 mg: Light orange/ light orange hard gelatin capsule (with a closed length of 18 mm ±0.5 mm) of size "2" imprinted with "RIVA 3mg" on body with black ink.

4.5 mg: Caramel/caramel hard gelatin capsule (with a closed length of 18 mm ±0.5 mm) of size "2" imprinted with "RIVA 4.5mg" on body with black ink.

6 mg: Light orange/caramel hard gelatin capsule (with a closed length of 18 mm ±0.5 mm) of size "2" imprinted with "RIVA 6mg" on body with black ink.

The qualitative composition is as follows:

- Microcrystalline cellulose
- Hypromellose 5cP
- Silica, colloidal anhydrous
- Magnesium stearate
- Capsule: Yellow iron oxide E172, Titanium dioxide E171, Red iron oxide E172 (only in 3, 4.5 and 6 mg capsules) and Gelatin.
- Printing ink: Shellac, black iron oxide E-172

The hard capsules are packed in transparent PVC/Aluminium blisters.

**Pharmaceutical development**
The pharmaceutical development has been adequately described.
The company has identified the physico-chemical properties of the active substance that are relevant for the product performance. The function and compatibility of the excipients have been adequately discussed.
An *in vitro* release test has been developed. The data provided support its use and the release specification.

**Manufacture of the product and process controls**
The manufacturing process is sufficiently described and the process controls are appropriate, considering the nature of the product and the manufacturing method.
The commercial batch size is defined.
The dossier includes sufficient validation data to guarantee that the manufacturing process is controlled and to ensure batch to batch reproducibility and compliance with product specifications.

**Excipients**
The information provided is adequate. The specifications for the different excipients are justified by their official adoption in the relevant Ph.Eur. monograph, by specifications in accordance with Commission Directive 95/45/EC laying down specific purity criteria concerning colours for use in foodstuffs or by the quality standards of USP-NF. The CEPs of the capsules suppliers have been provided. The supplier of the magnesium stearate has certified its vegetable origin and thus is not involved in the BSE/TSE risk.

**Product specification**
The finished product specification is acceptable. All the analytical methods are sufficiently described. Validation data of methods according to ICH requirements have been submitted.

**Container closure system**
The proposed packaging material is commonly used in pharmaceutical industry. The certificates of compliance for the packaging materials with European legislation on plastic materials and articles intended to come into contact with food and with Ph.Eur., have been provided.

**Stability of the product**
The stability studies have been performed following the ICH guidelines. The stability data support the proposed shelf-life and storage conditions.

## II-2 Non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of rivastigmine hydrogen tartrate are well known. As rivastigmine hydrogen tartrate is a widely used, well-known active substance, the Applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

**Environmental Risk Assessment (ERA)**
No Environmental Risk Assessment was submitted. This was justified by the Applicant as the introduction of Rivastigmine Brill Pharma manufactured by Genepharm S.A. is considered unlikely to result in any significant increase in the combined sales volumes for all rivastigmine containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.
The justification for the absence of ERA is considered acceptable.

## II.3 CLINICAL ASPECTS

### INTRODUCTION

To support the application, the Applicant has submitted two bioequivalence studies:

- A single centre, open-label, single-dose, randomized, 2-way cross-over, 2-period, 2-sequence design administered as a 1 x 6 mg capsule in fed conditions with a wash-out period of 7 days.
- A single centre, open-label, single-dose, randomized, 2-way cross-over, 2-period, 2-sequence design administered as a 1 x 1.5 mg capsule in fed conditions with a wash-out period of 7 days.

The application concerns an oral immediate release formulation (capsules) with systemic action of a known active substance with a more than dose-proportional increase in AUC and $C_{max}$. In addition, as described in the reference product SmPC, rivastigmine should be taken with food. Therefore, one single dose bioequivalence study under fed conditions with the highest strength (6 mg) is considered suitable for the application with a possible biowaiver for 1.5 mg, 4.5 mg and 3 mg strengths.

Furthermore, a bioequivalence study with the 1.5 mg dose rivastigmine was also conducted in fed conditions as the Applicant considers that when proof of linear absorption is lacking or if evidence of non-linearity is available, bioequivalence between the test and reference formulations should be established with both the lowest and the highest strengths. This approach is considered by the Applicant the most sensitive for detecting differences in rate and extent of absorption for substances with dose-dependent pharmacokinetics.

Therefore, the bioequivalence was assessed in two BE studies at 1.5 mg and 6.0 mg strengths.

According to the Guideline on the investigation of bioequivalence if several strengths of a test product are applied for, it may be sufficient to establish bioequivalence at only one or two strengths, depending on the proportionality in composition between the different strengths. In addition, for products where the general biowaiver criteria are fulfilled, it is sufficient to establish bioequivalence with only one strength and this strength for drugs with non-linear pharmacokinetics characterised by a more than proportional increase in AUC with increasing dose over the therapeutic dose range should in general be conducted at the highest strength. In this case, as rivastigmine exhibits a more than dose proportional increase in AUC and $C_{max}$ and the general biowaiver criteria are fulfilled (please refer to biowaiver section) a bioequivalence study with the highest strength (6 mg) might have been sufficient.

The trial has been conducted in compliance with GCP requirements. Monitoring reports have been submitted. QA statement of audits assuring compliance to GCP were issued by Head-QA. The clinical, the analytical, the pharmacokinetic and the statistical sites were inspected by Regulatory Authorities of the European Union without critical findings.

**Biowaiver**

The application concerns 1.5 mg, 3 mg, 4.5 mg and 6 mg hard capsules. The bioequivalence studies were carried out with the 1.5 mg and the 6 mg strength. A biowaiver for 3 mg and 4.5 mg strengths is claimed based on the following general requirements described in section 4.1.6 of the Guideline on Investigation of BE.

These data can be extrapolated to the additional strengths (i.e., 3 mg and 4.5 mg) since all the requirements described in section 4.1.6 of the Bioequivalence Guideline are fulfilled.

**Bioequivalence**

The Applicant has submitted two bioequivalence studies for this application.

Study Code: 70467

This was a single-dose, randomized, open-label, 2-way cross-over, bioequivalence study between Rivastigmine 6 mg hard capsules (Genepharm, S.A., Greece) and Exelon 6 mg hard capsules (Novartis Farmacéutica, S.A., Spain) in healthy male and female volunteers under fed conditions with a wash-out period of seven (7) days.

The study was performed from May 30$^{th}$, 2008 to June 10$^{th}$, 2008 at Anapharm 4101 Yonge Street, Suite 600 P.O. BOX 222 Toronto (Ontario), Canada and the principal investigator was Shafik Dharamshi, M.D.

The analytical part was conducted at Anapharm 2500, rue Einstein Quebec (Quebec), Canada G1P OA2, from June 17$^{th}$, 2008 to July 21$^{st}$, 2008.

The application concerns an immediate release capsule that should be taken with food as described in the innovator SmPC, therefore a single dose study under fed conditions is considered acceptable to demonstrate bioequivalence with the reference product.

The wash-out period of 7 days (greater than 5 half-lives) is considered adequate since the drug half-life is approx. one hour and pre-dose levels was not detected.

Considering the expected time to peak concentration (0.8-1.2 hours) and the elimination half-life of rivastigmine, the sampling schedule and the sampling time period of 12 hours seems long enough to estimate PK parameters.

Sampling is reasonably frequent every 20 minutes up to 3 hours and should be sufficient to allow an accurate measurement of $C_{max}$ and $t_{max}$.

Test and reference products

Test Product: Rivastigmine 6 mg hard capsules manufactured by Genepharm S.A., Greece. Batch number: DRV-6-2. Batch size: 100,000 hard capsules. Expiry date (Re-test): March 2009 (as per CoA). Assay (content): 101.7 % of label claim.

Reference Product: Exelon 6 mg hard capsules, manufactured by Novartis Farmacéutica, S.A. (from the Spanish market). Batch number: B8028. Expiry date: May 2012. Assay (content): 102.8% of label claim. Both batches were tested before expiry date and the CoA shows a similar content. Therefore, content correction is not necessary.

The test and reference product are adequate for a generic application. The reference product is from the Spanish market.

After a supervised overnight fast of at least 10 hours, subjects were served a normocaloric breakfast. Subjects were required to completely consume this breakfast within 30 minutes prior to drug administration. Subjects were dosed on the mornings as a single oral dose of 1 capsule containing 6 mg of rivastigmine, with 240 mL of water.

The study was conducted using normo-caloric diet instead of high-caloric diet as no recommendation on the composition of the meal is given on the SmPC of the reference product, Exelon®, but taking into account the kind of patients that will take the product, these patients are not expected to take a high-fat diet.

Thirty-six (36) subjects received the study medication according to the randomization list in period I and twenty-seven (27) subjects in period II. Twenty-four (24) subjects finalized the study and twenty-four (24) were analysed and included in the statistical analysis.

The following subjects were withdrawn:

- Subjects No. 05 and No. 06 for test product and subject No. 01 and No. 25 for the reference product in period I and subject No. 18 for test product and subject No. 08 for reference product in period II due to vomiting within 8 hours after dosing.
- Subject No. 11 in period I for personal reason.
- Subject No. 12 in period I due to adverse event (increased blood pressure).
- Subject No. 23 in period II due to adverse events (decreased blood pressure and pre-syncope).
- Subject No. 27 in pre-dose due to adverse event (dizziness). This subject was replaced by stand by subject B.
- Subject No. 31 in period I due to adverse event (nausea).
- Subject No. 33 in period I due to adverse event (headache and loose stools).
- Subject No. 35 in period I did not show-up for confinement in period II
- Subject No. 36 in pre-dose due to adverse event (increased blood pressure). This subject was replaced by stand by subject A.

The study population is considered acceptable with regards to demographic characteristics. The inclusion and exclusion criteria are considered to be acceptable.

Protocol deviation

The drawing blood time deviations were minor and they had no impact on the study outcome as actual time points were used for pharmacokinetic and statistical analysis.

*Analytical methods*

The analytical method has been adequately validated before the conduct of the study and during the analysis of the subject samples. Therefore, the analytical method is considered acceptable for analysis of the plasma samples.

*Pharmacokinetic data analysis*

Pharmacokinetic analysis of the plasma concentrations for rivastigmine was carried out using SAS® version 8.2. This software performed non-compartmental analyses for pharmacokinetic parameters and statistical analyses (via SAS® version 8.2)

*Primary Parameters*

The following pharmacokinetic parameters were calculated $AUC_{0-t}$ (calculated using linear trapezoidal method), $AUC_{0-\infty}$ and $C_{max}$.

*Secondary Parameters*

The following pharmacokinetic parameters were calculated $t_{max}$, AUC_%Extrap_obs (%), $\lambda z$, and $t_{1/2}$.

*Statistical analysis*

Using GLM procedure in SAS® (version 8.2), analysis of variance (ANOVA) was performed on the ln-transformed pharmacokinetic parameters $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$. The ANOVA model included sequence, treatment and period as and subjects nested within sequence as fixed effect.

Two one-sided 90% confidence intervals for the ratio of means between drug formulations were calculated for Ln-transformed data of $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$.

The results are summarized in the tables below.

| Parameter | Ratio (Test/Reference) | 90% Confidence Interval | CV% |
|---|---|---|---|
| Ln ($AUC_{0-t}$) | 98.60% | 91.86%-105.53% | 14.30% |
| Ln ($C_{max}$) | 95.61% | 86.78%-105.34% | 19.67% |
| Ln ($AUC_{0-\infty}$) | 98.28% | 91.72%-105.31% | 13.95% |

Based on the statistical analysis submitted by the Applicant, the test product is equivalent to the reference with respect to the extent and rate of absorption/exposure as the 90% confidence intervals for the ln-transformed $AUC_{0-\infty}$, $AUC_{0-t}$ and $C_{max}$ are within the acceptance range of 80-125%.

Study Code: 70324

This was a single-dose, randomized, open-label, 2-way cross-over, bioequivalence study between Rivastigmine 1.5 mg hard capsules (Genepharm, S.A., Greece) and Exelon® 1.5 mg hard capsules (Novartis Europharm Limited, France) in healthy male and female volunteers under fed conditions with a wash-out period of seven (7) days.

The study was performed from February 07th, 2008 to February 14th, 2008 at Anapharm 2500, rue Einstein Quebec, Canada and the principal investigator was Denis Audet, M.D.

The analytical portion was conducted at Anapharm Europe S.L. C/ Encuny 22, 2nd floor 08038 Barcelona, Spain, from February 26th, 2008 to March 04th, 2008.

The application concerns an immediate release capsule that should be taken with food as described in the innovator SmPC, therefore a single dose study under fed conditions is considered acceptable to demonstrate bioequivalence with the reference product.

The wash-out period of 7 days (greater than 5 half-lives) is considered adequate since the drug half-life is approx. one hour and pre-dose levels were not detected.

Considering the expected time to peak concentration (0.8-1.2 hours) and the elimination half-life of rivastigmine, the sampling schedule and the sampling time period of 10 hours seems long enough to estimate PK parameters.

Sampling is reasonably frequent every 20 minutes up to 3 hours and should be sufficient to allow an accurate measurement of $C_{max}$ and $t_{max}$.

Test and reference products

Test Product: Rivastigmine 1.5 mg hard capsules manufactured by Genepharm S.A., Greece. Batch number: DRV-1.5-1. Batch size: 100,000 hard capsules. Expiry date (Re-test): November 2008 (as per CoA). Assay (content): 102.7 % of label claim.

Reference Product: Exelon® 1.5 mg hard capsules, manufactured by Novartis Europharm Limited, France (from the Spanish market). Batch number: B5090. Expiry date: April 2012. Assay (content): 103.9% of label claim.

The test and reference product are adequate for a generic application. The reference product is from the French market. Both batches were tested before expiry date and the CoA shows a similar content. Therefore, content correction is not necessary.

After a supervised overnight fast of at least 10 hours, subjects were served a normocaloric breakfast. Subjects were required to completely consume this breakfast within 30 minutes prior to drug administration. Subjects were dosed on the mornings as a single oral dose of 1 capsule containing 1.5 mg of rivastigmine, with 240 mL of water.

The study was conducted using normo-caloric diet instead of high-caloric diet as no recommendation on the composition of the meal is given on the SmPC of the reference product, Exelon, but taking into account the kind of patients that will take the product, these patients are not expected to take a high-fat diet.

Thirty-six (36) subjects (24 male and 12 female) received the study medication according to the randomization list in period I and thirty-two (32) subjects in period II. Thirty-two (32) subjects finalized the study and thirty-two (32) were analysed and included in the statistical analysis.

Descriptive statistics of the subjects included in the pharmacokinetic analyses (n=32):

The following subjects were withdrawn:

- Subjects No. 03 and No. 20 (car accident) for personal reason.
- Subject No. 22 in pre-dose due to adverse event (hypotension). This subject was replaced by stand by subject A.
- Subject No. 32 in period I due to adverse event (Superficial phlebitis).
- Subject No. 36 in period 2 due to adverse events (infect urine tract).

The study population is considered acceptable with regards to demographic characteristics. The inclusion and exclusion criteria are considered to be acceptable.

*Protocol deviation*

The drawing blood time deviations were minor and they had no impact on the study outcome as actual time points were used for pharmacokinetic and statistical analysis.

*Analytical methods*

The analytical method has been adequately validated before the conduct of the study and during the analysis of the subject samples. Therefore, the analytical method is considered acceptable for analysis of the plasma samples.

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*Secondary Parameters*

The following pharmacokinetic parameters were calculated $t_{max}$, AUC_%Extrap_obs (%), λz, and $t_{1/2}$.

*Statistical analysis*

Using GLM procedure in SAS® (version 8.2), analysis of variance (ANOVA) was performed on the ln-transformed pharmacokinetic parameters $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$. The ANOVA model included sequence, treatment and period and subjects nested within sequence as random effect.

The 90% confidence intervals for the ratio of means between drug formulations were calculated for Ln-transformed data of $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$.

The results are summarized in the tables below.

| Parameter | Ratio (Test/Reference) | 90% Confidence Interval | CV% |
|---|---|---|---|
| Ln ($AUC_{0-t}$) | 103.32% | 97.38%-108.95% | 12.53% |
| Ln ($C_{max}$) | 103.30% | 96.06%-111.09% | 17.23% |
| Ln ($AUC_{0-\infty}$) | 103.43% | 98.30%-108.83% | 12.01% |

Based on the statistical analysis submitted by the Applicant, the test product is equivalent to the reference with respect to the extent and rate of absorption/exposure as the 90% confidence intervals for the ln-transformed $AUC_{0-\infty}$, $AUC_{0-t}$ and $C_{max}$ are within the acceptance range of 80-125%.

**Risk Management Plan**

A risk management plan in accordance with the requirements of Directive 2001/83/EC as amended has been submitted.

No additional risk minimization activities were required beyond those included in the product information.

**Discussion on the clinical aspects**

Efficacy and safety of the active substance rivastigmine are well documented for the reference medicinal product. The design of the submitted bioequivalence studies is adequate and the results conclude bioequivalence with the reference medicinal product.

## III OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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

The SmPC, PIL and labelling are considered satisfactory and consistent with the information for the reference medicinal product. The user testing of the Package Information Leaflet has been tested in accordance with Article 59(3) of Directive 2001/83/EC, as amended by Directive 2004/27/EC.

The benefit/risk balance was considered to be positive.

Agreement between Member States was reached during the procedure. The decentralised procedure was finalised with a positive outcome in May 2016.