RIVASTIGMINE 1.5 MG HARD CAPSULES
RIVASTIGMINE 3 MG HARD CAPSULES
RIVASTIGMINE 4.5 MG HARD CAPSULES
RIVASTIGMINE 6 MG HARD CAPSULES

(Rivastigmine hydrogen tartrate)

PL 24668/0117-20

UKPAR

TABLE OF CONTENTS

RIVASTIGMINE 1.5 MG HARD CAPSULES
RIVASTIGMINE 3 MG HARD CAPSULES
RIVASTIGMINE 4.5 MG HARD CAPSULES
RIVASTIGMINE 6 MG HARD CAPSULES

PL 24668/0117-20

LAY SUMMARY

The MHRA granted Caduceus Pharma Limited Marketing Authorisations (licences) for the medicinal products Rivastigmine 1.5 mg, 3 mg, 4.5 mg and 6 mg hard capsules on 14 December 2012. These products are prescription-only medicines (POM) used for the treatment of memory disorders in patients with Alzheimer's disease and the treatment of dementia in patients with Parkinson's disease.

Rivastigmine 1.5 mg, 3 mg, 4.5 mg and 6 mg hard capsules contain the active ingredient rivastigmine which belongs to a class of substances called cholinesterase inhibitors.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Rivastigmine 1.5 mg, 3 mg, 4.5 mg and 6 mg hard capsules outweigh the risks, hence Marketing Authorisations have been granted.

RIVASTIGMINE 1.5 MG HARD CAPSULES
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RIVASTIGMINE 4.5 MG HARD CAPSULES
RIVASTIGMINE 6 MG HARD CAPSULES

PL 24668/0117-20

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Caduceus Pharma Limited, Marketing Authorisations for the medicinal products Rivastigmine 1.5 mg, 3 mg, 4.5 mg and 6 mg hard capsules (PL 24668/0117-20) on 14 December 2012. These products are prescription-only medicines (POM) indicated for symptomatic treatment of:

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

These abridged applications submitted under Article 10(1) of Directive 2001/83/EC as amended, are for Rivastigmine 1.5 mg, 3 mg, 4.5 mg and 6 mg hard capsules, claiming to be generic medicinal products of the originator medicinal products Exelon 1.5 mg, 3 mg, 4.5 mg and 6 mg hard capsules (Novartis Europharm Limited, UK), which were authorised in the EEA via the Centralised Procedure on 12 May 1998. The reference products have been authorised in the EU for more than 10 years, thus the period of exclusivity has expired.

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.

No new non-clinical data have been submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

Two bioequivalence studies (single-dose) were submitted to support these applications, comparing the applicant's test products Rivastigmine 1.5 mg and 6 mg hard capsules (manufactured by Actavis Group PTC ehf) with the reference products Exelon 1.5 mg and 6 mg hard capsules (Novartis Europharm Limited, UK). The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence studies, no new clinical studies were performed, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

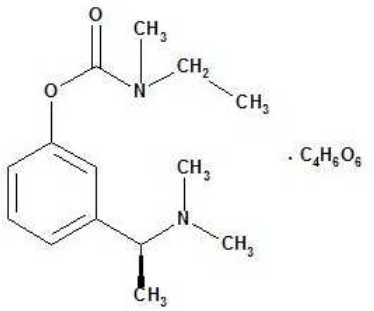
No new or unexpected safety concerns were raised during the assessment of these applications and it was, therefore, judged that the benefits of taking Rivastigmine 1.5 mg, 3 mg, 4.5 mg and 6 mg hard capsules outweigh the risks; hence Marketing Authorisations have been granted.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

INN: Rivastigmine hydrogen tartrate
Chemical name: 2,6-dioxo-4-phenyl-piperidine-3-carbonitrile

Structure:



Molecular formula: $C_{14}H_{22}N_2O_2 \cdot C_4H_6O_6$
Molecular weight: 400.42
Appearance: Rivastigmine hydrogen tartrate is a white to off-white powder.
Solubility: Rivastigmine hydrogen tartrate is soluble in water, methanol and ethanol.

Rivastigmine hydrogen tartrate is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

MEDICINAL PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients magnesium stearate, anhydrous colloidal silica, hypromellose, microcrystalline cellulose, titanium dioxide (E171), yellow iron oxide (E172) and gelatin. In addition:

- The 3 mg, 4.5 mg and 6 mg strengths also contain red iron oxide (E172).
- The 1.5 mg, 3 mg and 6 mg strengths also contain printing ink S-1-9460HV (consisting of shellac glaze, red iron oxide (E172), n-butyl alcohol, purified water, industrial methylated spirit 74 OP, lecithin (soya) (E322) and antifoam DC 1510-US).
- The 4.5 mg strength contains printing ink S-1R-7085 (consisting of shellac glaze, titanium dioxide (E171), isopropyl alcohol, ammonia solution, n-butyl alcohol, propylene glycol and antifoam DC 1510-US).

Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monograph with the exception of yellow iron oxide (E172) and red iron oxide (E172) [present in the capsule shell] and the capsule printing inks S-1-9460HV and S-1R-7085 which are controlled to suitable in-house specifications. The colourings, yellow iron oxide (E172) and red iron oxide (E172), are in compliance with current EU Directives concerning the use of colouring agents. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of gelatin none of the excipients contain materials of animal or human origin. The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines (EDQM) to show that they are manufactured in-line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/transmissible Spongiform Encephalopathies (BSE/TSE).

No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical development

The aim of the development programme was to formulate safe, efficacious capsules that could be considered generic medicinal products of the innovator's products Exelon 1.5 mg, 3 mg, 4.5 mg and 6 mg hard capsules (Novartis Europharm Limited, UK)

Suitable pharmaceutical development data have been provided for these applications.

Comparable *in vitro* dissolution and impurity profiles have been provided for these products and their respective reference products.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of all strengths of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot scale and has shown satisfactory results.

The marketing authorisation holder (MAH) has committed to perform further process validation studies on future commercial scale batches for all product strengths.

Finished product specification
The finished product specifications are satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container Closure System
All strengths of the finished product are packaged in:

- aluminium/polyvinyl chloride blister strips and are available in pack sizes of 28, 56 and 112 capsules.
- High density polyethylene (HDPE) containers with low density polyethylene (LDPE) caps in pack sizes of 250 capsules.

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability
Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years with the storage conditions ‘Do not store above 25°C.’

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence studies.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PILs and labelling are satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) Forms
The MAA forms are satisfactory.

Expert Report
A quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
It is recommended that marketing authorisations are granted for these applications.

NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY

No new non-clinical data were submitted, which is acceptable given that the proposed products are generic medicinal products of originator products that have been licensed for over 10 years.

NON-CLINICAL EXPERT REPORT

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

ENVIRONMENTAL RISK ASSESSMENT

Since Rivastigmine 1.5 mg, 3 mg, 4.5 mg and 6 mg hard capsules are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment (ERA) is therefore not deemed necessary.

CONCLUSION

It is recommended that marketing authorisations are granted for these applications.

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

The clinical pharmacology of rivastigmine is well-known. With the exception of the bioequivalence studies, no pharmacokinetic or pharmacodynamic data were submitted for these applications, and none were required for applications of this type.

Rivastigmine has been shown to have non-linear pharmacokinetics. The non-linearity gives about 50% higher AUCs than expected when doubling the dose. According to the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev 1/ Corr**, the bioequivalence study should in general be conducted at the highest strength for drugs with non-linear pharmacokinetics characterised by a more than proportional increase in AUC with increasing dose over the therapeutic dose range. The MAH therefore submitted a bioequivalence study comparing the highest (6 mg) strength, Rivastigmine 6 mg hard capsules with the reference product Exelon 6 mg hard capsules.

As the pharmacokinetics of rivastigmine are very variable, a study comparing the lowest strength, 1.5 mg was also submitted.

The following two bioequivalence studies were submitted:

STUDY 1.

A randomised, open-label, single-dose, crossover study to compare the pharmacokinetics of the test product Rivastigmine 1.5 mg hard capsules (manufactured by Actavis Group PTC ehf) versus the reference product Exelon 1.5 mg hard capsules (Novartis Europharm Limited, UK) in healthy adult volunteers under fed conditions.

Following an overnight fast of at least 10 hours, all volunteers received a single oral dose of either the test or the reference product administered with 240ml of water 30 minutes after completing a standardised high-fat, breakfast. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 14 hours post dose. The washout period between treatment periods was at least 7 days.

The pharmacokinetic results for rivastigmine are presented below (non-transformed values, arithmetic mean, ± Standard Deviation (SD), t_{max}, median, range, ratios and confidence intervals [CI]):

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	**4762.8**	**4825.4**	**1623.2**	**3.13**	**0.86**
Reference	**4900.3**	**4951.5**	**1630.7**	**3.13**	**0.87**
*Ratio (90% CI)	**99.56 (93.89 - 105.57)**	**99.83 (94.20 - 105.78)**	**102.92 (95.09-111.40)**		
CV (%)	**19.03**	**18.82**	**25.90**		

$AUC_{0-\infty}$ **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

STUDY 2.

A randomised, open-label, single-dose, 2-way, 2-sequence, crossover study to compare the pharmacokinetics of the test product Rivastigmine 6 mg hard capsules (manufactured by Actavis Group PTC ehf) versus the reference product Exelon 6 mg hard capsules (Novartis Europharm Limited, UK) in healthy adult volunteers under fed conditions.

Following an overnight fast of at least 10 hours, all volunteers received a single oral dose of either the test or the reference product administered with 240ml of water 30 minutes after completing a standardised high-fat, breakfast. In order to minimise the possibility of nausea associated with rivastigmine, all subjects, in each study period, were given a single intramuscular injection of dimenhydrinate (Gravol® 50 mg / 1 mL) within approximately 45 to 30 minutes prior to rivastigmine dosing in each study period and at approximately 3 hours following dosing. Subjects were withdrawn from the study if they vomited within 5.4 hours after dosing (two times the mean t_{max} of rivastigmine) Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 12 hours post dose. The washout period between treatment periods was at least 7 days.

The pharmacokinetic results for rivastigmine are presented below (non-transformed values, arithmetic mean, ± Standard deviation (SD), tmax, median, range, ratios and confidence intervals [CI]):

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	**63.77**	**65.49**	**16.57**	1.875
Reference	**63.55**	**65.56**	**16.56**	**2.00**
*Ratio (90% CI)	**1.02 (0.98-1.06)**	**1.02 (0.98-1.06)**	**1.00 (0.93-1.08)**	
CV (%)	**10.4**	**10.3**	**18.2**	

$AUC_{0-\infty}$ **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**

*ln-transformed values

The 90% confidence intervals for AUC and C_{max} for test versus reference product for rivastigmine for both studies are within predefined acceptance criteria specified in "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**). Thus, the data support the claim that the test products Rivastigmine 1.5 mg and 6 mg hard capsules (manufactured by Actavis Group PTC ehf) are bioequivalent to the reference products Exelon 1.5 mg and 6 mg hard capsules (Novartis Europharm Limited, UK) under fed conditions.

A biowaiver has been granted to the 3.0 mg and 4.5 mg strength hard capsules based on the studies conducted, in line with current bioequivalence guideline.

Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for these applications.

Efficacy
No new efficacy data were submitted and none were required for these applications.

Safety
With the exception of the data generated during the bioequivalence studies, no new safety data were submitted and none were required for these applications. No new or unexpected safety issues were raised by the bioequivalence data.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPCs, PIL and labels are acceptable. The SmPC for each strength is consistent with that for it's respective originator product. The PIL is consistent with the SmPC and in-line current guidelines. The labelling is in-line with current guidelines.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a Risk Management Plan for these products.

Conclusion
There are no objections to the approval of these products from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The quality characteristics of Rivastigmine 1.5 mg, 3 mg, 4.5 mg and 6 mg hard capsules are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY

With the exception of the bioequivalence studies, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant's 1.5 mg and 6 mg strength hard capsules and the reference products Exelon 1.5 mg and 6 mg capsules; the results can be extrapolated to the 3 mg and 4.5 mg strength hard capsules.

SAFETY

With the exception of the bioequivalence studies, no new data were submitted and none are required for applications of this type. As the safety profile of rivastigmine is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence studies.

PRODUCT LITERATURE

The SmPCs, PIL and labelling are satisfactory and consistent with that for the reference product, where appropriate, and consistent with current guidelines.

BENEFIT-RISK ASSESSMENT

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The bioequivalence studies support the claim that the applicant's products and the originator products are interchangeable. Extensive clinical experience with rivastigmine is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

RIVASTIGMINE 1.5 MG HARD CAPSULES
RIVASTIGMINE 3 MG HARD CAPSULES
RIVASTIGMINE 4.5 MG HARD CAPSULES
RIVASTIGMINE 6 MG HARD CAPSULES

PL 24668/0117-20

STEPS TAKEN FOR ASSESMENT

1 The MHRA received the marketing authorisation applications on 16 July 2010.

2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 11 August 2010.

3 Following assessment of the applications the MHRA requested further information relating to the quality dossier on 03 December 2010, 13 April 2011, 24 June 2011, 19 July 2011 and 25 August 2011 and the clinical dossier on 18 January 2012.

4 The applicant responded to the MHRA's requests, providing further information on the quality dossier on 14 March 2011, 03 June 2011, 14 July 2011, 23 August 2011 and 26 August 2011 and the clinical dossier on 10 February 2012

5 The applications were determined on 14 December 2012.

RIVASTIGMINE 1.5 MG HARD CAPSULES
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RIVASTIGMINE 6 MG HARD CAPSULES

PL 24668/0117-20

STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Module 3
PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

LABELLING

The following text is the approved labelling text. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the labelling mock-ups has been obtained.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine 1.5 mg hard capsules

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 capsule contains rivastigmine 1.5 mg present as rivastigmine hydrogen tartrate.

3. LIST OF EXCIPIENTS

Contains soya lecithin (E322).See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 hard capsules
56 hard capsules
112 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

To be swallowed whole without crushing or opening.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited
6th Floor 94 Wigmore Street
London
W1U 3RF

12. MARKETING AUTHORISATION NUMBER(S)

PL 24668/0117

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rivastigmine 1.5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine 1.5 mg hard capsules

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

CARTON AND LABEL FOR CAPSULE CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine 1.5 mg hard capsules

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 capsule contains rivastigmine 1.5 mg present as rivastigmine hydrogen tartrate.

3. LIST OF EXCIPIENTS

Contains soya lecithin (E322).See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

250 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

To be swallowed whole without crushing or opening.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited
6th Floor 94 Wigmore Street
London
W1U 3RF

12. MARKETING AUTHORISATION NUMBER(S)

PL 24668/0117

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rivastigmine 1.5 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine 3 mg hard capsules

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 capsule contains rivastigmine 3 mg present as rivastigmine hydrogen tartrate

3. LIST OF EXCIPIENTS

Contains soya lecithin (E322).See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 hard capsules
56 hard capsules
112 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

To be swallowed whole without crushing or opening.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited
6th Floor 94 Wigmore Street
London
W1U 3RF

12. MARKETING AUTHORISATION NUMBER(S)

PL 24668/0118

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rivastigmine 3 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine 3 mg hard capsules

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

CARTON AND LABEL FOR CAPSULE CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine 3 mg hard capsules

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 capsule contains rivastigmine 3 mg present as rivastigmine hydrogen tartrate

3. LIST OF EXCIPIENTS

Contains soya lecithin (E322).See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

250 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

To be swallowed whole without crushing or opening.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited
6th Floor 94 Wigmore Street
London
W1U 3RF

12. MARKETING AUTHORISATION NUMBER(S)

PL 24668/0118

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rivastigmine 3 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine 4.5 mg hard capsules

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 capsule contains rivastigmine 4.5 mg present as rivastigmine hydrogen tartrate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 hard capsules
56 hard capsules
112 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

To be swallowed whole without crushing or opening.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited
6th Floor 94 Wigmore Street
London
W1U 3RF

12. MARKETING AUTHORISATION NUMBER(S)

PL 24668/0119

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rivastigmine 4.5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine 4.5 mg hard capsules

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

CARTON AND LABEL FOR CAPSULE CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine 4.5 mg hard capsules

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 capsule contains rivastigmine 4.5 mg present as rivastigmine hydrogen tartrate.

3. LIST OF EXCIPIENTS

Contains soya lecithin (E322).See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

250 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

To be swallowed whole without crushing or opening.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11.	NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited
6th Floor 94 Wigmore Street
London
W1U 3RF

12.	MARKETING AUTHORISATION NUMBER(S)

PL 24668/0119

13.	BATCH NUMBER

Lot

14.	GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

POM

15.	INSTRUCTIONS ON USE

16.	INFORMATION IN BRAILLE

rivastigmine 4.5 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine 6 mg hard capsules

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 capsule contains rivastigmine 6 mg present as rivastigmine hydrogen tartrate

3. LIST OF EXCIPIENTS

Contains soya lecithin (E322).See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 hard capsules
56 hard capsules
112 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

To be swallowed whole without crushing or opening.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited
6th Floor 94 Wigmore Street
London
W1U 3RF

12. MARKETING AUTHORISATION NUMBER(S)

PL 24668/0120

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rivastigmine 6 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine 6 mg hard capsules

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

CARTON AND LABEL FOR CAPSULE CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine 6 mg hard capsules

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 capsule contains rivastigmine 6 mg present as rivastigmine hydrogen tartrate

3. LIST OF EXCIPIENTS

Contains soya lecithin (E322).See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

250 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

To be swallowed whole without crushing or opening.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited
6th Floor 94 Wigmore Street
London
W1U 3RF

12. MARKETING AUTHORISATION NUMBER(S)

PL 24668/0120

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rivastigmine 6 mg