23 January 2014
EMA/111203/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rivastigmine 3M Health Care Ltd

International non-proprietary name: Rivastigmine

Procedure No. EMEA/H/C/003824

Note

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 3M Health Care Limited submitted on 6 September 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Rivastigmine 3M Health Care Ltd 4.6 mg/24h & 9.5 mg/24h Transdermal Patches, through 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 eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 3 July 2013.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication: Symptomatic treatment of mild to moderately severe Alzheimer's dementia.

The legal basis for this application refers to Article 10(1) of Directive No 2001/83/EC, as amended.

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Exelon.

Information on paediatric requirements

Not applicable

This application is submitted as a multiple of Rivastigmine Actavis 4.6mg/24 hours, and 9.5 mg/24 hours transdermal patches authorised on 16 June 2011 in accordance with Article 82.1 of Regulation (EC) No 726/2004.

The chosen reference product is:

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

- Product name, strength, pharmaceutical form: Exelon 4.6mg/24h and 9.5mg/24h transdermal patches
- Marketing authorisation holder: Novartis Europharm Limited.
- Date of authorisation: 12/05/1998
- Marketing authorisation granted by: Community
- EU registration. Marketing authorisation number: EU/1/98/066/019-026

■ Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Exelon 4.6 mg/24 h & 9.5 mg/24 h transdermal patches
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: 12/05/1998

- Marketing authorisation granted by: Community
- EU registration. Marketing authorisation number: EU/1/98/066/019-026

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Exelon transdermal patch, 9.5mg/24 h
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: 12/05/1998
  - Marketing authorisation granted by:Community
  - (Community) Marketing authorisation number(s): EU/1/98/066/023 – 026
- Bioavailability study number(s): C11-1612

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. Manufacturers

Manufacturer(s) of the active substance

Interquim S.A.
Joan Buscalla, 10
E-08173 – Sant Cugat del Valles
Barcelona
Spain

Manufacturer(s) of the finished product

3M DRUG DELIVERY SYSTEMS
19901 NORDHOFF STREET
NORTHRIDGE
CA 91328
USA

Manufacturer(s) responsible for batch release

Enestia
Klöcknerstraat 1, 3930 Hamont-Achel
Belgium

1.3. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP and the evaluation team was Bengt Ljungberg

- The application was received by the EMA on 6 September 2013.
- The procedure started on 24 November 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 27 December 2013.
- The Rapporteur circulated an updated Assessment Report addressing the comments from CHMP members and applicant clarifications on 20 January 2014.
- During the meeting on 23 January 2014, 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 3M Health Care Ltd.

2. Scientific discussion

2.1. Introduction

The application for Rivastigmine 3M Health Care Ltd 4.6mg/24 hours, and 9.5 mg/24 hours, transdermal patches is a duplicate to the product, Rivastigmine Actavis 4.6mg/24 hours, and 9.5 mg/24 hours. Rivastigmine Actavis however, is also authorised as 1.5 mg, 3 mg, 4.5 mg and 6 mg hard capsules. Rivastigmine Actavis was authorised as a generic application according to Article 10(1) of Directive 2001/83/EC in the centralised procedure.

The indication for Rivastigmine 3M Health Care Ltd transdermal patches is the same as the reference medicinal product: symptomatic treatment of mild to moderately severe Alzheimer's dementia.

2.2. Quality aspects

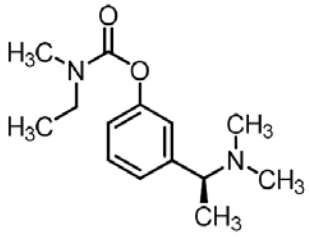
2.2.1. Introduction

Rivastigmine 3M Health Care Ltd is presented in the form of transdermal patches containing rivastigmine base. The patches are packed in heat-sealed pouches made of paper/aluminium/acrylonitrile-methacrylate copolymer laminate.

The composition is described in section 6.1. of the SmPC

2.2.2. Active substance

The chemical name of rivastigmine is 3-[(1S)-1-(dimethylamino)ethyl]phenyl ethyl(methyl) carbamate and has the following structure:



Rivastigmine base is a colourless or slightly yellowish transparent liquid which is very soluble in several organic solvents and slightly soluble in water. The molecular structure of rivastigmine has been confirmed by FT-IR, MS, ^{13}C-NMR, ^{1}H-NMR and elemental analysis. The Rivastigmine's structure presents a chiral centre. The (S) enantiomer is consistently synthesised. The active substance does not exhibit polymorphism.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

Manufacture

The synthetic process of the active substance Rivastigmine involves three chemical transformations and is using well characterised starting materials. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Specification

The active substance specification includes tests for appearance (visual, Identification (IR, HPLC, water (KF), specific optical rotation (Ph. Eur), residue on ignition (Ph. Eur), heavy metals (Ph. Eur), related substances (HPLC), enantiomeric purity (HPLC), potentiometrical assay on the anhydrous basis (Ph. Eur) and residual solvents (GC).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data of seven full scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability studies under ICH conditions have been conducted on 6 production and pilot scale batches from the proposed manufacturer stored in a container closure system representative of that intended for the market. Studies were performed for 36 months under long term conditions at 5°C±3°C, and for up to 6 months under accelerated conditions at 25°C, 60% RH according to the ICH guidelines. This was presented in the ASMF. The test parameters evaluated in these

studies were appearance, water content, related substances by HPLC, assay by potentiometry, and enantiomeric purity by HPLC.

Forced degradation studies were performed by treatment with heat (110°C for 24 hours), under acidic and alkaline conditions, under oxidizing conditions as well as under light stress conditions.

During long-term and accelerated stability studies the active substance is stable.

The stability results indicate that the active substance is sufficiently stable and justify the proposed retest period.

2.2.3. Finished medicinal product

Pharmaceutical development

The objective of the development of the finished product was to develop a transdermal rivastigmine system that is bioequivalent to the transdermal patch of the reference medicinal product.

During formulation development different modifications of the formulation were evaluated. Both, in vitro and in vivo proof of concept clinical trials (POC BE study I, PoC BE study II, Pivotal BE/A and SI study I and PoC BE study III) were performed before the final formulation was tested and found bioequivalent in a bioequivalence study (BE study 211-1012) with a pilot scale batch.

The formulation efforts sought to load rivastigmine with comparable total active substance amounts to see if the acrylate copolymer adhesives could accommodate the required active substance loading while retaining suitable skin adhesion properties. Since the reference patch did not require the use of permeation enhancing or solubilising excipients for meeting delivery requirements, compositions without these excipients were initially explored.

A formulation without additional excipients was developed and used in a pivotal BE/A and SI study I. This formulation was found to match reference product in PK and SI but failed adhesion. The product was reformulated with the addition of an excipient as a tackifier to increase the adhesion of the product while leaving the PK of the product unchanged.

The excipients used in the final formulation comply with compendial requirements.

In vitro test methods were also used during the development, checking the permeation and also physical tests such as Tack, 180° peel from steel, release from liner and shear/creep compliance.

The primary packaging is stated in the SmPC and it is adequate to support the stability and use of the product. The material complies with Ph Eur and EC requirements, and the choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Adventitious agents

No excipients of human or animal origin are used in the manufacture of the transdermal patch.

Manufacture of the product

The manufacturing process of Rivastigmine 3M Health Care Ltd is satisfactorily described, and it has been clearly detailed in flow-chart diagrams. The manufacturing process is typical of transdermal patches.

The manufacturing process is performed in three steps. The steps consist of mixing the components in order to create the active formulation, the coating and the creation of the patches.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this pharmaceutical form.

The production process is performed in compliance with the principle of Good Manufacturing Practices.

The batch analysis data shows that the transdermal patches can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this pharmaceutical form.

Product specification

The product specification includes as appropriate parameters for the dosage and pharmaceutical form. Validations of the analytical procedures have been presented. The results of the batch analysis presented show that the finished product meets the proposed specification.

The release and shelf life specification of the finish product contains test with suitable limits for appearance (visual, identification (HPLC), assay (HPLC), uniformity of dosage units (HPLC), related substances (HPLC), dissolution (HPLC), microbiology (Ph. Eur). The acceptance criteria and test methods are justified.

Batch analysis results are provided for seven full scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability studies were performed under ICH conditions. Stability data is presented for 7 batches for 12 months at 25 °C / 60% RH and 30 °C / 65% RH, and 6 months at 40 °C / 75% RH. The batches of Rivastigmine 3M Health Care Ltd are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

All data meet the specification limits at all-time points and no trends were observed except for a slight increase of release from liner.

The proposed shelf life as indicated in the SmPC with no special temperature storage condition is found acceptable.

According to the draft monograph on rivastigmine, the active substance is light sensitive. No photostability testing of the patches has been performed. Since the finished product is packaged

in heat-sealed pouches consisting of an aluminium foil among other constituents, it is considered acceptable.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of this new pharmaceutical form has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Rivastigmine 3M Health Care Ltd manufactured by 3M Health Care Ltd 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 Environmental Risk is expected to be similar and not increased.

2.3.3. Discussion and Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Rivastigmine 3M Health Care Ltd and justifications that the active substance does not differ significantly from the reference product in properties with regards to safety and efficacy, was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional non clinical studies were not considered necessary.

2.4. Clinical aspects

2.4.1. Introduction

This application concerns a generic version of Rivastigmine transdermal patch and it is a duplicate pharmaceutical form of Rivastigmine Actavis patch. To support the marketing authorisation application the applicant refers to one bioequivalence study, Study C11-1612.

GCP

The Clinical trial was performed in accordance with GCP as claimed by the applicant.

The applicant provided a statement to the effect that the clinical trial, conducted outside the community, was carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4.2. Pharmacokinetics

Methods

Study design

The study was a randomised, single-application and multiple-application, two-way open-label crossover relative bioavailability and adhesion study. 38 non-smoking male and female volunteers were included. Each treatment period was 7 days, and on day 1 as well as day 3-7 a patch was applied on the upper back after an overnight fast and was removed after 24 hours. There was a 7-days washout between the periods.

The patches were applied on the upper back, and each new patch was positioned approximately 2 cm from the previous. The patches in period 2 were aligned 2 cm below the first series of patches. The subjects were not allowed to bath/shower or apply heat/cold to the application site.

Blood sample collections were obtained within 15 minutes prior to patch application (0 hour) on Day 1, and Days 3-7, and after patch application at 0.5, 1, 2, 4, 6, 8, 10, 11, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, and 36 hours on Day 1-2 and 0.5, 1, 2, 4, 6, 8, 10, 11, 12, 14, 16, 18, 20, 22, and 24 hours on Day 7. A total of 41 blood samples were collected for pharmacokinetic analysis per study period for a total of 82 samples or 492 mL total blood volume. Samples were cooled on ice-bath, centrifuged at 3000 rpm for 10 minutes and plasma aliquots were mixed with eserine solution (1:1, conc 1 µg/mL) and vortexed. The samples were frozen at -70 °C (maximum time from sample collection 1.5 h) and shipped frozen to the analytical facility.

Adherence was judged by an evaluator according to a 5-grade scale just after application and before removal of each patch. On day 1, adherence was also evaluated at 7 additional time points. Local tolerability and skin appearance was monitored before each administration and 0.5 and 12 h after removal of each patch.

Test and reference products

Product	Treatment Product	Reference Product
Treatment ID	A	B
Product Name	Rivastigmine 9.5 mg/24 h Transdermal Patch	Exelon 9.5 mg/24 h Transdermal Patch
Manufacturer	3M Drug Delivery Systems Division (for Actavis Group PTC, ehf)	Novartis Europharm Ltd
Batch/Lot No.	110111	199212
Manufacture Date	10-Feb-2011	NA
Expiration Date	10-Feb-2012	May-2012
Strength	9.5 mg	9.5 mg
Dosage Form	Patch	Patch
Dose Administered	6 x 9.5 mg	6 x 9.5 mg
Route of Administration	Transdermal	Transdermal
Cumulative Maximum Dose	57 mg	57 mg

Population studied

38 healthy men and women (10 + 28) were included (7 African Americans, 31 white), mean age was 41 years. Two subjects discontinued due to patch falling off in the multiple-dose part of the study, and their data were not included in the multiple-dose PK evaluation. Data from all 38 subjects were used in the single-dose evaluation.

Analytical methods

Rivastigmine concentrations in eserine (acetylcholine esterase inhibitor) treated plasma were measured after a solid phase extraction procedure using a validated reversed phase liquid chromatography assay with tandem-MS detection with deuterium labelled rivastigmine as internal standard. K2-EDTA was used as an anticoagulant.

Pre-study validation

Specificity was shown employing 7 independent sources of human plasma. Sensitivity at the limit of quantification, 100 pg/ml, was shown. Satisfactory between- and within-run accuracy and precision was shown for low, medium and high QC (quality control) sample concentrations. Linearity was demonstrated within the calibration range 100 – 10 000 pg/ml. Dilution integrity for a factor of 10 was demonstrated. Stability in plasma was demonstrated for 24 h at room temperature, for 6 days at – 20°C and over 6 freeze-thaw cycles. The clinical summary claims long-term stability in plasma up to 54 days at -20°C as well as -70°C. Matrix effect was evaluated in 6 lots of blank matrix.

Within-study validation

3087 samples were run in 49 batches. Inter-run precision was ≤4.3% and the mean accuracy ranged from 96.1 to 101.2%. LLOQ (Lower Limit of Quantification) was below 1/20 of average Cmax. About 150 re-assays (5%) were performed, due to measured values above LOQ, raised LLOQ (to Std 2) in the run, high internal standard or extraction error. Incurred sample reanalysis

was performed on 220 samples, of which 12 deviated more than 20% from the original value, which is acceptable.

Pharmacokinetic variables

Pharmacokinetic parameters were evaluated using a standard non-compartmental approach. For the single dose, AUCo-t, AUCo-inf, Cmax, Tmax, Kel and T1/2 was evaluated. For the multiple-dose part, AUCτ, Cavg(ss), Cmax (ss), Cmin (ss), Tmax (ss), Flux (fluctuation in % of Cavg) and Swing (fluctuation in % of Cmin).

Statistical methods

A steady-state evaluation was performed on pre-dose concentrations using Helmert contrasts. ANOVA was performed on ln-transformed pharmacokinetic parameters including sequence, formulation and period as fixed effects and subject nested within sequence as the error term. 90% confidence intervals for the ratios between geometric means were constructed, and bioequivalence criteria were 0.8-1.25.

Results

The results of the bioequivalence studies are presented below.

Single dose

Bioequivalence was shown both for Cmax and AUC0-t (Table 1). The extrapolated AUC was less than 10% in all subjects. No pre-dose concentrations were detected and no subjects reached tmax at the first sampling point.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for rivastigmine n=38

Treatment	AUC0-t pg*h/ml	AUC0-∞ pg*h/ml	Cmax pg/ml	tmax h
Test	136 112 (56 278)	137 408 (56 404)	7 709 (3 036)	15 (8-26)
Reference	134 414 (54 171)	136 142 (54 288)	8 026 (3 495)	14 (8-26)
*Ratio (90% CI)	1.02 (0.97-1.07)	1.01 (0.96-1.07)	0.98 (0.91-1.06)	-
	AUC0-t area under the plasma concentration-time curve from time zero to t hours Cmax maximum plasma concentration tmax time for maximum plasma concentration			

*calculated based on ln-transformed data

Multiple dose

Steady state conditions were verified by showing that mean Day 5 concentration was not significantly different from the average of the concentrations on Days 6 and 7. Bioequivalence was shown both for Cmax, Cmin and AUCτ using predefined acceptance criteria (Table 2).

Table 2. Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD, tmax median, range) for rivastigmine, n=36

Treatment	AUC0-τ pg*h/ml	Cmax pg/ml	Cmin pg/ml	tmax h
Test	125 872 (48 801)	7 648 (3 218)	2 892 (1 154)	10 (0-24)
Reference	133 636 (49 691)	7 857 (2 930)	3 199 (1 327)	10 (0-24)
*Ratio (90% CI)	0.94 (0.87-1.02)	0.97 (0.89-1.05)	0.92 (0.83-1.02)	-

AUC0-τ area under the plasma concentration-time curve during one dosing interval
Cmax maximum plasma concentration
Cmin minimum plasma concentration
tmax time for maximum plasma concentration

*calculated based on ln-transformed data

- **Patch Adhesion**

One subject was not included in the patch adhesion evaluation because no assessment was performed on day 1 in one of the periods.

0 = 90% or more adhered (essentially no lift off of the skin)
1 = 75% to <90% adhered (some edges only lifting off of the skin)
2 = 50% to <75% adhered (less than half of the system lifting off the skin)
3 = <50% adhered but not detached (more than half the system lifting off of the skin but not detached)
4 = patch detached (patch completely off the skin)

The cumulative adhesion score (CAS) on day 1 was evaluated, derived by totalling the adhesion score on the 9 time points evaluated on day 1.

Table 11.4.8 Number and Percent of Subjects per CAS on Day 1

CAS over 24 hours on Day 1	Test Total N=37	Reference Total N=37
0	22 (59.46%)	24 (64.86%)
1	8 (21.62%)	6 (16.22%)
2	3 (8.11%)	2 (5.41%)
3	1 (2.70%)	3 (8.11%)
4	1 (2.70%)	0 (0%)
5	0 (0%)	1 (2.70%)
6	0 (0%)	0 (0%)
7	0 (0%)	0 (0%)
8	1 (2.70%)	0 (0%)
9	0 (0%)	1 (2.70%)
10	1 (2.70%)	0 (0%)

The mean score for the test product (1.1; SD 2.2) was somewhat higher than for the reference product (0.9; 1.8), but there was no statistically significant difference between treatments when the Wilcoxon Signed Rank Test was used for treatment comparison (p= 0.0882). A non-inferiority test was also performed concluding that Rivastigmine 3M attachment was considered non-inferior to Exelon attachment.

No patches detached on day 1, but on day 7, two subjects had detached patches, in both cases it was the test formulation, and detachment occurred at 8-10 h in one subject and at 24 h in the other.

2.4.3 Pharmacodynamics

No new pharmacodynamic studies were presented, as no such studies are required for this type of application.

2.4.3. Safety data

Overall, considering the limited number of subjects in the study and study design, the AE pattern reported in the study is in line with what could be expected.

An analysis of the Local Tolerability and Skin Appearance Check results have been provided. The analysis showed no skin appearance with either patch exceeded score 2 (Definite visible erythema) in the dermal response scale. The scores of 1 and 2 tended to be evenly distributed between the two products. From the analysis it can be concluded that the two patches behaved similarly as far as local tolerability and appearance changes were concerned.

2.4.4 Discussion on clinical aspects

To support this duplicate application the applicant submitted one single- and multiple dose bioequivalence study on the highest patch strength (9.5 mg/24 h), showing bioequivalence both after single dose application and at steady state between Rivastigmine 3M Health Care Ltd patches and the reference Exelon. The applicant has also submitted data presenting

pharmaceutical similarity between the strengths, as well as adherence data for the lower strength, making it possible to extrapolate bioequivalence to the lower patch strength (4.6 mg/24 h). In addition, the applicant has provided data on the intra-individual variability of the two formulations in the bioequivalence study, by calculating variability of pre-dose concentrations at steady state. Variability was of the same magnitude for both test and reference.

The bioequivalence study also included investigations on patch adherence, showing non-inferiority to the original Exelon in patch adherence day 1. A study patch adherence of the lower patch strength (4.6mg/24h) was submitted, with similar results. A tendency towards higher frequency of slightly detached patches in the test group was seen in both studies, and in the two studies three patches in total detached completely, all of them in the test group. The majority of patches, however, had a good adherence in both studies, and the difference is not considered to be of clinical importance. The patch adhesiveness is therefore considered similar between formulations and acceptable.

2.4.5 Conclusions on clinical aspects

A summary of the literature with regard to clinical data of Rivastigmine 3M Health Care Ltd transdermal patch and justifications that the active substance does not differ significantly in properties from the reference product with regards to safety and efficacy, was provided and was accepted by the CHMP. This is in accordance with the relevant guidelines and additional clinical studies were not considered necessary.

The results of study C11-1612 with 9.5 mg/24 h formulation can be extrapolated to the other strength applied for (4.6 mg/24 h), according to conditions in the relevant Guidelines.

The patch adhesiveness is considered similar between formulations and acceptable.

The AE pattern reported in the study is in line with what could be expected. Local tolerability was similar to the original Exelon patch.

Based on the presented bioequivalence study Rivastigmine 3M Health Care Ltd 4.6 mg/24h & 9.5 mg/24h transdermal patch is considered bioequivalent with Exelon 4.6 mg/24h & 9.5 mg/24h transdermal patch.

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk management plan

The applicant submitted a risk management plan, which included a risk minimisation plan.

No safety concerns were identified which require additional pharmacovigilance activities beyond routine measures as described in the Pharmacovigilance system master file.

The following tables present the summary Safety concerns and Risk minimization measures, as proposed by the MAH in RMP version 4.1 (PhV-20131437, dated 2013.10.01).

VI.1.1 Summary table of Safety concerns

Summary of Safety concerns	
Important identified risk	NA
Important potential risks	Misuse and dosing errors resulting in overdose
Missing information	NA

VI.1.4 Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Risk of misuse and dosing errors resulting in overdose	Section 4.2 Patients and caregivers should be instructed on important administration instructions: - The previous day's patch must be removed before applying a new one every day. - The patch should be replaced by a new one after 24 hours. Only one patch should be worn at a time. - The patch should be pressed down firmly for at least 30 seconds using the palm of the hand until the edges stick well. - If the patch falls off, a new one should be applied for the rest of the day, then it should be replaced at the same time as usual the next day. - The patch can be used in everyday situations, including bathing and during hot weather. - The patch should not be exposed to any external heat sources (e.g. excessive sunlight, saunas, solarium) for long periods of time. - The patch should not be cut into pieces. Section 4.4 Misuse of the medicinal product and dosing errors resulting in overdose. Misuse of the medicinal product and dosing errors with rivastigmine transdermal patch have resulted in serious adverse reactions; some	Educational materials: patient reminder card including 1. instruction for use, 2. illustration showing proper patch application and body locations 3. patient medication record

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	cases have required hospitalisation, and rarely led to death. Most cases of misuse of the medicinal product and dosing errors have involved not removing the old patch when putting on a new one and the use of multiple patches at the same time. Patients and their caregivers must be instructed on important administration instructions for rivastigmine transdermal patch.	

The following additional risk minimisation activities were required:

The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where Rivastigmine 3M Health Care Ltd is marketed, at launch and after launch of the transdermal patch all physicians who are expected to prescribe Rivastigmine 3M Health Care Ltd are provided with an information pack containing the following elements:

- Summary of Product Characteristics
- Patient reminder card
- Instructions to provide patients and caregivers with the patient reminder card

The patient reminder card should contain the following key messages:

- Take off the previous patch before putting ONE new patch on.
- Only one patch per day.
- Do not cut the patch into pieces.
- Press the patch firmly in place for at least 30 seconds using the palm of the hand.
- How to use the reminder card to record patch application and removal.

PSUR submission

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 and published on the European medicines web-portal.

User consultation

No full user consultation with target patient groups on the package leaflet has been performed

on the basis of a bridging report making reference to the duplicate application Rivastigmine Actavis and Exelon 4.6mg & 9.5mg/24hr transdermal patch. The bridging report submitted by the applicant has been found acceptable. In addition, a justification for not performing additional user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable

3. Benefit-risk balance

This application concerns a generic version of Rivastigmine transdermal patch. The reference product, Exelon patch, is indicated for "symptomatic treatment of mild to moderately severe Alzheimer's dementia". No non-clinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects, based on information from published literature, was considered sufficient.

The bioequivalence study (BE study C11-1612) was a randomised, single-application and multiple-application, two-way open-label crossover relative bioavailability and adhesion study. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective EU requirements. Choice of dose, sampling points, overall sampling time, and wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of rivastigmine 3M patch met the protocol-defined criteria for bioequivalence when compared with Exelon patch. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Rivastigmine 3M Health Care Ltd in the treatment of Symptomatic treatment of mild to moderately severe Alzheimer's dementia is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where Rivastigmine 3M Health Care Ltd is marketed, at launch and after launch of the transdermal patch all physicians who are expected to prescribe Rivastigmine 3M Health Care Ltd are provided with an information pack containing the following elements:

- Summary of Product Characteristics
- Patient reminder card
- Instructions to provide patients and caregivers with the patient reminder card
- The patient reminder card should contain the following key messages:
- Take off the previous patch before putting ONE new patch on.
- Only one patch per day.
- Do not cut the patch into pieces.
- Press the patch firmly in place for at least 30 seconds using the palm of the hand.
- How to use the reminder card to record patch application and removal.

- ***Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.***

Not applicable.