EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 February 2013
EMA/CHMP/739928/2012
Committee for Medicinal Products for Human Use (CHMP)

Rivastigmine Actavis

International non-proprietary name: rivastigmine

Procedure No.: EMEA/H/C/002036/X/0005

Marketing authorisation holder: Actavis Group hf

Assessment report for an extension of indication variation

Assessment report as adopted by the CHMP with all commercially confidential information deleted

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List of abbreviations

AD Alzheimer's Disease
AE Adverse Event
AUC Area Under The Curve
BE/A Bioequivalence and adhesion
BL Baseline
Cmax Peak Plasma Concentrations
CI Confidence Interval
OC Observed Case
PK/PD Pharmacokinetic/ Pharmacodynamic
POC Proof of concept
SAE Serious Adverse Event
SI Sensitisation and irritation

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Actavis Group PTC ehf submitted on 5 January 2012 an application for an extension of the Marketing Authorisation to the European Medicines Agency (EMA) for Rivastigmine Actavis 4.6 mg/24h & 9.5 mg/24h Transdermal Patches, through the centralised procedure falling within the Article 19 (1) and Annex I (point 2 indents (c) and (d) of the Commission Regulation (EC) No 1234/2008.

Actavis Group PTC ehf is already the Marketing Authorisation Holder for Rivastigmine Actavis 1.5mg, 3mg, 4.5mg, 6mg hard capsules (EU/1/11/693/001-016).

The applicant applied for the following indication: Symptomatic treatment of mild to moderately severe Alzheimer's dementia. Symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease.

The application submitted is composed of administrative information, complete quality data, and a clinical bioequivalent study

Information on paediatric requirements

Not applicable

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 Limitied.
- Date of authorisation: 12/05/1998
- Marketing authorisation granted by: Community
- EU registration. Marketing authorisation number: EU/1/98/066/019-026

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

Rivastigmine Actavis transdermal patch was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer(s) responsible for batch release

Capsule, hard

Actavis ehf.

Reykjavíkurvegur 76 - 78

IS-220 Hafnarfjördur

Iceland

Transdermal Patch

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:

Rapporteur: Kristina Dunder

- The application was received by the EMA on 5 January 2012.
- The procedure started on 25 January 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 April 2012
- During the meeting on 21 - 24 May 2012 the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 May 2012
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 August 2012
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 September 2012
- During the CHMP meeting on 15 - 18 October 2012,the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 12 November 2012.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding issues to all CHMP members on 26 November 2012
- During the CHMP meeting on 10 – 13 December 2012, the CHMP agreed on a second list of outstanding issues to be addressed in writing by the applicant The applicant submitted the responses to the CHMP second List of Outstanding Issues on 18 January 2013.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the second List of Outstanding issues to all CHMP members on 15 February 2013
- During the meeting on 18 - 21 February 2013, 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 Actavis transdermal patch on 21 December 2012.

2. Scientific discussion

2.1 Introduction

The application for Rivastigmine Actavis, 4.6 mg/24 hours, and 9.5 mg/24 hours, transdermal patches is a an extension to the product, Rivastigmine Actavis 1.5 mg, 3 mg, 4.5 mg and 6 mg hard capsules approved as a generic application according to Article 10(1) of Directive 2001/83/EC in the centralised procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Exelon, 4.6 mg/24 hours and 9.5 mg/24 hours, transdermal patches authorised in the community since 1998, with Novartis Europharm Limited as marketing authorisation holder.

The reference product used in the bioequivalence study is Exelon, 9.5 mg/24 hours, transdermal patches marketed by Novartis Europharm Limited. Drug product sourced in the UK was used in the bioequivalence study.

The active substance is not considered a new active substance. The indication for Rivastigmine Actavis transdermal patches is the same as the reference medicinal product.

2.2. Quality aspects

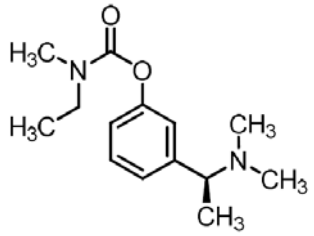
2.2.1. Introduction

Rivastigmine Actavis is presented in the form of transdermal patches containing rivastigmine base instead of rivastigmine hydrogen tartrate as per the capsules. The patches are packed in heat-sealed pouches made of paper/foil/Barex® laminate.

The composition is described in section 6.1. of the SmPC

2.2.2. Active substance

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.



Chemical name: 3-[(1S)-1-(dimethylamino)ethyl]phenyl ethyl(methyl)carbamate

Manufacture

The synthetic process of the active substance Rivastigmine involves three chemical transformations and is using well characterised starting materials.

A detailed description and a flow chart for all synthetic steps including details about the used equipment, quantities of reagents, reaction conditions (reaction time and temperature, drying conditions and drying time, purification etc.), and in process controls have been presented.

Specification

The drug 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)

Stability

Stability studies under ICH conditions have been conducted on 6 production and pilot scale batches. 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. The drug substance is found to be labile under these conditions.

It was also observed that rivastigmine is enantiomerically stable. No racemization has been observed in any of the stress testing conditions.

During long-term and accelerated stability studies the drug substance is stable. No trends are observed in any of the parameters tested.

The stability results indicate that the drug 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 drug product was to develop a transdermal rivastigmine system that is bioequivalent to the transdermal patch of the reference 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 C11-1612) with a pilot scale batch.

The formulation efforts sought to load rivastigmine with comparable total drug amounts to see if 3M proprietary acrylate copolymer adhesives could accommodate the required drug 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, 3M initially explored compositions without these excipients.

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 reference patch also utilizes an antioxidant (vitamin E) in its composition to address degradant/impurity issues. 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 proposed is stated in the SmPC and it is adequate to support the stability and 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 Transdermal System is satisfactorily described, and it has been clearly detailed in flow-chart diagrams.

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. Critical process parameters in the manufacturing process were defined and in-process controls tests were imposed to confirm that these steps had been performed successfully.

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 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.

Stability of the product

Stability studies were performed under ICH conditions. Stability data is presented for 7 batches with 12 months data available. The study is planned for 36 months in 25 °C / 60% RH and 30 °C / 65% RH and 6 months in 40 °C / 75% RH.

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 drug substance is light sensitive. No photostability testing of the patches has been performed. Since the drug 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.

2.2.6. Recommendation(s) for future quality development

Not applicable.

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.

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

Ecotoxicity/Environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Rivastigmine Actavis transdermal patch 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.

2.3.2 Discussion and Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Rivastigmine Actavis and justifications that the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product 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 is an application for a new pharmaceutical form (patch) containing Rivastigmine. To support the marketing authorisation application the applicant conducted one bioequivalence study, Study C11-1612.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

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

2.4.2 Pharmacokinetics

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 -70oC (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	N/A
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 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 – 20oC and over 6 freeze-thaw cycles. Data on long-term stability data was not found by the assessor, but the clinical summary claims long-term stability in plasma up to 54 days at -20oC as well as -70 oC. Matrix effect was evaluated in 6 lots of blank matrix, but data was not presented according to current guidelines.

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 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 doses

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 Actavis 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.

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.

2.4.3 Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4 Discussion on clinical aspects

The applicant has 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 Actavis 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 subsequently 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 Actavis transdermal patch and justifications that the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional clinical studies were not considered necessary.

Based on the presented bioequivalence study Rivastigmine Actavis 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 table presents the summary of risk minimisation activities, as proposed by the MAH in RMP version 3.1.

Table 1. Summary of the risk minimisation measures

Safety issue	Routine risk minimisation activities	Additional risk minimisation measures
Important identified risks		
NA	None proposed	None proposed
Important potential risks		
Risk of misuse and dosing errors resulting in overdose	Information included in summary of product characteristics	Educational materials: patient reminder card including instruction for use, illustration showing proper patch application and body locations patient medication record
Important missing information		
NA	None proposed	None proposed

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 ACTAVIS is marketed, at launch and after launch of the transdermal patch all physicians who are expected to prescribe RIVASTIGMINE ACTAVIS 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

The applicant has submitted a bridging report together with a focus user test. The bridging package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a generic version of Rivastigmine Actavis transdermal patch. The reference product Exelon patch is indicated for"symptomatic treatment of mild to moderately severe Alzheimer's dementia". No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical 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 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 European 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 Actavis 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 Actavis 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

Risk management system

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.

CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where RIVASTIGMINE ACTAVIS is marketed, at launch and after launch of the transdermal patch all physicians who are expected to prescribe RIVASTIGMINE ACTAVIS 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 cycle

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.