6 June 2011
EMA/454217/2011
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Rivastigmine Actavis

International nonproprietary name: Rivastigmine

Procedure No. EMEA/H/C/2036

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 Actavis Group PTC ehf submitted on 09/03/2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Rivastigmine Actavis, through the centralised procedure falling within the scope of the Article 3 (3) – 'Generic of a Centrally authorised product' of Regulation (EC) No. 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24/09/2009.

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 the Community on the basis of a complete dossier in accordance with Article 6 of Directive 2001/83/EC, as amended.

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 legal basis for this application refers to:

Article 10(1) of Directive 2001/83/EC, as amended.

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

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 1.5mg,3mg, 4.5mg, 6mg Hard capsules
- Marketing authorisation holder: Novartis Europharm Limitied.
- Date of authorisation: 12/05/1998
- Marketing authorisation granted by: Community
- EU registration. Marketing authorisation number: EU/1/98/066/001-012, 014-017

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

- Product name, strength, pharmaceutical form: Exelon 1.5mg,3mg, 4.5mg, 6mg Hard capsules
- Marketing authorisation holder: Novartis Europharm Limitied.
- Date of authorisation: 12/05/1998
- Marketing authorisation granted by: Community

- EU registration. Marketing authorisation number: EU/1/98/066/001-012, 014-017

■ 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 1.5mg hartkapseln (hard-capsules)
- Marketing authorisation holder: Novartis Europharm Limitied.
- Date of authorisation: 12/05/1998
- Marketing authorisation granted by: Community
- EU registration. Marketing authorisation number EU/1/98/066/001-3, EU/1/98/066/014
- Bioavailability study number(s): 1061

And

- Product name, strength, pharmaceutical form: Exelon 6 mg hartkapseln (hard-capsules)
- Marketing authorisation holder: Novartis Europharm Limitied.
- Date of authorisation: 12/05/1998
- Marketing authorisation granted by: Community
- EU registration. Marketing authorisation number EU/1/98/066/010-12, EU/1/98/066/017
- Bioavailability study number(s): AA85018

Licensing status:

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

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP and the evaluation team were:

Rapporteur: Dr. Tomas Salmonson.

- The application was received by the Agency on 09 March 2010.
- The procedure started on 26 May 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 August 2010 .
- During the meeting on 23 September 2010, 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 23 September 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 November 2010.

- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 03 January 2011.
- During the CHMP meeting on 20/01/2011, 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 adopted List of Outstanding Issues on 14 March 2011
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the CHMP consolidated List of Outstanding Issues on 08 April 2011.
- During the meeting on 14 April 2011, 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 on 14 April 2011. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 11 April 2011.

2. Scientific discussion

2.1. Introduction

Rivastigmine is an acetyl- and butyrylcholinesterase inhibitor of the carbamate type, thought to facilitate cholinergic neurotransmission by slowing the degradation of acetylcholine released by functionally intact cholinergic neurones. Thus, Rivastigmine may have an ameliorative effect on cholinergic-mediated cognitive deficits in dementia associated with Alzheimer's disease and Parkinson's disease.

Rivastigmine interacts with its target enzymes by forming a covalently bound complex that temporarily inactivates the enzymes. Activity of the enzyme returns to baseline levels about 9 hours after the maximum inhibitory effect has been achieved.

Rivastigmine 1.5 mg, 3 mg, 4.5 mg and 6 mg hard capsules are generic of the centrally authorised Exelon 1.5 mg, 3 mg, 4.5 mg, 6 mg Hard capsules

The efficacy and safety of Rivastigmine has been demonstrated in several well-controlled studies. A summary of these studies can be found in the EPAR of the reference product Exelon.

The reference product was authorized in the Community on 12 May 1998 for Novartis Europharm Limited. Bioequivalence to the reference product was demonstrated comparing Rivastigmine Actavis 1.5 mg capsules and Rivastigmine 6 mg capsules with the innovator 1.5 mg capsules and 6 mg capsules. The data supports the biowaiver for the 3 mg and 4.5 mg strengths.

The indication proposed for Rivastigmine Actavis is the same as for the reference medicinal product:

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,

2.2. Quality aspects

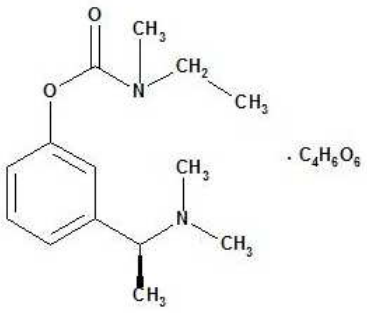
2.2.1. Introduction

Rivastigmine Actavis is presented as Hard capsules, containing 1.5, 3, 4.5 and 6 mg of rivastigmine (as rivastigmine hydrogen tartrate) as the active substance. Other ingredients are defined in the SmPC section 6.1.

The hard capsules are packaged in alu/PVC Blister packs and HDPE bottles.

2.2.2. Active Substance

Rivastigmine hydrogen tartrate is soluble in water, methanol and ethanol, the pKa value is 8.85. It is hygroscopic and is deliquescent. Rivastigmine base is chiral, containing one stereogenic centre with S configuration. The tartrate moiety contains two stereocentres, both with R configuration.



Chemical name: 2,6-dioxo-4-phenyl-piperidine-3-carbonitrile

Rivastigmine hydrogen tartrate has positive specific optical rotation. It does not exhibit polymorphism.

Manufacture

An ASMF is used for information on the drug substance. The synthesis of rivastigmine hydrogen tartrate is well described. The structure of rivastigmine hydrogen tartrate has been adequately proven and its physico-chemical properties sufficiently described.

Specification

The drug substance specification includes tests for appearance (visual), identification (IR, HPLC), Loss on drying (Ph Eur), Specific optical rotation (DMF), Sulphated ash (Ph Eur), Related substances (HPLC), Assay (on dry) by HPLC, Heavy metals (Ph. Eur), Residual solvents (GC).

Stability

Stability studies at long term and intermediate storage conditions have been performed with the drug substance. No significant changes in any parameters were observed. Based on the stability data presented a justified retest period has been accepted.

2.2.3. Medicinal Product

Pharmaceutical Development

The objective was to develop a generic drug product that is comparable to the reference product.
Rivastigmine Actavis hard capsules 1.5 mg, 3 mg, 4.5 mg and 6 mg are oral immediate release capsules. Both, the reference product and the generic contain the same excipients in similar proportions.
Special controls on the manufacturing process had to be taken into account in order to guarantee the correct development of the process. The four strengths are manufactured from a separate powder blend

Adventitious agents

The gelatin used for the capsules are from animal origin, valid CEP TSE certificates have been provided.

Manufacture of the Product

The manufacturing process is satisfactorily described. A flow-chart of the process including in-process control and validation test has been submitted.

The production process is performed in compliance with the principle of Good Manufacturing Practices, as laid down in volume IV of the rules Governing Medicinal Products in the European Community.

The manufacturing process is considered to be a standard manufacturing process.

Product Specification

The product specifications cover appropriate parameters for the dosage forms. Validations of the analytical methods have been presented. Batch analyses are provided. The batch analyses results show that the finished products meet the specifications proposed.
The release and shelf-life specifications of the finished product contains tests with suitable limits for Capsule description (visually), Identification of Rivastigmine (UV, HPLC), Disintegration in water 37°C (Ph Eur), Assay: Rivastigmine (HPLC. Ph Eur) uniformity of dosage units (HPLC. PhEur.), uniformity of content (HPLC-UV PhEur.), related substances (HPLC), Dissolution: Rivastigmine (HPLC), Microbiology (Ph.Eur). The specifications, acceptance criteria and test methods are justified.

Stability of the Product

Batch analysis results are presented for at least two pilot scale batches of each strength.

The batches are tested according to the drug product specification. All results comply with the specification.

The stability program consisted of:

Real time studies: a) Test conditions: 30°C/75% RH. b) Test conditions: 25°C/60% RH. c) Bulk stability study d) In-use stability study: 25°C/60% RH.

Accelerated stability:

Photostability

Directly exposed: Both raw material and capsule powder were stable when exposed to UV and visible light for up to two weeks. The results indicate that rivastigmine capsules are not light sensitive. This is in accordance with the innovator SPC which does not recommend any specific protection from light.

Long term stability:

30°C/75%RH (alu/PVC blister and HDPE containers). No increase is observed in impurities. All results are within the specification limit.

Bulk stability

The batches were stored at 25°C/60%RH. Same batches were included in the long-term stability program, packed in alu/PVC blister and HDPE containers. Comparable results are observed for the bulk stability and the long term stability of packaged product. It is therefore concluded that the product is stable in bulk.

Open HDPE containers

Results are available for up to 6 months for two 1.5 mg batches of the primary registration batches. All parameters are within specification limits for up to 6 months. The product is therefore considered stable throughout the period of use.

Based on the stability data presented, the shelf-life as specified in the SmPC when stored below 30°C was accepted.

2.2.4. Discussion and conclusion on chemical, pharmaceutical and biological aspects

The active substance and medicinal product have been adequately described. Excipients used in the formulation of the medicinal product and the manufacturing process selected are typical for capsules formulations and are the same as the reference product. The results of the tests indicate that the active substances and the medicinal product can be reproducibly manufactured and therefore the product should have a satisfactory and uniform performance in the clinic.

2.3. Non-Clinical aspects

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.

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Rivastigmine Actavis manufactured by Actavis Group PTC ehf. 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.

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

2.4. Clinical Aspects

2.4.1. Introduction

This is an abridged application for capsules containing rivastigmine. To support the marketing authorisation application the applicant conducted 2 bioequivalence studies with cross-over design under fed conditions, as recommended for the conditions of intake for the reference medicinal product Exelon. These studies were the pivotal studies for the assessment.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of rivastigmine based on published literature; this was considered acceptable. The SmPC is in line with the SmPC of the reference product.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment *Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98* and the "Questions and Answers on the bioavailability and bioequivalence guideline" of July 2006 EMEA/CHMP/EWP/40326/2006 are of particular relevance.

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.

The GCP statement for the clinical site was verified by audit statement provided by the MHRA, and the analytical facilities for Study 1061 and Study AA85018 have been inspected by the FDA and by the Austrian authority, respectively.

Clinical studies

To support the application, the applicant has submitted 2 bioequivalence studies.

Rivastigmine has been shown to have nonlinear 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, , 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 Applicant therefore submitted a bioequivalence study comparing Rivastigmine Actavis 6 mg to Exelon 6 mg.

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

With reference to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98), the applicant considered that the criteria for biowaivers are met for the 3 and 4.5 mg strengths applied for.

2.4.2. Pharmacokinetics

Study 1061 (1.5 mg hard capsules)

Methods

Study design

This was a single-dose, randomized, open-label, crossover bioavailability study performed on 60 healthy male and female volunteers under fed conditions.

A 1.5 mg single dose of rivastigmine was administered each period and the administrations were separated by a washout period of 7 days.

Subjects fasted overnight for at least 10 hours prior to their scheduled dosing times when they were given a standard high fat breakfast, which was administered 30 minutes prior to dosing. Subjects completely consumed this meal in 30 minutes or less. The dose was administered with 240 ml water. Blood samples were collected at the following time points: pre-dose (2 samples) and at 0.33, 0.67, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.25, 3.5, 3.75, 4.0, 4.5, 5.0, 6.0, 8.0, 10.0, 12.0 and 14.0 hours.

The study was complying with GCP, as claimed by the applicant.

Test and reference products

Rivastigmine Actavis 1.5 mg capsule manufactured by Actavis Group PTC ehf (batch No. D31730, manufacturing date: 14/02/2008) has been compared to Exelon 1.5 mg hard capsule manufactured by Novartis Europharm Limited (Batch No: B5081, expiry. date: 02/2012).

Population studied

Sixty (60) healthy men and women (1:1) aged from 18 to 54 years were included. Two subjects dropped out of the study, both due to adverse events after treatment A (the test product). One of them was dismissed for safey reasons; the other withdrew due to an AE just before starting the second period. The subjects were not replaced. Thus 58 subjects were included in the pharmacokinetic analysis.

Analytical methods

Results of pre-study and inter-study have been provided for the performance and reliability of the assay (e.g accuracy, precision, stability). These were considered satisfactory and the method was considered sufficiently characterised and validated.

Pharmacokinetic Variables

PK variables included: Cmax, Tmax, AUCt, AUCinf, AUCt/AUCinf, T1/2. and λ.

Statistical methods

Descriptive statistics of relevant pharmacokinetic parameters were provided for the test and reference products. Analyses of variance (ANOVA) include sequence, subjects nested within sequence, period and treatment on the natural logarithm-transformed data for AUCt, AUCinf and Cmax, and on the raw data for AUCt, AUCinf, Cmax, Tmax, λ and T1/2 was performed. Tmax was compared between test and reference products using an additional non-parametric method using Wilcoxon two-sample test, two-sided normal (Z) approximation. The 90% confidence intervals (CI) of the Test/Reference ratios of geometric means for AUCt, AUCinf, and Cmax were calculated based on the least square means (LSMEANS) and ESTIMATE of the ANOVA.

To establish bioequivalence, the calculated 90% confidence interval for the ratio of geometric means for AUCt and Cmax for rivastigmine should fall within 0.80 and 1.25.

Results

The results of the study are presented in table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) – Rivastigmine 1.5 mg

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

Bioequivalence was shown with regard to Cmax and AUC. The confidence intervals were quite narrow. The non-parametric analysis of Tmax for rivastigmine did not detect a significant difference in Tmax between the Test and Reference products (p=0.5716.

Conclusions

Based on the presented bioequivalence study, Rivastigmine Actavis 1.5 mg capsule is considered bioequivalent with Exelon 1.5 mg hard capsule.

Study AA85018 (6 mg hard capsules)

Methods

Study design

This was a single-dose, randomised, open-label, 2-way crossover, 2-sequence, comparative bioavailability study performed on 40 healthy adult volunteers (29 males and 11 females).

A 6 mg single dose of rivastigmine was administered each period and the administrations were separated by a washout period of 7 days.

Subjects faster overnight fast of at least 10 hours until 30 minutes prior to their scheduled dosing times when they were given a standard high fat breakfast. Subjects completely consumed this meal in 30 minutes or less. The dose was administered with 240 ml of water. In order to minimize 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 tmax of rivastigmine). Blood samples were collected at the following time points: pre-dose and at 0.333, 0.667, 1, 1.25, 1.5, 1.75, 2, 2.333, 2.667, 3, 3.333, 3.667, 4, 4.5, 5, 6, 8, 10 and 12 hours.

Test and reference products

Rivastigmine Actavis 6 mg manufactured by Actavis Group PTC ehf (batch No. D32399, manufacturing date: 15/04/2009) has been compared to Exelon 6,0 mg hard capsule, manufactured by Novartis Farmacéutica, S.A. (Batch No: B8021, exp. Date: 01/2012).

Population studied

A total of 40 healthy adult non-smoking or moderate smoking subjects (29 males and 11females) were enrolled in the study and were randomised to the study treatment. Thirty-four subjects (24 males and 10 females) completed the study. Four subjects were withdrawn due to vomiting, 2 or 2.5 hours post-dose. One was withdrawn due to a positive cocaine test and one subject did not return for period 2 check-in.

Analytical methods

The samples were treated, filtered and extracted using an online extraction procedure. The filtered samples were analyzed using a cohesive turbulent flow system equipped with a triple quadruple mass spectrometer.

The performance of the analytical method appeared satisfactory.

Pharmacokinetic Variables

PK parameters included AUC 0-t, AUCinf, AUC/AUCinf, Cmax, tmax, half-life and kel PK parameters were calculated for rivastigmine in plasma.

Statistical methods

Arithmetic means, standard deviations, coefficients of variation, geometric means, median, minimum and maximum values were calculated for the plasma concentrations and the pharmacokinetic parameters. Analyses of variance (ANOVA) were performed on the ln-transformed AUC 0-t, AUCinf and Cmax. The ANOVA model included sequence, formulation, and period as fixed effects, and subject nested within sequence as a random effect. Each ANOVA included calculation of LSM, the difference between formulation LSM, and the standard error associated with this difference. To determine bioequivalence in this comparative bioavailability study, the standard that the 90% confidence interval of the ratios of least-squares means of AUC 0-t and Cmax of the test to the reference formulation should be within 0.80 to 1.25 was used.

Results

The results of the study are presented in table 2 below.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) – Rivastigmine 6 mg

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

Bioequivalence was shown with regard to Cmax and AUC. The confidence intervals were quite narrow.

Conclusions

Based on the presented bioequivalence study, Rivastigmine Actavis 6 mg capsule is considered bioequivalent with Exelon 6 mg hard capsule.

2.4.3. Pharmacodynamics

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

2.4.4. Post marketing experience

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

2.4.5. Discussion on Clinical aspects

The applicant has submitted two well-designed studies showing bioavailability of the 1.5 and 6 mg formulation under fed conditions, which is the recommended condition of intake in the SmPC. The doses that were used for those studies cover the therapeutic dose range.

Rivastigmine shows non-linear pharmacokinetics which has been proposed to be caused by binding to the target enzyme. The non-linearity gives about 50% higher AUCs than expected when doubling the dose. Rivastigmine does not have full bioavailability. Thus, there is a possibility that the nonlinearity seen is due to the elimination/1st pass. However, rivastigmine is eliminated through choline esterase mediated hydrolysis, and therefore the nonlinearity is considered less likely at a metabolism level. Furthermore, bioequivalence has been shown between a rivastigmine oral solution and capsules of the reference medicinal product Exelon). Thus it seems unlikely that differences in rate of dissolution between the original and test product would affect the bioavailability. Therefore, the CHMP considered acceptable that 3 and 4.5 mg are not studied and thextrapolation of the results obtained for the 1.5 mg and 6 mg rivastigmine capsules to the 3 mg and 4.5 mg capsules was deemed acceptable. This is in accordance with the *Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1*).

There were no deaths or SAE reported. The safety of rivastigmine is well documented and both test and reference products are expected to have a comparable adverse event profile.

2.4.6. Conclusions on clinical aspects

Bioequivalence between Rivastigmine Actavis and the reference product Exelon has been adequately demonstrated.

2.5. Pharmacovigilance

PSUR

The next data lock point for the reference medicinal product is 31 January 2012.

The PSUR submission schedule should follow the PSUR schedule for the reference product

Detailed description of the Pharmacovigilance system

The CHMP considers that 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.

Risk Management Plan

The application is based on a reference medicinal product for which no safety concerns requiring additional risk minimization activities have been identified.

Routine pharmacovigilance activities according to volume 9A/ICH will be undertaken whilst the product is in the market, including careful review of individual case safety reports, literature review, signal detection procedures and generation of the required safety reports. Specific risk minimisation activities are not envisaged as the safety aspects of the product are well characterised and therefore a Risk Minimisation plan is not required.

2.6. User consultation

The user testing of the package leaflet was performed. The criterion for a successful Readability Test was fulfilled. The user testing of the package leaflet was judged acceptable.

2.7. Benefit/risk assessment and recommendation

Overall conclusion and Benefit/risk assessment

This application concerns a generic version of rivastigmine capsule. The reference product Exelon is indicated for the symptomatic treatment of mild to moderately severe Alzheimer's dementia and symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease.

No nonclinical studies have been provided for this generic 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 study design of the two bioequivalence studies that were submitted was considered adequate to evaluate the bioequivalence of rivastigmine capsule with Exelon hard capsules, and was in line with the respective European requirements.

Choice of dose, sampling points, overall sampling time, as well as wash-out period, were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Rivastigmine Actavis met the protocol-defined criteria for bioequivalence when compared with Exelon. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-∞, and Cmax were all contained within the protocol-defined acceptance range of 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.

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

Recommendation

Based on the CHMP review of available data, the CHMP considered by consensus that the benefit/risk ratio of Rivastigmine Actavis in the treatment of

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

was favourable and therefore recommended the granting of the marketing authorisation.