Bundesamt für Sicherheit im Gesundheitswesen

CMDh/223/2005
February 2014

Public Assessment Report

Scientific discussion

Rivastigmin Sandoz 4,6 mg/24 Stunden - transdermales Pflaster
Rivastigmin Sandoz 9,5 mg/24 Stunden - transdermales Pflaster
Rivastigmin Sandoz 13,3 mg/24 Stunden - transdermales Pflaster

Rivastigmine

Date: 09.07.2015

This module reflects the scientific discussion for the approval of Rivastigmin Sandoz 4,6 mg/24 Stunden - transdermales Pflaster, Rivastigmin Sandoz 9,5 mg/24 Stunden - transdermales Pflaster and Rivastigmin Sandoz 13,3 mg/24 Stunden - transdermales Pflaster. The procedure for the first two strengths was finalised at 18.11.2013 of day 210. The procedure for the third strength was finalised at 29.04.2015 of day 210. For information on changes after these dates please refer to the module 'Update'.

Bundesamt für Sicherheit im Gesundheitswesen
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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Rivastigmin Sandoz 4,6 mg/24 Stunden - transdermales Pflaster, Rivastigmin Sandoz 9,5 mg/24 Stunden - transdermales Pflaster and Rivastigmin Sandoz 13,3 mg/24 Stunden - transdermales Pflaster, from Sandoz GmbH.
The product is indicated for: symptomatic treatment of mild to moderately severe Alzheimer's dementia.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

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.

II. QUALITY ASPECTS

II.1 Introduction

Rivastigmin Sandoz is a transdermal patch which is presented in a sachet.

II.2 Drug Substance

The active substance in Rivastigmin Sandoz is rivastigmine. The specification of the active substance meets the current scientific requirements. The adequate quality of the active substance has been shown by submitting the appropriate control data. The stability of the active substance has been tested under ICH conditions. The results of the stability studies support the established retest-period.

II.3 Medicinal Product

Rivastigmin Sandoz contains the following excipients:

Backing layer:
- Polyethylene terephthalate film, lacquered

Medicinal product matrix:
- All-rac-α Tocopherol
- Poly(butylmethacrylate, methyl-methacrylate) copolymer (3:1)

- Acrylic copolymer

Adhesive matrix:
- All-rac-α Tocopherol
- Silicone
- Dimeticone

Release liner:
- Polyester film, fluoropolymer-coated

Printing Ink:
- Resin
- Pigments
- Organic polymers/resins

The manufacturers responsible for batch release are:

Novartis Pharma GmbH
Roonstrasse 25, 90429 Nürnberg, Germany

Hexal AG
Industriestrasse 25, 83607 Holzkirchen, Germany

Salutas Pharma GmbH
Otto-von-Guericke-Allee 1, 39179 Barleben, Germany

Lek Pharmaceuticals d.d.
Verovškova 57, 1526 Ljubljana, Slovenia

The development of the product has been sufficiently made and deemed appropriate. The usage of all the excipients has been described.
The release specification includes the check of all parameters relevant to this pharmaceutical form. Appropriate data concerning the control of the finished product support the compliance with the release specifications.
The packaging of the medicinal product complies with the current legal requirements.
Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SmPC, with a shelf life of 24 months when stored below 25°C and stored in the original sachet.

The pharmaceutical quality of Rivastigmin Sandoz has been adequately shown.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of active substance and medicinal product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of rivastigmine are well known. As rivastigmine is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.
The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Rivastigmin Sandoz is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

The indication claimed is in accordance with that of the innovator product Exelon transdermal patch.
The efficacy of rivastigmine is established and documented in controlled clinical studies. No additional data have been submitted and none are required.

IV.2 Pharmacokinetics

Rivastigmin Sandoz will be produced with the same qualitative and quantitative composition, at the same manufacturing site, using the same manufacturing procedure and the same source of active substance as the currently manufactured reference product Exelon.
Therefore no bioequivalence studies are required and all data regarding to safety and efficacy available of the reference medicinal product also apply for this application.

IV.3 Pharmacodynamics, Clinical efficacy and safety

Pharmacotherapeutic group: psychoanaleptics, anti-dementia drugs, anticholinesterases,
ATC code: N06DA03

The clinical overview on the clinical pharmacology, efficacy and safety is adequate. The claimed indication is the same than the indication of the originator product.
From the clinical point of view, there seem to be no signs that Rivastigmin Sandoz differs from the reference product with regard to efficacy or safety.

IV.4 Risk Management Plan

The MAH has submitted a risk management plan (version 2.1; date of final sign off 24.02.15), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to
-Rivastigmin Sandoz 4,6 mg/24 Stunden - transdermales Pflaster
-Rivastigmin Sandoz 9,5 mg/24 Stunden - transdermales Pflaster
-Rivastigmin Sandoz 13,3 mg/24 Stunden - transdermales Pflaster

Summary table of safety concerns as approved in RMP (version 2.1.; date of final sign off 24.02.15)

Table 3-1 Summary of safety concerns

Important identified risks	Gastrointestinal symptoms (nausea, vomiting, and diarrhea)
	Worsening of motor symptoms associated with Parkinson's disease
	Pancreatitis
	Cardiac arrhythmias
	Exacerbations of asthma and COPD
	Application site skin reactions and irritations
	Hypertension
	Gastrointestinal ulceration, hemorrhage, and perforation
	Seizures
	Hallucinations
	Syncope and loss of consciousness
	Medication misuse
	Medication errors
	Liver disorders
	Severe skin reactions (bullous reactions)
Important potential risks	Myocardial infarction
	Cerebrovascular accident
	Pulmonary infections
	Death
Missing information	None

Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in RMP version 2.1.; date of final sign off 24.02.2015

Safety Concern	**Routine Risk Minimisation Measures**	**Additional Risk Minimisation Measures**
Important Identified Risks		

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Gastrointestinal symptoms (nausea, vomiting, and diarrhea)	The risk of gastrointestinal symptoms (nausea, vomiting, and diarrhea) is mentioned in section 4.4 "Special warnings and precautions for use", section 4.8 "Undesirable effects" and in section 4.9 "Overdose" of the SmPC. The PIL also describes this safety concern adequately to the patient.	None
Worsening of motor symptoms associated with Parkinson's disease	The risk of worsening of motor symptoms associated with Parkinson's disease is mentioned in section 4.4 "Special warnings and precautions for use" and section 4.8 "Undesirable effects" of the SmPC. The PIL also describes this safety concern adequately to the patient.	None
Pancreatitis	The risk of pancreatitis is mentioned in section 4.8 "Undesirable effects" of the SmPC. The PIL also describes this safety concern adequately to the patient.	None
Cardiac arrhythmias	The risk of cardiac arrhythmias is mentioned in section 4.8 "Undesirable effects" of the SmPC. The PIL also describes this safety concern adequately to the patient.	None
Exacerbations of asthma and COPD	The risk of exacerbations of asthma and COPD is mentioned in section 4.4 "Special warnings and precautions for use" of the SmPC. The PIL also describes this safety concern adequately to the patient.	None
Application site skin reactions and irritations	The risk of application site skin reactions and irritations is mentioned in sections 4.4 "Special warnings and precautions for use" and 4.8 "Undesirable effects" of the SmPC. The PIL also describes this safety concern adequately to the patient	None
Hypertension	The risk of hypertension is mentioned in section 4.8 "Undesirable effects" and in section 4.9 "Overdose" of the SmPC. The PIL also describes this safety concern adequately to the patient.	None
Gastrointestinal ulceration, haemorrhage, and perforation	The risk of gastrointestinal ulceration, haemorrhage, and perforation is mentioned in sections 4.4 "Special warnings and precautions for use" and 4.8 "Undesirable effects" of the	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	SmPC. The PIL also describes this safety concern adequately to the patient.	
Seizures	The risk of seizures is mentioned in sections 4.4 "Special warnings and precautions for use" and 4.8 "Undesirable effects" of the SmPC. The PIL also describes this safety concern adequately to the patient.	None
Hallucinations	The risk of hallucinations is mentioned in section 4.8 "Undesirable effects" and in section 4.9 "Overdose" of the SmPC. The PIL also describes this safety concern adequately to the patient.	None
Syncope and loss of consciousness	The risk of syncope and loss of consciousness is mentioned in section 4.7. "Effects on ability to drive and use machines", section 4.8 "Undesirable effects" and in section 4.9 "Overdose" of the SmPC. The PIL also describes this safety concern adequately to the patient.	None
Medication misuse	The risk of medication misuse is mentioned in section 4.2 "Posology and method of administration", section 4.4 "Special warnings and precautions for use" and section 4.9 "Overdose" of the SmPC. The PIL also describes this safety concern adequately to the patient.	Patient/caregiver reminder card Objective and justification of why needed: To remind healthcare professionals of the importance of the proper use and application of rivastigmine transdermal patch and the need to instruct patients and caregivers on correct application techniques for the use of rivastigmine transdermal patch. The combined medication record and instructions for use is a tool to be distributed globally through the marketing and sales organizations in all CPOs (care plan oversight) to physicians and pharmacists who will then distribute to patients and caregivers. It is intended as a device whereby the daily application of the patch is recorded and acts as a daily reminder to the patient or caregiver. It also contains body diagrams which can be used for instruction of the patient, as well as clearly indicating application site of each patch. Proposed actions/components and rationale: The information in this

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
		memory tool has been user tested. The tool will include key statements including the following concepts: □ Take off the previous patch before putting One new patch on □ Only apply 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. An analysis of the efficacy of this tool to be reported in PSURs and in a separate report, including CIOMS, every 6 months.
Medication errors	The risk of medication errors is mentioned in section 4.2 "Posology and method of administration", section 4.4 "Special warnings and precautions for use" and section 4.9 "Overdose" of the SmPC. The PIL also describes this safety concern adequately to the patient.	Patient/caregiver reminder card Objective and justification of why needed: To remind healthcare professionals of the importance of the proper use and application of rivastigmine transdermal patch and the need to instruct patients and caregivers on correct application techniques for the use of rivastigmine transdermal patch. The combined medication record and instructions for use is a tool to be distributed globally through the marketing and sales organizations in all CPOs to physicians and pharmacists who will then distribute to patients and caregivers. It is intended as a device whereby the daily application of the patch is recorded and acts as a daily reminder to the patient or caregiver. It also contains body diagrams which can be used for instruction of the patient, as well as clearly indicating application site of each patch. Proposed actions/components and rationale: The information in this memory tool has been user tested. The tool will include key statements including the following concepts: □ Take off the previous patch before putting One new patch on □ Only apply one patch per day □ Do not cut the patch into pieces

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
		□ Press the patch firmly in place for at least 30 seconds using the palm of the hand. An analysis of the efficacy of this tool to be reported in PSURs and in a separate report, including CIOMS, every 6 months.
Liver disorders	The risk of liver disorders is mentioned in section 4.2 "Posology and method of administration", section 4.4 "Special warnings and precautions for use", section 4.8 "Undesirable effects" and 5.2 "Pharmacokinetic properties" of the SmPC. The PIL also describes this safety concern adequately to the patient.	None
Severe skin reactions (bullous reactions)	The risk of severe skin reactions (bullous reactions) is mentioned in section 4.4 "Special warnings and precautions for use" and section 4.8 "Undesirable effects" of the SmPC. The PIL also describes this safety concern adequately to the patient.	None
Important Potential Risks		
Myocardial infarction	**C**urrently available data do not support the need for risk minimization measure	None
Cerebrovascular accident	Currently available data do not support the need for risk minimization measure	None
Pulmonary infections	Currently available data do not support the need for risk minimization measure	None
Death	Currently available data do not support the need for risk minimization measure	None
Missing Information		
None		

IV.5 Discussion on the clinical aspects

The indication claimed is in accordance with that of the reference product Exelon.
The efficacy of rivastigmine is established and documented in controlled clinical studies. No additional data have been submitted and none are required.

Rivastigmin Sandoz will be produced with the same qualitative and quantitative composition, at the same manufacturing site, using the same manufacturing procedure and the same source of active substance as the currently manufactured reference product Exelon.
Therefore no bioequivalence studies are provided and none are required.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Novartis' Exelon, EMEA Product number EMEA/H/C/000169. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Recommendations not falling under Article 21a/22 of Directive 2001/83 and conditions pursuant to Article 21a or 22 of Directive 2001/83/EC:
For Rivastigmin Sandoz 13,3 mg/24 Stunden - transdermales Pflaster the marketing authorisation holder commits that he will evaluate the data for peel force and adhesion force from the completed and current on-going stability studies and will consider tightening of the stability/shelf life limits for these two parameters by 31 Jan 2016 if the company observe results supporting tightening of acceptance criteria.

The pharmaceutical quality of Rivastigmin Sandoz has been adequately shown and no new non-clinical or clinical concerns have been identified.

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Public Assessment Report

Update

Rivastigmin Sandoz 4,6 mg/24 Stunden - transdermales Pflaster
Rivastigmin Sandoz 9,5 mg/24 Stunden - transdermales Pflaster
Rivastigmin Sandoz 13,3 mg/24 Stunden - transdermales Pflaster

Rivastigmine

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

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Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)