LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Rasagiline Orion
(rasagiline hemitartrate)

SE/H/1527/01/DC

This module reflects the scientific discussion for the approval of Rasagiline Orion. The procedure was finalised on 2016-05-16. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

The application for Rasagiline Orion, 1 mg, tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Orion Corporation, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK, FI and NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Azilect, 1 mg, tablet, authorised in the Community since 2005, with Teva Pharma GmbH as marketing authorisation holder.

The reference product used in the bioequivalence study is Azilect, 1 mg, tablet, from ES with Teva Pharma GmbH as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Rasagiline has an oral bioavailability of 36 %. Following an oral dose of rasagiline maximal plasma concentrations occur at approximately 0.5 hours. Food does not affect the T_{max} of rasagiline, although C_{max} and exposure (AUC) are decreased by approximately 60% and 20%, respectively, when the medicinal product is taken with a high fat meal. Since AUC is not substantially affected, there are no restrictions with respect to food in the SmPC of the originator. Rasagiline pharmacokinetics is linear with dose over the range of 0.5-2 mg. The terminal half-life is 0.6-2 hours.

Bioequivalence was evaluated in one single-dose, three-way crossover study conducted in 48 healthy volunteers, comparing two test formulations, Test-1, Rasagiline, 1 mg, tablet (with mannitol) and Test-2, Rasagiline, 1 mg, tablet (with trehalose) with Azilect, 1 mg, tablets under fasting conditions. The present application refers to Test-2 (with trehalose as diluent). Blood samples were collected pre-dose and up to 10 hours post-dose. The study design is considered acceptable. Plasma concentrations of rasagiline were determined with an adequately validated LC/MS/MS method. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for both test products. Two pair-wise comparisons were planned, Test-1 vs. Reference and Test-2 vs. Reference, with apparently no approach to handle multiplicity. However, with both the test formulations shown to be bioequivalent to the reference formulation, i.e. the formulation selected, Rasagiline with trehalose as a diluent, was not the only one that succeeded, this is of no further concern. In addition, the choice of formulation was made based on patent reasons.

Rasagiline Orion is considered bioequivalent with Azilect. In addition, the alternative test-1 formulation (with mannitol) is also considered bioequivalent with Azilect.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, 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 Rasagiline Orion.

Safety specification

IMPORTANT IDENTIFIED RISKS	• Orthostatic hypotension • Serotonin syndrome • Impulse control disorders • Concomitant use with antidepressants (SSRI, SnRI, tricyclic and tetracyclic antidepressants), CYP1A2 inhibitors or MAO inhibitors
IMPORTANT POTENTIAL RISKS	• Hypertension • Malignant Melanoma • Concomitant use with pethidine or sympathomimetics
MISSING INFORMATION	• Pregnant and lactating women

The safety concerns are aligned with another recently approved RMP for rasagiline products.

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The RMP is approved.

An updated RMP should be submitted:
- At the request of the RMS;
- 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 dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

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 with reference regarding content to Azilect EMEA/H/C/574 and with reference regarding layout to Venlafaxin Orion (DE/H/1420/01-03/DC) and Topiramat Orion (DE/H/1325/01-04/DC).
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Rasagiline Orion, 1 mg, tablet is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Rasagiline Orion, 1 mg, tablet was positively finalised on 2016-05-16.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se