CBG MEB

Public Assessment Report

Scientific discussion

Rasagiline DOC Generici 1 mg, tablets

(rasagiline tartrate)

NL/H/3425/001/DC

Date: 7 July 2016

This module reflects the scientific discussion for the approval of Rasagiline DOC Generici 1 mg, tablets. The procedure was finalised on 23 October 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Rasagiline DOC Generici 1 mg, tablets from DOC Generici S.r.l.

The product is indicated for the treatment of idiopathic Parkinson's disease (PD) as monotherapy (without levodopa) or as adjunct therapy (with levodopa) in patients with end of dose fluctuations.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Azilect 1 mg tablets (EU/1/04/304/001-007) which has been registered in the EEA by Teva B.V. since 21 February 2005 through a centralised procedure.

The concerned member state (CMS) involved in this procedure was Italy.

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

II. QUALITY ASPECTS

II.1 Introduction

Rasagiline DOC Generici is a white to off-white, oblong, biconvex tablet, debossed with 'R9SE' on one side and '1' on the other side. Each tablet contains 1.44 mg rasagiline tartrate, equivalent to 1 mg of rasagiline base.

The tablets are packed in oPA/Al/PVC/Al blister packs or PVC/PVDC/Al blister packs.

The excipients are:
- Cellulose, microcrystalline
- Tartaric acid
- Maize starch
- Starch, pregelatinised maize
- Talc
- Stearic acid

II.2 Drug Substance

The active substance is rasagiline tartrate, an established active substance not described in the European or British Pharmacopoeia (Ph.Eur.; BP). The active substance is soluble in water, sparingly soluble in methanol, very slightly soluble in isopropanol and practically insoluble in toluene. It has a chiral centre leading to one potential stereoisomer. The stable crystalline form is used.

For both manufacturers, the Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the two manufacturers of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

For the manufacturing process of rasagiline tartrate two (manufacturer-I) or three steps (manufacturer-II) are used. The information presented on the manufacturing process is sufficient.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for five (manufacturer-I) and three (manufacturer-II) batches.

Stability of drug substance
Manufacturer-I
Stability data on the drug product has been provided on four batches stored at 40°C/75% RH (6 months) and 25°C/60% RH (three up to 24 months and one up to 12 months). No or only little change over time in any of the parameters studied at both storage conditions were observed during storage. No trends in the results are seen. The retest period of 36 months is approvable.

Manufacturer-II
Stability results for nine batches are provided. Batches were stored at 40°C/75% RH (three of nine up to 6 months) and at 25°C/60% RH (three for 6 months, three for 24 months and three for 36 months). All results are within specification and no obvious trend can be observed. The proposed retest period of 48 months is acceptable. No storage restriction is considered necessary, based on the results at accelerated conditions. However, there is no objection to the proposed restriction: “Store at a temperature comprised between 15ºC and 30ºC”.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The packaging material is accepted. Impurity studies were performed as part of the development. Because of intellectual properties, the pharmaceutical development focused on selecting a different rasagiline salt as used by the originator and on replacing the filler as used in Azilect (mannitol). The MAH has provided sufficient information on the selection of microcrystalline cellulose as an alternative filler.

The active substance used is rasagiline tartrate, while the reference medicinal product Azilect contains rasagiline mesilate. In accordance with EU Guideline on the Investigation of Bioequivalence, different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered as the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. For the two forms of rasagiline salts, such a difference has been determined inconceivable. Mesilate and tartrate forms of rasagiline are shown to be comparable in pharmacological activity *in vitro* and *in vivo*. One bioequivalence study has been performed with the test product versus the reference product. The test batch used in the bioequivalence study was manufactured according to the finalised composition and manufacturing process. Dissolution tests do not show differences between the two salt forms. Both are classified as BCS Class III drugs (highly soluble, low permeable) and show similar dissolution (>85% in 15 minutes) in all conditions tested (0.1M HCl and pH 1.2, 4.5 and 6.8). Together, this provides adequate evidence for the use of rasagiline tartrate instead of rasagiline mesilate in the drug product.

Manufacturing process
The manufacturing process consists of a wet granulation process followed by drying, milling, sifting, blending, lubrication and compression. Based on the low active substance concentration, the manufacturing process is non-standard. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three commercial scaled batches. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, uniformity of dosage units, disintegration time, identification, assay, impurities and microbial contamination. Limits in the specification have been

justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three batches stored at 25°C/60% RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). Furthermore one batch was put on a photostability study. The conditions used in the stability studies and photostability study are in accordance with applicable European guidelines. Tablets were stored in the proposed packages. The results at accelerated, intermediate and long term conditions are all within specification. Also, the photostability study showed no trends. On basis of the data submitted, a shelf life was granted of 30 months. The labelled storage conditions are 'Do not store above 25˚C'.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Rasagiline DOC Generici has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Rasagiline DOC Generici 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.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Azilect which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. Dissolution tests do not show differences between the mesilate and tartrate salt forms of the active substance as both salts comparably dissociate to rasagiline base under various physiological conditions. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Rasagiline tartrate is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

Bioequivalence study

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Rasagiline DOC Generici 1 mg, tablets (DOC Generici S.r.l., Italy) is compared with the pharmacokinetic profile of the reference product Azilect 1 mg tablets (Teva B.V., the Netherlands).

The choice of the reference product

The choice of the reference products in the bioequivalence study is accepted, as Azilect has been registered through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing and the batch size was full production scale.

Design

A randomised, two treatment, four period, two sequence, single dose, replicate crossover bioequivalence study was carried out under fasted conditions in 30 healthy male subjects, aged 19-39 years. After an overnight fast of approximately 8 hours, a single oral dose (1 mg) of one of the two rasagiline formulations was administered with 200 mL of drinking water at room temperature as per the randomization schedule. Subjects were fasted for additional 4 hours after drug administration. Drinking water restriction was maintained 1 hour before dosing to 1 hour after dosing and all the subjects were refrained from taking water during this period. There were four dosing periods, separated by a washout period of 7 days. The order of receiving treatment was randomized to avoid bias in allocation of sequence to the subjects.

Blood samples were collected pre-dose and at 0.083, 0.16, 0.33, 0.50, 0.67, 0.83, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 hours after administration of the products.

The design of the study is acceptable. Rasagiline may be taken regardless of food. Thus, studies using fasting conditions are appropriate as this is considered to be the most sensitive condition to detect a potential difference between formulations. The study was performed using a full replicate design, which is common for highly variable drug products like rasagiline. The intra-subject variability was high (>30%) for the reference product. Therefore, as predefined in the protocol, the full replicate design allows the bioequivalence acceptance interval for C_{max}, to be widened to 69.84% - 143.19%.
Because of the known pharmacokinetic profile of rasagiline, it was determined that a 7 day washout period between drug administrations would be sufficient, i.e. more than 5 half-lives of rasagiline (half-life is 0.5-2 hours).

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Two subjects were withdrawn due to an adverse event after dosing in Period I. Two subjects dropped out as they did not report for period II, III and IV. One subject did not report for period II and III, however completed two study periods successfully and was therefore still included in the analysis. In total, 26 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of rasagiline under fasted conditions.

Treatment N=26	AUC_{0-t} ng.h/ml	C_{max} ng/ml	t_{max} h
Test	5270 ± 2410	6761 ± 3425	0.52 ± 0.21
Reference	5558 ± 2683	7200 ± 3399	0.56 ± 0.27
***Ratio (90% CI)**	0.96 (0.91-1.01)	0.93 (0.85-1.03)	--

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*

Conclusion on bioequivalence study
The reference product Azilect was found to be highly variable for C_{max} with an intra-subject variability of 34.71%. Widening of the acceptance intervals was allowed but, based on the study results, proved not to be necessary. The 90% confidence intervals calculated for AUC_{0-t}, and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Rasagiline DOC Generici 1 mg, tablets is considered bioequivalent with Azilect 1 mg tablets.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Safety
A total of six adverse events were reported during the clinical phase of the study (fever, vomiting, headache, high eosinophils, low haemoglobin and high white blood cell count all occurred once), of which three adverse event were expected and related to the study drug, three adverse events were unexpected and unrelated to the study drug. All the adverse events were moderate to mild in severity and were resolved, except for two subjects who were lost for follow up. No serious adverse events were observed during the study periods.

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 DOC Generici.

Summary table of safety concerns as approved in RMP:

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	• Use in pregnant and lactating women

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Azilect. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed, and sufficient evidence has been provided that rasagiline tartrate does not differ from rasagiline mesilate with regard to safety and efficacy. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The MAH has used the last approved version of the Azilect 1 mg tablets package leaflet (PL) as a basis for the proposed PL of Rasagiline 1 mg, tablets. Additionally, the MAH refers to previously performed successful user tests for other products to confirm that any changes made to the proposed PL due to differences in formulation, pack sizes and the MAH's house style (related to formatting only) do not affect the readability of the leaflet. The member states agree that further user testing is not required.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Rasagiline DOC Generici 1 mg, tablets has a proven chemical-pharmaceutical quality and is a generic form of Azilect 1 mg tablets. Azilect is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Rasagiline DOC Generici with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23 October 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached