Public Assessment Report

Decentralised Procedure

Rasagiline 1mg Tablets

(Rasagiline tartrate)

Procedure No: UK/H/5959/001/DC

UK Licence Number: PL 24668/0302

Caduceus Pharma Ltd.
LAY SUMMARY

Rasagiline 1mg Tablets
(rasagiline tartrate, tablets, 1mg)

This is a summary of the Public Assessment Report (PAR) for Rasagiline 1mg Tablets (PL 24668/0302; UK/H/5959/001/DC). It explains how Rasagiline 1mg Tablets was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Rasagiline 1mg Tablets.

The product will be referred to as Rasagiline Tablets throughout the remainder of this public assessment report (PAR).

For practical information about using Rasagiline Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Rasagiline Tablets and what are they used for?
Rasagiline Tablets are a ‘generic medicine’. This means that Rasagiline Tablets are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Azilect 1 mg tablets (Teva Pharma GmbH).

Rasagiline Tablets are used for the treatment of Parkinson’s disease. It can be used together with or without levodopa (another medicine that is used to treat Parkinson’s disease).

How does Rasagiline Tablets?
This medicine contains the active ingredient, rasagiline tartrate.

With Parkinson’s disease, there is a loss of cells that produce dopamine in the brain. Dopamine is a chemical in the brain involved in movement control. Rasagiline Tablets helps to increase and sustain levels of dopamine in the brain.

How are Rasagiline Tablets used?
The pharmaceutical form of this medicine is a tablet and the route of administration is oral (by mouth).

The patient should always take this medicine exactly as their doctor has told them. The patient should check with their doctor or pharmacist if they are not sure.

The recommended dose is one tablet of 1 mg taken by mouth once daily. Rasagiline Tablets may be taken with or without food.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

What benefits of Rasagiline Tablets have been shown in studies?
Because Rasagiline Tablets are a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine Azilect 1 mg tablets (Teva Pharma GmbH). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.
What are the possible side effects of Rasagiline Tablets?
Because Rasagiline Tablets is a generic medicine and is bioequivalent to the reference medicine Azilect 1 mg tablets (Teva Pharma GmbH), its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Rasagiline Tablets, see section 4 of the package leaflet available on the MHRA website.

Why was Rasagiline Tablets approved?
It was concluded that, in accordance with EU requirements, Rasagiline Tablets have been shown to have comparable quality and to be bioequivalent to Azilect 1 mg tablets (Teva Pharma GmbH). Therefore, the MHRA decided that, as for Azilect 1 mg tablets (Teva Pharma GmbH); the benefits are greater than the risks and recommended that they can be approved for use.

What measures are being taken to ensure the safe and effective use of Rasagiline Tablets?
A risk management plan (RMP) has been developed to ensure that Rasagiline Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Rasagiline Tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Lamivudine
The Marketing Authorisation for Rasagiline Tablets was granted in the UK on 28 August 2015.

The full PAR for Rasagiline Tablets follows this summary.

For more information about treatment with Rasagiline Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in September 2015.
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I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Caduceus Pharma Ltd, a marketing authorisation for the medicinal product Rasagiline 1mg Tablets (PL 24668/0302; UK/H/5959/001/DC) The product is a prescription-only medicine (POM) 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.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Luxembourg as Concerned Member State (CMS). The applicant subsequently withdrew the application in the CMS during the procedure, leaving no CMS. The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for this application is Azilect 1 mg tablets (EU/1/04/304/001-007), which was authorised to Teva Pharma GmbH on 21 February 2005.

Rasagiline belongs to the pharmacotherapeutic group of medicines called ‘anti-Parkinson drugs, monoamine oxidase-B inhibitors.’ Rasagiline was shown to be a potent, irreversible MAO-B selective inhibitor, which may cause an increase in extracellular levels of dopamine in the striatum. The elevated dopamine level and subsequent increased dopaminergic activity are likely to mediate rasagiline's beneficial effects seen in models of dopaminergic motor dysfunction. 1-Aminooindan is an active major metabolite and it is not a MAO-B inhibitor.

One bioequivalence study (conducted under fasting conditions) was submitted to support this application. The applicant has stated that the bioequivalence study was conducted in accordance with the Declaration of Helsinki (Seoul 2008) and in compliance with Good Clinical Practices (GCP), applicable principles of Good Laboratory Practices (GLP) and applicable regulatory requirements.

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that this application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product.
II QUALITY ASPECTS

II.1 Introduction
Each tablet contains 1 mg of rasagiline (as tartrate), as the active ingredient. Other ingredients consist of the pharmaceutical excipients calcium sulfate dehydrate, pregelatinised starch, maize starch, stearic acid, tace, anhydrous citric acid and colloidal anhydrous silica.

Rasagiline Tablets are packaged in aluminium/aluminium blister packs of 28 tablets. Not all pack sizes may be marketed. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance
INN: Rasagiline tartrate
Chemical name: (1R)-2,3-dihydro-N-2-propyn-1-yl-1H- inden-1-amine (2R, 3R)-2,3-dihydroxybutanedioate (2:1)

Structure:

Molecular formula: C_{12}H_{13}N*0.5C_{4}H_{6}O_{6}
Molecular weight: 246.28
Description: White to off white crystalline powder
Solubility: Very slightly soluble in isopropanol, slightly soluble in ethanol, sparingly soluble in methanol and soluble in dimethylsulfoxide.

Rasagiline tartrate is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analyses data are provided that comply with the proposed specification.

Satisfactory certificates of analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.
II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious tablets containing 1mg of rasagiline (as tartrate) per tablet, that are a generic version of the reference product Azilect 1 mg tablets (Teva Pharma GmbH). A satisfactory account of the pharmaceutical development has been provided.

Comparative \textit{in-vitro} dissolution and impurity profiles have been provided for the proposed and originator products.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients used contain material of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

 Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale batch size and has shown satisfactory results.

 Finished Product Specification
The finished product specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

 Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years with the storage condition, ‘Store in the original package in order to protect from light.’

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.
III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of rasagiline tartrate are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Rasagiline Tablets are 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.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology of rasagiline tartrate is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for this application.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of rasagiline tartrate.

Based on the data provided, Rasagiline Tablets can be considered bioequivalent to Azilect 1 mg tablets (Teva Pharma GmbH).

IV.2 Pharmacokinetics
In support of this application, the applicant submitted the following bioequivalence study:

STUDY
An open label, randomised, two-treatment, four-period, two-sequence, single dose, crossover, fully replicate study to compare the pharmacokinetics of the applicant’s test product Rasagiline 1mg Tablets (Caduceus Pharma Ltd) versus the reference product, Azilect 1 mg tablets (Teva Pharma GmbH), in healthy adult subjects under fasting conditions.
The subjects were administered a single dose (1 mg) of either the test or the reference product under fasting conditions. Blood samples were collected for plasma levels before dosing and up to and including 12 hours after each administration. The washout period between the treatment phases was 3 days. The pharmacokinetic results are presented below:

### Table: Summary of pharmacokinetic parameters for test and reference product for rasagiline (geometric and arithmetic mean and standard deviation):

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Geometric mean</th>
<th>Arithmetic mean</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R1</td>
<td>R2</td>
<td>R1</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (pg.h/mL)</td>
<td>3605.53</td>
<td>4889.60</td>
<td>3856.13</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (pg/mL)</td>
<td>4784.87</td>
<td>5960.88</td>
<td>5165.60</td>
</tr>
</tbody>
</table>

**Rasagiline (Test Product)**

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Geometric mean</th>
<th>Arithmetic mean</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1</td>
<td>T2</td>
<td>T1</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (pg.h/mL)</td>
<td>3607.07</td>
<td>5102.21</td>
<td>3730.18</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (pg/mL)</td>
<td>4334.19</td>
<td>6446.97</td>
<td>4485.43</td>
</tr>
</tbody>
</table>

AUC<sub>0-t</sub>: area under the plasma concentration-time curve from zero to t hours
C<sub>max</sub>: maximum plasma concentration

### Table: Summary of pharmacokinetic parameters for test and reference product for rasagiline (test/reference ratios, 90% confidence intervals and intra subject variability):  

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Ratio (%&lt;br&gt;AUC&lt;sub&gt;0-t&lt;/sub&gt;)</th>
<th>90% Confidence Intervals</th>
<th>Intra Subject Variability (%)&lt;br&gt;(Reference)</th>
<th>Acceptance Limits (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower 90% CI (%) &lt;br&gt;(%&lt;br&gt;AUC&lt;sub&gt;0-t&lt;/sub&gt;)</td>
<td>Upper 90% CI (%) &lt;br&gt;(%&lt;br&gt;AUC&lt;sub&gt;0-t&lt;/sub&gt;)</td>
<td>Variability (%)&lt;br&gt;(Reference)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt;</td>
<td>101.51</td>
<td>95.76</td>
<td>106.49</td>
<td>15.11</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>98.70</td>
<td>91.29</td>
<td>106.72</td>
<td>27.55</td>
</tr>
</tbody>
</table>

**Conclusion**

The 90% confidence intervals of the test/reference ratio for AUC and C<sub>max</sub> values for rasagiline lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant’s test product is bioequivalent to the reference product Azilect 1 mg tablets (Teva Pharma GmbH).

**IV.3 Pharmacodynamics**

No new pharmacodynamic data were submitted and none were required for an application of this type.

**IV.4 Clinical efficacy**

No new efficacy data were submitted and none were required for an application of this type.
IV.5 Clinical safety
No new safety data were submitted and none were required for this application.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), 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 Tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary table of safety concerns:

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Orthostatic hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serotonin syndrome</td>
</tr>
<tr>
<td></td>
<td>Impulse control disorders</td>
</tr>
<tr>
<td>Concomitant use with antidepressants (SSRI, SNRI, tricyclic and tetracyclic antidepressants), CYP1A2 inhibitors or MAO inhibitors</td>
<td></td>
</tr>
<tr>
<td>Important potential risks</td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>Malignant melanoma</td>
</tr>
<tr>
<td></td>
<td>Concomitant use with pethidine or sympathomimetics</td>
</tr>
<tr>
<td>Missing information</td>
<td>Pregnant and lactating women</td>
</tr>
</tbody>
</table>

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects
With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

Bioequivalence has been demonstrated between the applicant’s test product Rasagiline Tablets (Caduceus Pharma Ltd) versus the reference product, Azilect 1 mg tablets (Teva Pharma GmbH).

The grant of a marketing authorisation is recommended for this application.

V User consultation
The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the package leaflet was English.

The results 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.
VI  Overall conclusion, benefit/risk assessment and recommendation
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with rasagiline tartrate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Rasagiline Tablets is presented below: