Decentralised Procedure

Public Assessment Report

Rasagilin Egis 1 mg Tabletten

Rasagiline

DE/H/4368/001/DC

Reference Member State	DE

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product(s) in the RMS	Rasagilin Egis 1 mg Tabletten
Name of the drug substance (INN name):	Rasagiline
Pharmaco-therapeutic group (ATC Code):	N04BD02
Pharmaceutical form(s) and strength(s):	Tablets ; 1 mg
Reference Number(s) for the Decentralised Procedure	DE/H/4368/001/DC
Reference Member State:	DE
Concerned Member States:	CZ, HU, PL, RO, SK

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the application for *Rasagilin Egis 1 mg Tabletten* from EGIS Pharmaceuticals Private Limited Company, 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, is approved.

II. EXECUTIVE SUMMARY

II.1 Problem statement

N/A

II.2 About the product

Rasagiline is a chemical inhibitor of the enzyme monoamine oxidase (MAO) type B which has a major role in the inactivation of biogenic and diet-derived amines in the central nervous system. MAO has two isozymes (types A and B) and type B is responsible for metabolising dopamine in the central nervous system; as dopamine deficiency is the main contributing factor to the clinical manifestations of Parkinson's disease, inhibition of MAO-B should tend to restore dopamine levels towards normal values and this improve the condition. Rasagiline was developed for the symptomatic treatment of Parkinson's disease both as monotherapy in early disease and as adjunct therapy to levodopa + aminoacids decarboxylase inhibitor (LD + ADI) in patients with motor fluctuations.

II.3 General comments on the submitted dossier

This decentralised application concerns an abridged application, according to article 10(1) so called 'generic application" of rasagiline (tartrate), under the trade names Rasagilin Egis 1 mg Tabletten. In this Assessment Report, the name rasagiline is used.

The originator product is Azilect 1 mg tablets by TEVA Pharma GmbH, registered since 21.02.2005.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance

Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug Substance

Rasagiline tartrate is not described in the current European Pharmacopoeia. Two sources of rasagiline tartrate are proposed. The drug substance data is provided in the form of an Active Substance Master File respectively for each drug substance manufacturer. Letters of access are included in the dossier.
In general the chemical-pharmaceutical documentation and Quality Overall Summary in relation to rasagiline tartrate drug substance are of sufficient quality in view of the present European regulatory requirements.

The route of synthesis has been described and the designation of the starting materials justified. The structure of rasagiline tartrate has been confirmed by spectroscopic analyses. The proposed drug substance specification is acceptable. The analytical test methods used for analysing drug substance have been sufficiently described and validated.
Satisfactory batch analysis data of batches of rasagiline tartrate drug substance from each drug substance manufacturer have been presented.
Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The proposed retest period of 24 months for drug substance by manufacturer A has been justified by stability data presented. The proposed re-test period of 5 years for drug substance by manufacturer B is regarded acceptable.

Drug Product
The development of the product has been described, the choice of excipients is justified and their functions explained.
The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on three batches respectively for each drug product manufacturer. The batch analysis results show that the finished products meet the specifications proposed.
The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.
A shelf-life of 36 months without any labelled storage conditions for the drug product is accepted.

III.2 Non-clinical aspects
The pharmacological and toxicological properties of rasagiline are well known and have been summarised based on publicly available information in the Non-clinical Overview. However, the Non-clinical Overview lacks a discussion on potential impurities and degradants contained in the drug substance and drug product. Therefore, the Non-clinical Overview should be revised as outlined in the Annex I, Part I and II, of the European Dir. 2001/83/EC for generic products, before a marketing authorisation can be considered. In addition, the nonclinical overview is not dated, which should be revised.
The instructions on use of the compound during pregnancy and lactation and the preclinical safety data contained in the proposed SmPC and PL, respectively, essentially reflect the characteristics of the substance and have been adequately harmonised with the currently approved product information of the reference product “Azilect” (EMEA/H/C/000574 -PSUV/0060), which is acknowledged.

Environmental Risk Assessment (ERA)
Since Rasagilin Egis 1 mg Tabletten 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.3 Clinical aspects
Rasagiline is an irreversible selective inhibitor of monoamine oxidase type B, an enzyme involved in the metabolic degradation of dopamine in the brain. It enhances the effects of levodopa and is used in the treatment of Parkinson's disease, either alone or as an adjunct to levodopa therapy to reduce 'end-of-dose' fluctuations in response.

The indication of Rasagilin Egis 1 mg Tabletten is exactly in line with that of the originator Azilect which 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.

Pharmacokinetics
To support the application, the Applicant has submitted one bioequivalence study in healthy volunteers under fasting conditions:
An Open Label, 2-Period, 2-Sequence, 2-way Crossover, Randomized, Single-Dose Bioequivalence Study of Rasagiline Tablets 1 mg (Test formulation;) versus Azilect® 1 mg Tabletten (Reference formulation; Teva pharma GmbH Germany) in Healthy Volunteers under Fasting Condition (RSG-BESD-02-TFB/14).

The conducted study is sufficient for the applied product with respect to the pharmaceutical form (immediate release).

The study has been operated in Moldavia and conducted in accordance with ethical principles of Directive 2001/20/EC and ICH – GCP guidelines.

The acceptance criteria for bioequivalence were met in the pivotal study.

Pharmacodynamics
No pharmacodynamic studies have been presented.

Clinical efficacy and safety
No new clinical studies to support efficacy and safety of Rasagilin Egis 1 mg Tabletten have been provided.

Legal Status
Prescription only medicine

User Testing
Based on the fact that a corporate PL layout has been established which has been tested and accepted in several Readability User Tests and the fact that the text of the PL Azilect has been successfully user tested and is harmonised within the EEA it can be concluded that the text for the proposed daughter PL Rasagiline 1 mg tablets is equally compliant with article 59(3) of Council Directive 2001/83EC (Consultation with Target Patient Groups) an individual Readability User Test is deemed unnecessary.

Summary Pharmacovigilance system
The Applicants have submitted signed Summaries of the Applicant's and/or Proposed Future MAH's Pharmacovigilance Systems. Provided that the Pharmacovigilance System Master Files fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plans
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.

- Summary table of safety concerns as approved in RMP:

Summary of safety concerns	
Important identified risks	• Orthostatic hypotension • Impulse control disorders • Serotonine Syndrome • Concomitant use with Antidepressants (SSRI, SnRI, tricyclic and tetracyclic antidepressants), CYP1A2 inhibitors or MAO inhibitors
Important potential risks	• Concomitant treatment with pethidine or sympathomimetics • Malignant melanoma • Hypertension
Missing information	• Pregnant and lactating women

Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in RMPs:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Orthostatic hypotension	Warning in section 4.4 of the SmPC: There have been reports of hypotensive effects when rasagiline is taken concomitantly with levodopa. Patients with Parkinson's disease are particularly vulnerable to the adverse effects of hypotension due to existing gait issues. Listed in section 4.8 of the SmPC POM	None proposed
Impulse control disorders	Warning in section 4.4 of the SmPC: Impulse control disorders (ICDs) can occur in patients treated with dopamine agonists and/or dopaminergic treatments. Similar reports of ICDs have also been received post-marketing with rasagiline. Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware of the behavioural symptoms of impulse control disorders that were observed in patients treated with rasagiline, including cases of compulsions, obsessive thoughts, pathological gambling, increased libido, hypersexuality, impulsive behaviour and compulsive spending or buying. Warning in section 4.8 of the SmPC: Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments. A similar pattern of impulse control disorders has been reported post-marketing with rasagiline, which also included compulsions, obsessive thoughts and impulsive behaviour. POM	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Serotonin syndrome	Information in section 4.8 of the SPC: Serious adverse reactions are known to occur with the concomitant use of SSRIs, SNRIs, tricyclic/ tetracyclic antidepressants and MAO inhibitors. In the post-marketing period, cases of serotonin syndrome associated with agitation, confusion, rigidity, pyrexia and myoclonus have been reported by patients treated with antidepressants/SNRI concomitantly with rasagiline. POM	None proposed
Concomitant treatment with Antidepressants (SSRI, SnRI, tricyclic and tetracyclic antidepressants), CYP1A2 inhibitors or MAO inhibitors	Warning in section 4.5 of the SmPC: Serious adverse reactions have been reported with the concomitant use of SSRIs, SNRIs, tricyclic/ tetracyclic antidepressants and MAO inhibitors. Therefore, in view of the MAO inhibitory activity of rasagiline, antidepressants should be administered with caution. Warning in section 4.5 of the SmPC: In vitro metabolism studies have indicated that cytochrome P450 1A2 (CYP1A2) is the major enzyme responsible for the metabolism of rasagiline. Co-administration of rasagiline and ciprofloxacin (an inhibitor of CYP1A2) increased the AUC of rasagiline by 83%. Co-administration of rasagiline and theophylline (a substrate of CYP1A2) did not affect the pharmacokinetics of either product. Thus, potent CYP1A2 inhibitors may alter rasagiline plasma levels and should be administered with caution. Warning in section 4.8 of the SmPC: Serious adverse reactions are known to occur with the concomitant use of SSRIs, SNRIs, tricyclic/ tetracyclic antidepressants and MAO inhibitors. In the post-marketing period, cases of serotonin syndrome associated with agitation, confusion, rigidity, pyrexia and myoclonus have been reported by patients treated with antidepressants/SNRI concomitantly with rasagiline. POM	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Concomitant treatment with pethidine or sympathomimetics	Contraindication in section 4.3 of the SmPC: Concomitant treatment with other monoamine oxidase (MAO) inhibitors (including medicinal and natural products without prescription e.g. St. John's Wort) or pethidine. At least 14 days must elapse between discontinuation of rasagiline and initiation of treatment with MAO inhibitors or pethidine. Warning in section 4.4 of the SmPC: The concomitant use of rasagiline and dextromethorphan or sympathomimetics such as those present in nasal and oral decongestants or cold medicinal product containing ephedrine or pseudoephedrine is not recommended. Warning in section 4.5 of the SmPC: There have been reports of medicinal product interactions with the concomitant use of dextromethorphan and non-selective MAO inhibitors. Therefore, in view of the MAO inhibitory activity of rasagiline, the concomitant administration of rasagiline and dextromethorphan is not recommended. POM	None proposed
Malignant melanoma	Warning in section 4.4 of the SmPC: During the clinical development program, the occurrence of cases of melanoma prompted the consideration of a possible association with rasagiline. The data collected suggests that Parkinson's disease, and not any medicinal products in particular, is associated with a higher risk of melanoma. Any suspicious skin lesion should be evaluated by a specialist. Listed in section 4.8 of the SmPC. POM	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hypertension	Information in section 4.8 of the SPC: In the post-marketing period, cases of elevated blood pressure, including rare cases of hypertensive crisis associated with ingestion of unknown amounts of tyramine-rich foods, have been reported in patients taking rasagiline. In post marketing period, there was one case of elevated blood pressure in a patient using the ophthalmic vasoconstrictor tetrahydrozoline hydrochloride while taking rasagiline. POM	None proposed
Pregnant and lactating women	Information in section 4.6 of the SmPC: For rasagiline no clinical data on exposed pregnancies is available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women. Experimental data indicated that rasagiline inhibits prolactin secretion and thus, may inhibit lactation. It is not known whether rasagiline is excreted in human milk. Caution should be exercised when rasagiline is administered to a breast-feeding mother. POM	None proposed

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

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.

Periodic Safety Update Report (PSUR)
With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

IV. BENEFIT RISK ASSESSMENT

The application contains an adequate review of published clinical data.
By the study provided bioequivalence between Rasagiline Tablets 1 mg (Test formulation) and Azilect® 1 mg Tabletten has been shown.
The application is approved. For intermediate amendments see current product information.