20 November 2014
EMA/CHMP/684236/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rasagiline ratiopharm

International non-proprietary name: rasagiline

Procedure No. EMEA/H/C/003957

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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An agency of the European Union

Administrative information

Name of the medicinal product:	Rasagiline ratiopharm
Applicant:	Teva B.V. Swensweg 2031GA Haarlem The Netherlands
Active substance:	Rasagiline mesylate
International Nonproprietary Name:	Rasagiline
Pharmaco-therapeutic group (ATC Code):	Rasagiline (N04BD02)
Therapeutic indication(s):	Rasagiline ratiopharm 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.
Pharmaceutical form(s):	Tablet
Strength(s):	1 mg
Route(s) of administration:	Oral use
Packaging:	Blister (alu/alu) and Bottle (HDPE)
Package size(s):	10 tablets, 100 tablets, 112 tablets, 28 tablets, 7 tablets and 30 tablets

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Teva B.V. submitted on 28 August 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Rasagiline ratiopharm, through the centralised procedure. As this application concerns active substance already authorised via the centralised procedure, 'automatic' access was granted by the CHMP on 20 February 2014.

The applicant applied for the following indication.

Rasagiline ratiopharm 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.

The legal basis for this application refers to:

Article 10(c) of Directive 2001/83/EC – relating to informed consent from a marketing authorisation holder for an authorised medicinal product.

The application submitted is composed of administrative information, quality, non-clinical and clinical data with a letter from a MAH Teva Pharma GmbH allowing the cross reference to relevant quality, non-clinical and/or clinical data.

This application is submitted as a multiple of Azilect authorised on 21 February 2005 in accordance with Article 82.1 of Regulation (EC) No 726/2004.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

Not applicable

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application. The original medicinal product Azilect was approved in the EU on 21 February 2005.

1.2. Manufacturer

Manufacturer responsible for batch release

Teva Pharmaceuticals Europe B.V.
5 Swensweg
2031 GA Haarlem
The Netherlands

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bruno Sepodes Co-Rapporteur: David Lyons

- The application was received by the EMA on 28 August 2014.
- The procedure started on 21 September 2014.
- The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 20 October 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 23 October 2014.
- The PRAC Rapporteur's Risk Management Plan Assessment Report was endorsed by PRAC on 6 November 2014.
- During the meeting on 20 November 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Rasagiline Ratiopharm.

2. Scientific discussion

2.1. Quality aspects

Since Rasagiline ratiopharm is submitted as an informed consent application of Azilect, module 3 of the present dossier cross-refers to the up-to-date module 3 of the Azilect dossier. This has been assessed and approved, including all post-marketing procedures. A declaration submitted by the Applicant states that Rasagiline ratiopharm possesses the same qualitative and quantitative composition in terms of active substance and same pharmaceutical form as Azilect.

2.2. Non-clinical aspects

According to Article 10c of Directive 2001/83/EC, an informed consent declaration Letter on Access to Azilect Dossier EU/ 1104/304/00 1-007 has been submitted in the documentation. It is stated that Teva B.V. has full access to the dossier (Including Module 4). No non-clinical data except an Environmental Risk Assessment has been submitted in connection with this application.

2.2.1. Ecotoxicity / environmental risk assessment

Considering that the calculated value for PECsurface bellow the limit of 0.01microg. / L and the log kow is under 4.5, it is assumed that this medicinal product is unlikely to represent a risk for the environment.

2.3. Clinical aspects

2.3.1. Pharmacokinetics

This is a so called "*informed consent application*" (Article 10c) for a marketing authorization for the medicinal product *Rasagiline ratiopharm* which has the same qualitative and quantitative composition in terms of active substance and the same pharmaceutical form of *Azilect* (MAH: Teva Pharma GmbH).

Therefore, no new clinical/pharmacokinetic data was submitted and all clinical data in support of the *Rasagiline ratiopharm* application is identical to the clinical data of the *Azilect* dossier which have been previously assessed (EMEA/H/C/574).

Absorption

Rasagiline is rapidly absorbed, reaching peak plasma concentration (Cmax) in approximately 0.5 hours. The absolute bioavailability of a single rasagiline dose is about 36%. Food does not affect the Tmax of rasagiline, although Cmax and exposure (AUC) are decreased by approximately 60% and 20%, respectively, when the medicinal product is taken with a high fat meal. Because AUC is not substantially affected, rasagiline can be administered with or without food.

Distribution

The mean volume of distribution following a single intravenous dose of rasagiline is 243 l. Plasma protein binding following a single oral dose of 14C-labelled rasagiline is approximately 60 to 70%.

Metabolism:

Rasagiline undergoes almost complete biotransformation in the liver prior to excretion. The metabolism of rasagiline proceeds through two main pathways: N-dealkylation and/or hydroxylation to yield: 1-Aminoindan, 3-hydroxy-N-propargyl-1-aminoindan and 3-hydroxy-1-aminoindan. In vitro experiments indicate that both routes of rasagiline metabolism are dependent on cytochrome P450 system, with CYP1A2 being the major iso-enzyme involved in rasagiline metabolism. Conjugation of rasagiline and its metabolites was also found to be a major elimination pathway to yield glucuronides.

Excretion:

After oral administration of 14C-labelled rasagiline, elimination occurred primarily via urine (62.6%) and secondarily via faeces (21.8%), with a total recovery of 84.4% of the dose over a period of 38 days. Less than 1% of rasagiline is excreted as unchanged product in urine.

Linearity/non-linearity: Rasagiline pharmacokinetics are linear with dose over the range of 0.5-2 mg. Its terminal half-life is 0.6-2 hours.

Patients with hepatic impairment:

In subjects with mild hepatic impairment, AUC and Cmax were increased by 80% and 38%, respectively. In subjects with moderate hepatic impairment, AUC and Cmax were increased by 568% and 83%, respectively.

Patients with renal impairment:

Rasagiline's pharmacokinetics characteristics in subjects with mild (CLcr 50-80 ml/min) and moderate (CLcr 30-49 ml/min) renal impairment were similar to healthy subjects.

2.4. Clinical efficacy and safety

Since this application is an informed consent of the Azilect marketing authorisation, the clinical data in support of the Rasagiline ratiopharm application is identical to the clinical data of the Azilect dossier which have been assessed and approved at MA and renewal (including all post-marketing procedures finalised at the time of the submission of the informed consent application).

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.6. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 1.1 (7 November 2014) with the following content:

Safety concerns

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[8] • Malignant Melanoma • Concomitant use with pethidine or sympathomimetics
MISSING INFORMATION	• Pregnant and lactating women

"Potentiation of the pressor effect of tyramine in the patients ingested overdoses of rasagiline or concomitantly treated with other MAO inhibitors"

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Date for submission of interim or final reports (planned or actual)**
Assessing the risk of melanoma among PD patients (non-interventional, 3)	1) To estimate and compare the incidence rate of melanoma in patients with Parkinson's disease who start treatment with rasagiline and those who start treatment with other anti-Parkinson's drugs. 2) To examine the association between use of rasagiline and malignant melanoma among Parkinson's disease patients. 3) To compare the incidence rate of melanoma in patients with/ Parkinson's disease not treated with rasagiline with the rate in subjects without Parkinson's disease.	Malignant melanoma	Final study report June 2015

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
	In addition, the incidence rates of other (non-melanoma) malignant neoplasms of the skin will be evaluated to examine the presence of information bias secondary to potential increased monitoring of users of rasagiline.			

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
IMPORTANT IDENTIFIED RISKS		
Orthostatic hypertension	Labelling information (SmPC section 4.8, Package Leaflet)	None
Serotonin syndrome	Labelling information (SmPC sections 4.8 and 4.9, Package Leaflet)	None
Impulsive control disorders	Labelling information (SmPC sections 4.4 and 4.8, Package Leaflet)	None
Concomitant use with antidepressants (SSRI, SnRI, tricyclic and tetracyclic antidepressants), CYP1A2 inhibitors or MAO inhibitors	Labelling information (SmPC sections 4.3, 4.4, 4.5 and 4.8, Package Leaflet)	None
IMPORTANT POTENTIAL RISKS		
Hypertension	Labelling information (SmPC sections 4.5, and 4.9, Package Leaflet)	None
Malignant melanoma	Labelling information (SmPC sections 4.4 and 4.8, Package Leaflet)	None
Concomitant use with pethidine or sympathomimetics	Labelling information (SmPC sections 4.3, 4.4, 4.5 and 4.8, Package Leaflet)	None
MISSING INFORMATION		
Pregnant and lactating women	Labelling information (SmPC section 4.6, Package Leaflet)	None

2.7. Product information

The SmPC and the labelling texts are copied from the ones of the reference product Azilect.

3. Benefit-Risk Balance

This application has been submitted in accordance with Article 10c of Directive 2001/83/EC, as amended (Informed Consent Application) under “automatic access” of the centralised procedure.

The Rasagiline ratiopharm product is identical to Azilect product. The CHMP has previously reviewed data on quality, safety and efficacy of Azilect and considered the benefit/risk ratio favourable. The committee considers the risk-benefit balance of Rasagiline ratiopharm to be as favourable as for Azilect. Therefore the authorization for Rasagiline ratiopharm tablet for the proposed indication could be granted.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Rasagiline ratiopharm in 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 favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product 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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

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 European Medicines Agency;
- 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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.