28 January 2016
EMA/282791/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rasagiline Mylan

International non-proprietary name: rasagiline

Procedure No. EMEA/H/C/004064/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

ASMF	Active substance master file
AUC	Area under the curve
BCS	Biopharmaceutics classification system
CHMP	Committee for Medicinal Products for Human use
DoE	Design of experiments
EC	European Commission
EU	European Union
FDA	Food and Drug Administration
GC	Gas chromatography
GMP	Good manufacturing practice
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
IR	Infrared
LOD	Loss on drying
MCC	Microcrystalline cellulose
NMR	Nuclear magnetic resonance
oPA	*ortho*-phthalaldehyde
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
RH	Relative humidity
SmPC	Summary of product characteristics
T ½ el	Elimination half time
TLC	Thin layer chromatography
TTC	Threshold of toxicological concern
UV	Ultraviolet
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant MYLAN S.A.S. submitted on 25 February 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Rasagiline Mylan, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24 July 2014.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Rasagiline Mylan 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:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Azilect instead of non-clinical and clinical unless justified otherwise.

Information on paediatric requirements

Not applicable

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:
  - Product name, strength, pharmaceutical form: Azilect, 1 mg, tablets
  - Marketing authorisation holder: Teva Pharma GmbH, Germany
  - Date of authorisation: 21.02.2005
  - Marketing authorisation granted by:
    - Community

      Community Marketing authorisation number: EU/1/04/304/001-007

- Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:
  - Product name, strength, pharmaceutical form: Azilect, 1 mg, tablets
  - Marketing authorisation holder: Teva Pharma GmbH, Germany
  - Date of authorisation: 21.02.2005
  - Marketing authorisation granted by:

- Community

  Community Marketing authorisation number: EU/1/04/304/001-007

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Azilect, 1 mg, tablets
- Marketing authorisation holder: Teva Pharma GmbH, Germany
- Date of authorisation: 21.02.2005
- Marketing authorisation granted by:
  - Community

    Community Marketing authorisation number: EU/1/04/304/001-007
- Bioavailability study number(s): CT.RSE.tab1.10.001

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.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was Kolbeinn Gudmundsson

- The application was received by the EMA on 25 February 2015.
- The procedure started on 25 March 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 June 2015.
- The PRAC Rapporteur's Risk Management Plan Assessment Report was endorsed by PRAC on 9 July 2015.
- During the meeting on 23 July 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 July 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 14 October 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 23 November 2015.
- The PRAC Rapporteur's Risk Management Plan Assessment Report on the applicant's responses to the List of Questions was endorsed by PRAC on 3 December 2015.
- During the CHMP meeting on 17 December 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.

- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 22 December 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to List of Outstanding Issues on 6 January 2016, with an update on 15 January 2016.
- During the meeting on 28 January 2016, 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 Mylan.

2. Scientific discussion

2.1. Introduction

Rasagiline is a selective Monoamine Oxidase (MAO) type B (MAO-B) inhibitor. MAO inhibitors in Parkinson's disease (PD) inhibit MAO-B in the human brain thereby decreasing the oxidative deamination of both endogenous dopamine and dopamine produced from exogenous levodopa. Thus dopamine levels are increased and dopaminergic function is restored.
The active substance is present as a different salt than the active substance in the reference product - Azilect (mesylate).

The indication proposed for Rasagiline Mylan is the same as authorized for the Reference medicinal product. The proposed pack sizes are consistent with the dosage regimen and duration of use.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as tablets containing 1 mg of rasagiline (as tartrate) as active substance.

Other ingredients are microcrystalline cellulose, tartaric acid, maize starch, pre-gelatinized maize starch, talc and stearic acid.

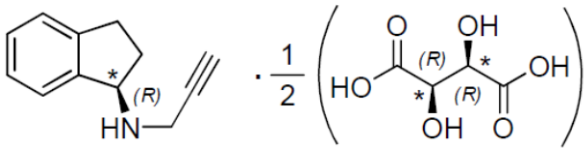
The product is available in oPA/Al/PVC/Al blisters and PVC/PVDC/Al blisters as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The information on rasagiline tartrate is provided according to the Active Substance Master File (ASMF) procedure. Two ASMFs from different manufacturers are proposed. No Ph. Eur. monograph exists for rasagiline tartrate.

The chemical name of rasagiline tartrate is (*R*)-*N*-(prop-2-ynyl)-2,3-dihydro-1*H*-inden-1-amine (2*R*,3*R*)-2,3-dihydroxybutanedioic acid salt 2:1 corresponding to the molecular formula $C_{14}H_{16}NO_3$ and a relative molecular mass of 246.28 g/mol and it has the following structure:



The structure of rasagiline tartrate was inferred from the route of synthesis and confirmed by a combination of ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, UV spectroscopy, (high resolution) mass spectrometry, elemental analysis and XRPD.

The active substance from either source is a white to off-white crystalline non-hygroscopic solid, soluble in aqueous media across the physiologically relevant pH range (1.2-6.8). Given the low active substance content in each tablet, solubility is not important for product performance.

Rasagiline base contains a single stereocentre which is introduced during the synthetic process. The tartrate counter ion contains two stereocentres and is used to resolve racemic rasagiline. Enantiomeric purity is controlled routinely by chiral HPLC on receipt by the applicant.

Polymorphism has not been observed for rasagiline tartrate and both sources of active substance consistently produce the same polymorphic form.

Manufacture, characterisation and process controls

Detailed information on the manufacturing process of the active substance has been provided in the restricted part of the ASMFs and it was considered satisfactory.

Rasagiline tartrate is synthesized from commercially available starting materials with acceptable specifications by both manufacturers. Different strategies are employed to allow introduction of the propargylamine fragment, generating racemic rasagiline. Both manufacturers then carry out a standard resolution procedure using L-tartaric acid to produce the required enantiomer which is then extensively purified.

In one ASMF, one starting material was re-defined during the procedure in response to a CHMP concern in order to ensure enough of the manufacturing process is carried out under GMP. As a result, a second manufacturer responsible for the additional steps was added to the ASMF dossier.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in PE bags inside a separate secondary container (depending on the manufacturer). The materials comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance, identity (IR, chiral HPLC, tartaric acid identity (Ph. Eur.)), LoD (Ph. Eur.), residue on ignition (Ph. Eur.), heavy metals (Ph. Eur.), residual solvents (GC), assay (HPLC), impurities (HPLC) and enantiomeric purity (chiral HPLC). A non-routine test for a potential genotoxic impurity is applied to one source of active substance.

The test for the potential genotoxic impurity is only applied to active substance from one source since it is only formed under the conditions used by that manufacturer. The test is carried out on a non-routine basis since batch data indicates its presence in levels far below the TTC. All other impurities are controlled according to ICH limits and related impurities are below the reporting thresholds.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standard used for assay testing has been presented.

Batch analysis data on two batches of the active substance from each supplier are provided. The results are within the specifications and consistent from batch to batch and from supplier to supplier. Additional data in the individual ASMFs on 3 commercial scale batches from one manufacturer and 7 from the other tested according to their specifications, which are each considered adequate, further support the robustness of the processes and consistency of active substance quality.

Stability

Stability data on four commercial scale batches of active substance from one manufacturer stored in the intended commercial package for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Samples were tested for appearance, identity, LoD, assay, impurities and enantiomer. No significant trends were observed for any of the measured parameters.

Stability data on three commercial scale batches of active substance from the other manufacturer stored in the intended commercial package for up to 48 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Samples were tested for appearance, colour and clarity of solution, water content, assay, impurities and tartaric acid content. No significant trends were observed for any of the measured parameters.

Photostability testing following the ICH guideline Q1B was performed on batches from each source indicating rasagiline tartrate is not photosensitive.

Forced degradation under stressed conditions (high temperature in solid state, high temperature neutral, basic, acidic and oxidising aqueous solutions) was also carried out by both manufacturers. The active substance is generally very stable though it degrades to an extent in base and significantly in the presence of peroxide. A small amount of a genotoxic impurity is generated in the presence of HCl although this is not relevant for patient safety since the drug substance is not exposed to this acid under routine conditions of production, storage or subsequent formulation.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable, irrespective of its origin. The stability results justify the proposed retest periods of 24 and 48 months respectively in the proposed containers. The difference in assigned re-test periods reflects only the difference in the amount of stability data currently generated by the different manufacturers.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product image is white to off-white oblong bioconvex tablets debossed with “R9SE” on one side and “1” on the other.

The overall aim was to develop an immediate release product with equivalent properties compared to the reference medicinal product, Azilect, specifically, dissolution and stability properties. Salt screens identified rasagiline hemitartrate (also called tartrate throughout this report) as a suitable active substance salt. Although it is more than twenty times less soluble than the rasagiline mesylate, it is still highly soluble throughout the physiological pH range. It has low permeability and is thus BCS class III. Since rasagiline tartrate constitutes only 0.7% of the total tablet weight given the low dose required, the reduced absolute solubility is not considered an issue considering that dissolution is not rate limiting in terms of bioavailability.

Since rasagiline is a secondary amine, it can undergo a Maillard reaction with reducing sugars so such excipients were avoided in development. Microcrystalline cellulose (MCC) was found to offer the best stability and dissolution properties of fillers tested. In addition, tartaric acid is added to prevent impurity formation in the finished dosage form. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. Compatibility between rasagiline tartrate and the excipients was demonstrated in a series of binary component studies and the long term stability data.

The FDA dissolution method for rasagiline was used. Dissolution is not important for bioavailability and manufacturing variables have been shown not to impact the dissolution rate. Therefore, it is acceptable that the dissolution method has not been shown to be discriminatory.

Since rasagiline tartrate is such a minor component of the finished product, a process to ensure content uniformity was sought. A wet granulation method was developed where the active substance can be fully dissolved in the granulation liquid, thus ensuring an even distribution.

Critical quality attributes of the finished product are loss on drying, blend uniformity, content uniformity, assay, hardness and friability, disintegration and dissolution. The impact of various manufacturing parameters such as granulation water content, intra-granular MCC content, mill speed, sieve size and compression force was investigated by DoE. The result of this study was used to define appropriate set-points for the various parameters. None of these is considered critical to quality though.

A bioequivalence study was carried out against commercially sourced Azilect and the two shown to be equivalent *in vivo*. The dissolution profiles of the biobatch and Azilect at pHs 1.2, 4.5 and 6.8 were generated in parallel and also shown to be similar, >85% of active substance being dissolved within 15 minutes in both cases. The composition differences between the originator and generic are not likely to impact the performance of the product, nor its safety.

The primary packaging is either oPA/Al/PVC/Al blisters or PVC/PVDC/Al blisters. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of five main steps: dissolution of the active substance and tartaric acid; wet granulation with intra-granular excipients followed by drying and milling; blending with extra-granular excipients; compression; packaging. The process is considered to be a non-standard manufacturing process since the active substance content is <1%.

Major steps of the manufacturing process have been validated by a number of studies. Three consecutive commercial scale batches were manufactured according to the described process resulting in a finished product meeting specification. As well as the planned IPCs, additional relevant properties of in-process materials, (granulate, pre-compression blend, bulk tablets), were measured in order to further characterize the process. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications reproduced below are appropriate for this kind of dosage form and include tests for appearance, water content (Ph. Eur.), identification (HPLC, TLC), assay (HPLC), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.), impurities (HPLC) and microbial contamination (Ph. Eur.). There is not test for enantiomeric purity as stability studies demonstrated no racemization occurs during formulation or storage and this property is therefore adequately controlled in the active substance specification. The dissolution test replaced a proposed disintegration test during the procedure as CHMP did not consider that sufficient correlation between the two methods had been demonstrated (as per ICH Q6A). The disintegration test is instead used as an in-process control during manufacture.

The impurities limits are in line with ICH guidance for a dose of 1 mg. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. All three batches were manufactured using active substance from one source only. However, the quality of the active substance from both sources is considered equivalent. Given that the first step during formulation is to dissolve the active substance in granulation liquid, and further, that it is BCS class III (highly soluble), the lack of batches of finished product made using active substance from the other manufacturer is not considered an issue.

Stability of the product

Stability data on three production scale batches of finished product stored for up to 30 months under long term conditions (25 ºC / 60% RH), for up to 12 months under intermediate conditions (30 ºC / 65% RH) and for up to 6 months under accelerated conditions at (40 ºC / 75% RH) according to the ICH guidelines was provided. The batches of Rasagiline Mylan are identical to and stored in the same primary packaging formats as those proposed for marketing. Samples were tested for appearance, disintegration time, identification, assay, impurities and microbial contamination (long term conditions only). The analytical procedures used are stability indicating. In general, there is not much variability in results for any of the studies. There is a slight increase in impurities under all conditions, more pronounced in the PVC/PVDC/Al blisters, but all results

remain within specification. Disintegration time increases dramatically under accelerated conditions and goes out of specification after 6 months. The observed physical and chemical changes are not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SmPC.

All batches of finished product tested were made using rasagiline tartrate from one manufacturer. However, the quality of the active substance from both sources is considered equivalent. Given the argumentation provided in the discussion of batch analysis above, (product specification section), no impact on finished product stability is foreseen when the source of active substance is changed.

In addition, one batch stored in both packaging formats and unpacked was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No changes were observed and thus, Rasagiline Mylan is not considered to be photosensitive.

Based on available stability data, the proposed shelf-life of 30 months stored not above 25 ^{o}C as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used. Stearic acid is of vegetal origin.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

A different salt form is used as compared to the reference product but both are soluble across the physiological pH range. The applicant has demonstrated that they perform equivalently in a bioequivalence study. The manufacturing process is considered non-standard, given the low active substance content and as such, validation was carried out on three consecutive commercial scale batches prior to submission.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Rasagiline Mylan, manufactured by Synthon Hispania S.L. Castelló 1, Polígono Las Salinas, 08830 Sant Boi de Llobregat, Spain, is considered unlikely to result in any significant increase in the combined sales volumes for all rasagiline containing products and the exposure of the environment to the active substance. Thus, the environmental risk is expected to be similar and not increased.

2.3.3. Discussion and Conclusion on the non-clinical aspects

There are no objections to approval of Rasagiline Mylan from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

The clinical overview on the clinical pharmacology, efficacy and safety has been provided and is adequate.

The Clinical sections of the SmPC of Rasagiline Mylan are in accordance with the reference product AZILECT 1 mg tablets, Teva Pharma GmbH.

Relevant for the assessment are the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) and the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09).

GCP

The clinical trial was performed in accordance with GCP as claimed by the applicant

Clinical studies

To support the application, the applicant has submitted one bioequivalence study.

Table 1. Tabular overview of clinical studies

Type of study	Study Identifier	Location of Study Report	Objective(s) of the study	Study Design and Type of control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	ARL/12/159	Sec. 5.3.1.2, Pgs 1-68	Compare clinical study and to-be-marketed formulation	Cross over	Rasagiline (as tartrate) 1 mg tablets single dose, oral	Enrolled: 30 and Evaluable: 26	Healthy subjects	Single dose	Complete; Abbreviated

2.4.2. Pharmacokinetics

Study ARL/12/159

Methods

The study was a randomized, two treatment, four period, two sequence, single dose, replicate crossover, bioequivalence study of rasagiline (as tartrate) 1 mg tablets, to Azilect® 1 mg tablets in healthy adult male and female volunteers under fasting conditions.

Test and reference products

Rasagiline Mylan, 1 mg tablets by Synthon Hispania S.L. Castelló 1, Polígono Las Salinas, 08830 Sant Boi de Llobregat, Spain (batch no. 130013AA, % of label claim 101.9%) has been compared to AZILECT® 1 mg tablets by Teva Pharmaceuticals Europe, B.V., Computerweg 10, 3542 DR Utrecht, The Netherlands (batch no. R87057, % of label claim 100%).

Population(s) studied

Thirty healthy subjects were enrolled and randomized for the study. Twenty-five (25) subjects completed all 4 periods of the study. A total of twenty six (26) subjects were considered for pharmacokinetic and statistical analysis.

Analytical methods

A validated LC-MS/MS method by solid-phase extraction was used to determine rasagiline concentrations in sodium heparin human plasma. The internal standard was rasagiline 13C3. The validated calibration concentration range was from 50.063 pg/mL to 10012.501 pg/mL. The quality control concentrations were LLQC: 50.159 pg/mL, LQC: 150.175 pg/mL, MQC: 3504.087 pg/mL and HQC: 7508.758 pg/mL.

The total number of samples as per protocol were 2040 but 249 samples were not received by the bioanalytical facility due to drop out and withdrawn subjects. A total of 1791 samples were received by the bioanalytical facility. A total of 1757 samples were analysed and 22 samples (1.25%) were reanalysed due to samples outside assay range. For incurred sample reanalysis 208 samples were run and 99.52% of the samples were found to be within a variation of 20% from the mean value. The duration of from the start of the clinical phase until the end of the bioanalytical phase was 63 days. The long term stability has been proven.

Pharmacokinetic Variables

The primary pharmacokinetic parameters for this study were AUC0-t and Cmax and the secondary pharmacokinetic parameters were AUC (0-∞), Residual area, Tmax, T1/2el, Kel and Swr. The pharmacokinetic parameters were calculated using standard methods and a non-compartmental approach.

The PK analysis software used was SAS® 9.2.

Statistical methods

Analysis of variance (ANOVA) was performed on the ln-transformed Cmax, AUC0-t and AUC0-∞. The fixed effects sequence, subject nested within sequence, period and treatment were used in the ANOVA model to calculate the pharmacokinetic parameters. The test to reference ratio of geometric LSmeans and the corresponding 90% confidence interval based on the ln-transformed Cmax and AUC0-t data were calculated. The parameter Tmax was analyzed using a non-parametric approach.

Criteria for conclusion of bioequivalence:

Bioequivalence was concluded if the test to reference ratio of geometric LSmeans and the corresponding 90% confidence interval for the Cmax and AUC0-t fell within the acceptance limits of 80.00 to 125.00%. Widening of the acceptance criteria for Cmax was proposed for conclusion of bioequivalence. However, since the results of the bioequivalence study for the pharmacokinetic parameter Cmax were within the normal acceptance criteria of 80-125% (as shown below) widening of the criteria for Cmax was not necessary.

Results

Table 2. Pharmacokinetic parameters for rasagiline (non-transformed values)

Pharmacokinetic parameter	**Test**		**Reference**	
	arithmetic mean	**SD**	**arithmetic mean**	**SD**
$AUC_{(0-t)}$ (pg*hr/mL)	5269.96	2409.75	5557.68	5557.68
$AUC_{(0-\infty)}$ (pg*hr/mL)	5427.64	2495.36	5718.57	5718.57
C_{max} (pg/mL)	6761.39	3425.24	7200.27	3398.95
T_{max}*				

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity

C_{max} maximum plasma concentration

T_{max} time for maximum concentration (* median, range)

Table 3. Statistical analysis for rasagiline (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	95.87	90.60 - 101.45	19.59
C_{max}	93.30	84.54 - 102.97	34.71
* estimated from the Residual Mean Squares			

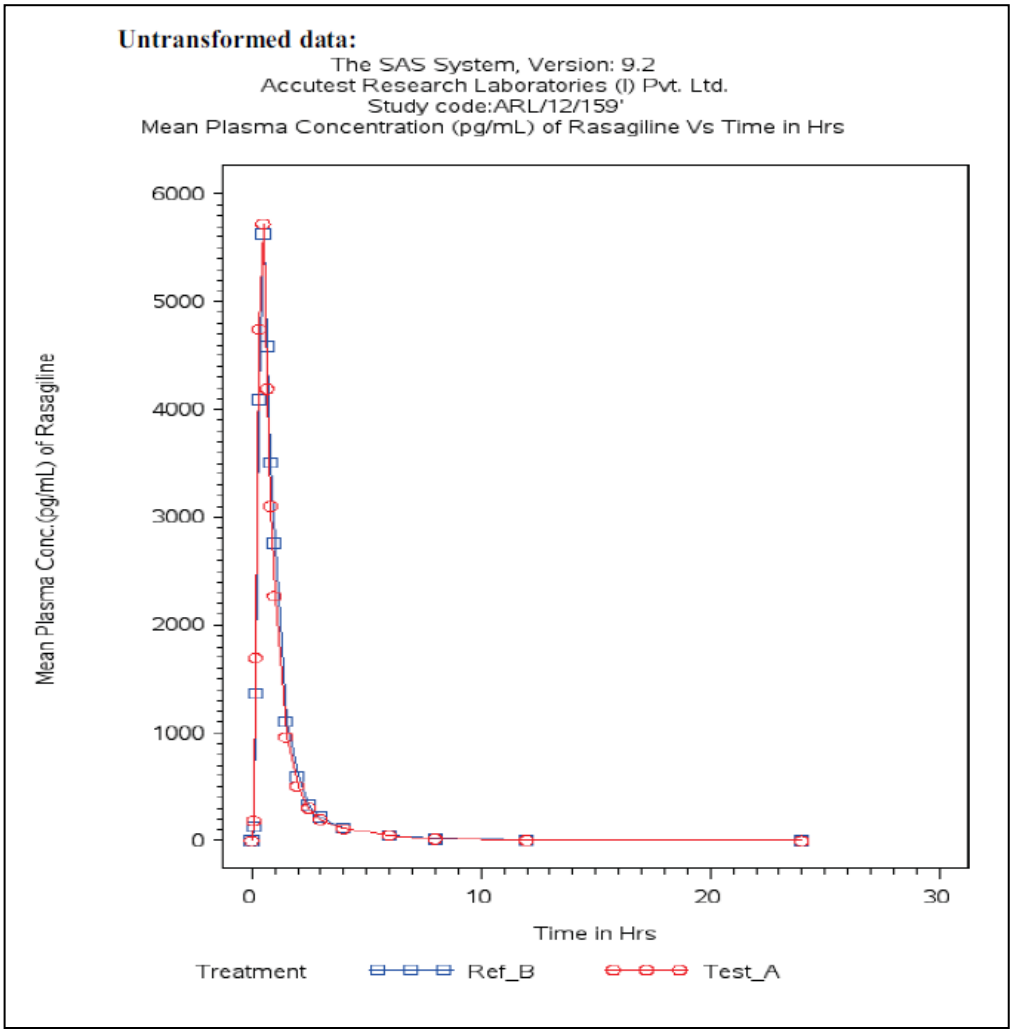


Figure 1. *Linear plot of mean plasma concentration (pg/mL) of rasagiline test and reference product vs. time in hrs.*

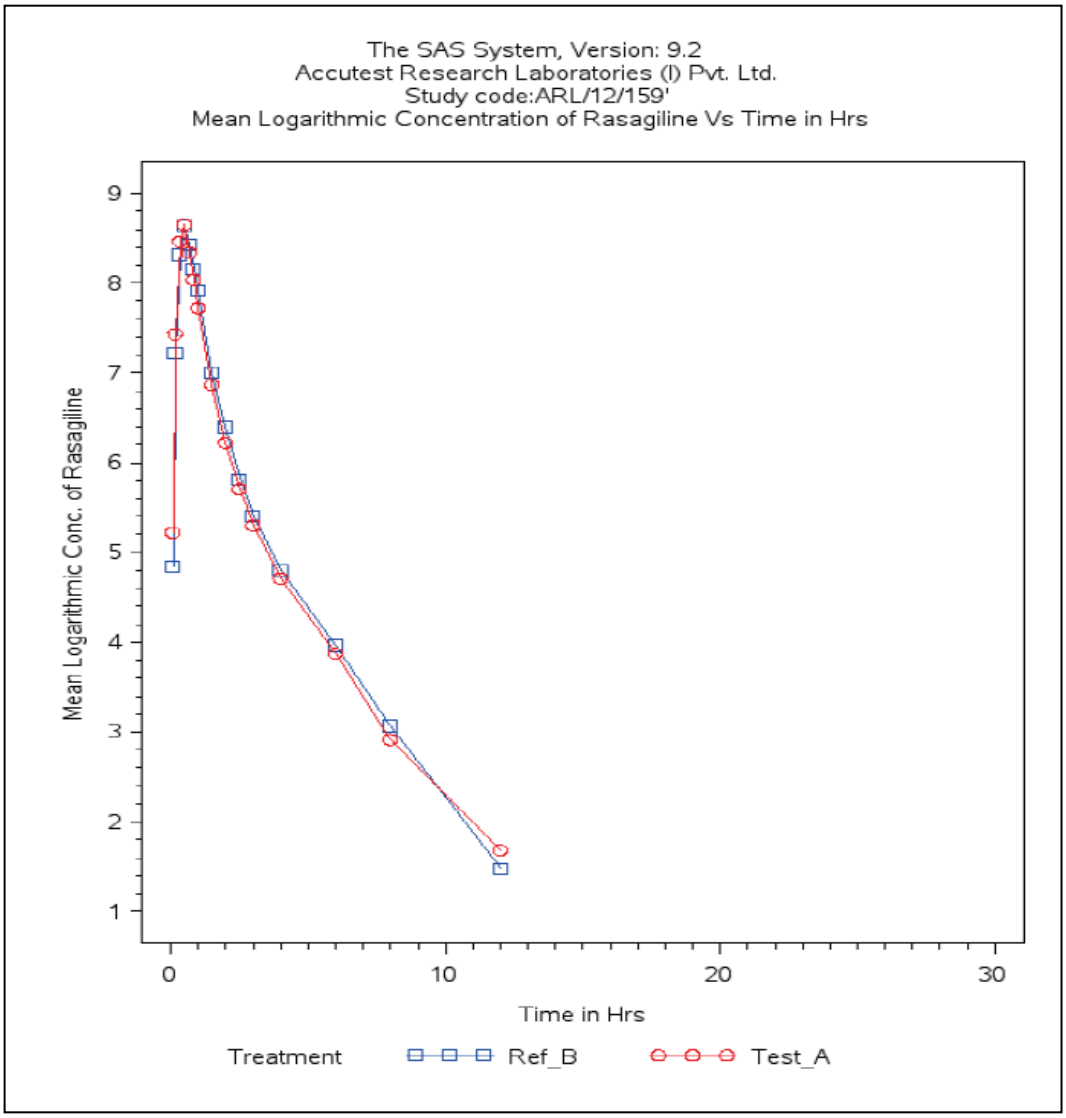


***Figure 2**: Logarithmic plot of mean plasma concentration of rasagiline test and reference product vs. time in hrs.*

The 90% confidence interval of the test/reference ratio (difference in least square means) derived from the ANOVA of the log-transformed pharmacokinetic parameters AUC_{0-t} and C_{max} for rasagiline in plasma was within the 80.00% - 125.00% acceptance range. Therefore the test formulation (Rasagiline Mylan, 1 mg tablets, manufactured by Synthon Hispania S.L. Castelló 1, Polígono Las Salinas, 08830 Sant Boi de Llobregat, Spain) is judged to be bioequivalent to the reference product (Azilect® 1 mg tablets, Teva Pharmaceuticals Europe B.V. Computerweg 10, 3542 DR Utrecht, The Netherlands) in healthy adult volunteers under fasting conditions.

Safety data

A total of 3 post-dose adverse events were reported by 3 of the 30 subjects included in the study. One (1.92 %) adverse event (fever) was observed in the test product treated subjects and two (3.70 %) adverse events (vomiting and headache) were observed in the reference product treated subjects. Two subjects were withdrawn from the study due to fever and vomiting.

All adverse events were moderate to mild in severity and all were resolved, except for 2 subjects who were lost for follow up. No serious adverse events or deaths were reported in this study.

Conclusions

Based on the presented bioequivalence study Rasagiline Mylan 1 mg tablets are considered bioequivalent with Azilect 1 mg tablets under fasting conditions.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Additional data

The in vitro dissolution tests were conducted using an USP type II apparatus (paddle), 500 ml volume and a speed of 50 rpm. Four different media were use, QC condition (0.1 M HCl, pH 1.0) and pH 1.2, 4.5 and 6.8 and a sampling time of 5, 10, 15, 30 and 45 minutes.

Comparison of 12 tablets of the test formulation (batch 130013) and the reference formulation (batch R87057) used in the bioequivalence study was performed. The dissolution profiles of the test and reference formulation batches were found to be similar at pH 1.2, 4.5 and 6.8 and at QC conditions with more than 85% dissolved in 15 minutes.

2.4.5. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.6. Discussion on clinical aspects

The clinical overview on the clinical pharmacology, efficacy and safety has been provided and is adequate.

The test to reference ratio of geometric LSmeans and the corresponding 90% confidence interval for the Cmax and AUC0-t were all within the acceptance range of 80.00 to 125.00%. The bioequivalence has been shown appropriately under fasting conditions. Both the test and the reference products were generally safe and well tolerated by the subjects included in the study.

2.4.7. Conclusions on clinical aspects

Approval is recommended from the clinical point of view for Rasagiline Mylan 1 mg tablets.

2.5. 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 2.0 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 2.0 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Concomitant use with antidepressants (SSRI, SNRI, tricyclic and tetracyclic antidepressants), CYP1A2 inhibitors or MAO inhibitors
	Impulse-control disorders
	Orthostatic hypotension
	Serotonin syndrome
Important potential risks	Concomitant use with pethidine or sympathomimetics
	Hypertension
	Malignant melanoma
Missing information	Use in pregnant and lactating women

SSRI = Selective serotonin reuptake inhibitors; SNRI = selective serotonin-norepinephrine reuptake inhibitors; CYP1A2 = Cytochrome P450 1A2; MAO = Monoamine oxidase.

Pharmacovigilance plan

No post authorisation PhV plan development is planned.

Risk minimisation measures

No additional risk minimisation measures have been proposed

2.6. PSUR submission

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8. Product information

2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Azilect 1 mg tablets and Memantine Mylan 10 mg film-coated tablets. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of rasagiline tablets . The reference product Azilect 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. No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with a randomized, two treatment, four period, two sequence, single dose, replicate crossover design. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Rasagiline Mylan met the protocol-defined criteria for bioequivalence when compared with Azilect. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Rasagiline Mylan 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 requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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.