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Public Assessment Report

Name of the Product:

Rasagiline Vipharm

1 mg tablets

(rasagiline)

Procedure number: HU/H/0423/001/DC

Marketing authorisation holder: Vipharm S.A.

Date: 2 June 2016

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UPGRADE: STEPS TAKEN AFTER THE INITIAL PROCEDURE WITH AN INFLUENCE ON THE PUBLIC ASSESSMENT REPORT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Rasagiline Vipharm 1 mg tablets. The holder of the marketing authorisation is Vipharm S. A.

The active substance is rasagiline. Each tablet contains 1 mg rasagiline (as hemitartrate).

The other ingredients are cellulose microcrystalline, (maize) starch (partially) pregelatinised, silica colloidal anhydrous, magnesium stearate.

Rasagiline Vipharm tablets are presented white to off white round, flat tablets with bevelled edges and engraved with "1" in one side, with a diameter of 8 mm in oPA/aluminium/PVC/aluminium blisters or in white, high-density polyethylene (HDPE) bottles closed with white plastic (LDPE) screw cap containing (2 g) silica gel.

Rasagiline Vipharm is 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).

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 Vipharm helps to increase and sustain levels of dopamine in the brain.

What patients need to know before you take Rasagiline Vipharm

Those who
- are allergic (hypersensitive) to rasagiline or any of the other ingredients of this medicine,
- have severe liver problems

should not take Rasagiline Vipharm.

Patients should not take the following medicines while taking Rasagiline Vipharm:
- monoamine oxidase (MAO) inhibitors (e.g. for treatment of depression or Parkinson's disease, or used for any other indication), including medicinal and natural products without prescription e.g. preparations of St. John's Wort,
- pethidine (a strong pain killer).

Patients must wait at least 14 days after stopping Rasagiline Vipharm treatment and starting treatment with MAO inhibitors or pethidine.

Warnings and precautions

Patients should consult their before taking Rasagiline Vipharm
- if they have mild to moderate liver problems,

- if they experience any suspicious skin changes.

Children and adolescents

Rasagiline Vipharm is not recommended for use under the age of 18.

Other medicines and Rasagiline Vipharm

Patients must inform their doctor if they are taking, have recently taken or might take any other medicines, including those obtained without prescription or if they are smoking or intend to stop smoking.

Patients must ask their doctor for advice before taking any of the following medicines together with Rasagiline Vipharm:
- certain antidepressants (selective serotonin reuptake inhibitors, selective serotonin-norepinephrine reuptake inhibitors, tricyclic or tetracyclic antidepressants),
- the antibiotic ciprofloxacin used against infections,
- the cough suppressant dextromethorphan,
- sympathomimetics such as those present in eye drops, nasal and oral decongestants and cold medicine containing ephedrine or pseudoephedrine.

The use of Rasagiline Vipharm together with the antidepressants containing fluoxetine or fluvoxamine should be avoided.

If the patient is starting treatment with Rasagiline Vipharm, he/she should wait at least 5 weeks after stopping fluoxetine treatment.

If the patient is starting treatment with fluoxetine or fluvoxamine, he/she should wait at least 14 days after stopping Rasagiline Vipharm treatment.

If the patient or his/her family/carer notices that the patient is developing unusual behaviours where he/she cannot resist the impulse, urges or cravings to carry out certain harmful or detrimental activities to him/herself or others, the doctor must be informed. These are called impulse control disorders. In patients taking Rasagiline Vipharm and/or other medications used to treat Parkinson's disease, behaviours such as compulsions, obsessive thoughts, addictive gambling, excessive spending, impulsive behaviour and an abnormally high sex drive or an increase in sexual thoughts or feelings have been observed. The doctor may need to adjust or stop your dose.

Rasagiline Vipharm with food and drink

Rasagiline Vipharm may be taken with or without food.

Pregnancy, breast-feeding and fertility

Those who are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, ask their doctor for advice before taking this medicine.

Driving and using machines

No studies on the effects on the ability to drive and use machines have been performed. The doctor must be consulted prior to driving or using machines.

How to take Rasagiline Vipharm

The usual dose of Rasagiline Vipharm is 1 tablet of 1 mg taken by mouth once daily.

Rasagiline Vipharm may be taken with or without food.

What to do if more Rasagiline Vipharm have been taken than it should have been?

Those who think that you they have taken too many Rasagiline Vipharm tablets, should contact their doctor immediately taking the Rasagiline Vipharm carton/bottle with them to show it the doctor.

What to do if taking Rasagiline Vipharm was forgotten?

Patients should not take a double dose to make up for a forgotten dose. They should take the next dose normally, when it is time to take it.

May taking Rasagiline Vipharm be stopped?

Patients should not stop taking Rasagiline Vipharm without first talking to the doctor.

Possible side effects

Like all medicines, Rasagiline Vipharm can cause side effects, although not everybody experiences them.

The following side effects have been reported in placebo controlled clinical trials:

Very common side effects (may affect more than 1 in 10 people):
- abnormal movements (dyskinesia),
- headache.

Common side effects (may affect up to 1 in 10 people):
- abdominal pain,
- fall,
- allergy,

- fever,
- flu (influenza),
- general feeling of being unwell (malaise),
- neck pain,
- chest pain (angina pectoris),
- low blood pressure when rising to a standing position with symptoms like dizziness/light-headedness (orthostatic hypotension),
- decreased appetite,
- constipation,
- dry mouth,
- nausea and vomiting,
- flatulence,
- abnormal results of blood tests (leucopenia),
- joint pain (arthralgia),
- musculoskeletal pain,
- joint inflammation (arthritis),
- numbness and muscle weakness of the hand (carpal tunnel syndrome),
- decreased weight,
- abnormal dreams,
- difficulty in muscular coordination (balance disorder),
- depression,
- dizziness (vertigo),
- prolonged muscle contractions (dystonia),
- runny nose (rhinitis),
- irritation of the skin (dermatitis),
- rash,
- bloodshot eyes (conjunctivitis),
- urinary urgency.

Uncommon side effects (may affect up to 1 in 100 people)
- stroke (cerebrovascular accident),
- heart attack (myocardial infarction),
- blistering rash (vesiculobullous rash).

In addition, skin cancer was reported in around 1% of patients in the placebo controlled clinical trials. Nevertheless, scientific evidence suggests that Parkinson's disease, and not any medicine in particular, is associated with a higher risk of skin cancer (not exclusively melanoma). Patients should speak with their doctor about any suspicious skin changes.

Parkinson's disease is also associated with symptoms of hallucinations and confusion. In *post-marketing experience* these symptoms have also been observed in Parkinson's disease patients treated with rasagiline.

There have been cases of patients who, while taking one or more medications for the treatment of Parkinson's disease, were unable to resist the impulse, drive or temptation to perform an action that could be harmful to themselves or others. These are called impulse control disorders.

In patients taking Rasagiline Vipharm and/or other medications used to treat Parkinson's disease, the following have been observed:

- obsessive thoughts or impulsive behaviour,
- strong impulse to gamble excessively despite serious personal or family consequences,
- altered or increased sexual interest and behaviour of significant concern to you or to others, for example, an increased sexual drive,
- uncontrollable excessive shopping or spending.

Having the doctor been consulted if the patient experiences any of these behaviours, can the ways of managing or reducing the symptoms be discussed.

How to store Rasagiline Vipharm?

For blisters: 'This medicinal product does not require any special temperature storage conditions. Store in the original blister to protect from light.'

For bottles: 'Do not store above 30ºC. Store in the original bottle to protect from light.'

Keep this medicine out of the sight and reach of children.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Rasagiline Vipharm 1 mg tablets. The procedure was finalised at 3 March 2016. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, an application has been submitted to the reference and competent authorities of the member states concerned.

This Decentralised Procedure application (reference member state, RMS: Hungary, concerned member states, CMS: the Czech Republic, Poland and the Slovak Republic) concerned the generic version of rasagiline 1 mg tablets (Rasagiline Vipharm 1 mg tablets).

The application has been filed pursuant to Article 10(1) of Directive 2001/83/EC and therefore contained no new clinical or preclinical data, except for showing bioequivalence, other than supporting literature where necessary.

The applicant has adequately demonstrated bioequivalence between the product and reference product. The latter was Azilect® (Rasagiline) 1 mg tablets (of Teva Pharma GmbH, Germany) and it has been initially authorised centrally in the European community in February 2005.

Based on the review of the quality, safety and efficacy data, the member states have granted marketing authorisation for Rasagiline Vipharm 1 mg tablets.

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

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics (SmPC).

II. QUALITY ASPECTS

II.1 Introduction

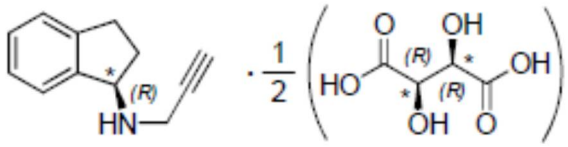
The chemical-pharmaceutical assessment report concerns the application of Rasagiline Vipharm 1 mg tablets via decentralized procedure according to Article 10(1) of Directive 2001/83/EC (generic application).

The reference medicinal product was Azilect 1 mg tablet by Teva.

II.2 Drug substance

Data on the quality and manufacture of the active substance were provided in the submission using the Active Substance Master File (ASMF) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: rasagiline tartrate
Chemical name: (R)-N-(prop-2-ynyl)-2,3-dihydro-1H-inden-1-amine (2R,3R)-2,3-dihydroxy-butanedioic acid salt 2:1
Structure:



The active substance is a white to off- white, non-hygroscopic crystalline solid, soluble in water, sparingly soluble in methanol, very slightly soluble in isopropanol, practically insoluble in toluene. The manufacturer consistently produces the only stable crystalline form.

The molecule has three chiral centres, one of them is included in the structure of the Rasagiline molecule, while the other two centres are located in the tartaric moiety. All stereo centres (in the Rasagiline molecule as well as in the tartaric moiety) have R configuration.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the drug substance is adequate.

Evidence of the structure has been confirmed by elemental analysis, IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopic studies. Chiral purity was confirmed by specific optical rotation and by chiral HPLC method. X-ray powder diffraction and DSC data proved that the manufactured rasagiline tartrate consistently yields the same, stable crystalline form.

Potential impurities originating from starting materials, intermediates, by-products and degradation products as well as their potential carry-over into the final drug substance have been discussed.

Rasagiline tartrate is not official in any pharmacopoeia. Therefore, an in-house specification has been set for the active substance, which includes the following tests: appearance, identification, colour and clarity of solution, water content, specific optical rotation, sulphated ash, heavy metals, related substances by HPLC, enantiomeric purity, assay of rasagiline, tartrates content and residual solvents.

The specification is in accordance the European Pharmacopoeia (Ph. Eur.) general chapter *Substances for pharmaceutical use* and with International Council of Harmonisation (ICH) Q6A, ICH Q3A and ICH Q3C guidelines. The substance complies with the requirements of the European Medicines Agency (EMA) guideline on genotoxic impurities.

Testing methods are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

The drug substance is packed in transparent polyethylene bag closed by sealing. The polyethylene bag is placed into a second bag made out of PET/Al/PE. The liner is heat-sealed and placed into cardboard containers.

Stability studies have been performed with the drug substance. According to the presented stability data the proposed re-test period is acceptable with the storage condition: „preserve in well-closed containers, protected from light, store at a temperature comprised between 15°C and 30°C".

Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

II.3 Medicinal product

The aim of the pharmaceutical development was to develop a stable tablet formulation containing 1 mg of rasagiline (as tartrate) comparable to the innovator product (Azilect 1 mg tablet) and exhibiting the same bioavailability.

A satisfactory package of data on pharmaceutical development has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance, composition and packaging was obtained: Rasagiline Vipharm 1 mg tablets are white to off-white, round, flat tablets with bevelled edges and engraved with "1" on one side, with a diameter of 8 mm.

The excipients used in the finished product are colloidal anhydrous silica, magnesium stearate, pregelatinised maize starch and microcrystalline cellulose. All excipients used comply with their respective Ph. Eur. monograph. Compliance of the product with the general monograph of the Ph. Eur. regarding the risk of TSE has been demonstrated by the applicant.

Description and flow chart of the manufacturing method have been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formula was also presented.

GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure system of the product is OPA/Al/PVC//Al blisters or white HDPE bottles closed with white LDPE cap containing 2 g silica gel.

Certificates of analysis demonstrating the conformity of the container closure systems to the Ph. Eur. and compliance with European Commissions' relevant regulations are provided.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the presented results, a shelf-life of 30 months in OPA/Al/PVC//Al blisters with the storage conditions **"**This medicinal product does not require any special temperature storage conditions. Store in the original blister to protect from light" and a shelf-life of 21 months in HDPE bottles with the storage conditions "Do not store above 30oC. Store in the original bottle to protect from light" have been approved.

The SmPC, Patient Information (Package) Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end

of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

Rasagiline Vipharm 1 mg tablets are, from chemical-pharmaceutical points of view, approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of rasagiline are well known. As rasagiline is a widely used, well-known active substance, no further non-clinical studies are required and the applicant provides none. The non-clinical overview is therefore based on a review of data available in several scientific databases or published in relation to the active ingredient, rasagiline. Overview based on literature review is appropriate for this kind of application.

III.2 Pharmacology

The drug product Rasagiline Vipharm contains the active substance rasagiline, which is a highly selective, potent and irreversible inhibitor of MAO type B. Rasagiline selectively inhibits the activity of monoamine oxidase B (MAO-B), inhibiting MAO-B blocks the metabolism of dopamine and, therefore, prolongs its activity. The propargyl-containing MAO inhibitors such as clorgyline, pergyline and selegiline inactivate MAO-A and -B selectively and irreversibly by time- and concentration-dependent mechanisms by interacting covalently with the cysteinyl-flavine adenine dinucleotide (FAD) cofactor of the enzymes at their active centres. This pharmacological mechanism explains also some part of the symptomatic anti-Parkinsonian efficacy of rasagiline. In contrast to selegiline, the propargyl component in rasagiline is bound to an aminoindan moiety. More specifically, the interaction between rasagiline and MAO in general, takes place between the N-propargyl group and N-5 of the FAD isoalloxazine component of liver and brain MAO. The inactivation of the enzyme 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 the beneficial effects of rasagiline seen in models of dopaminergic motor dysfunction.

The active substance is a well-known compound. No further information was provided regarding the pharmacology of rasagiline.

III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the applicant.

III.4 Toxicology

Published information on toxicological studies with rasagiline was the basis for the evaluation. No new toxicity studies were submitted by the applicant for the product, which is acceptable for this type of application.

III.5 Ecotoxicology/environmental risk assessment (ERA)

Since Rasagiline Vipharm 1 mg 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

Abridged applications avoid the need for repetitive tests on animals and humans.

Pharmacodynamics, pharmacokinetics and toxicology of rasagiline are well-known. As Rasagiline Vipharm is a generic product there is no need for further excessive non-clinical studies. The non-clinical part of the application is thus acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

Except for showing bioequivalence no new clinical pharmacological studies were conducted by the applicant as the application is submitted in accordance with Article 10(1) of Directive 2001/83/EC as amended.

The application contains an adequate review of published clinical data.

IV.2 Pharmacokinetics

IV.2.1 Literature data

Rasagiline is rapidly absorbed, reaching peak plasma concentration (C_{max}) in approximately 0.5 hours. The absolute bioavailability of a single rasagiline dose is about 36%.

Food does not affect the T_{max} of rasagiline, although C_{max} 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.

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

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

Rasagiline undergoes almost complete biotransformation in the liver prior to excretion. Its metabolism 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.

After oral administration of ^{14}C-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.

IV.2.2 Bioequivalence study

The development studies focused on obtaining a product having similar characteristics to the reference product, i.e. dissolution profile and bioavailability.

Essential similarity was demonstrated by means of a pivotal bioequivalence study between the test product and reference product. It was performed in order to support essential similarity between Rasagiline Vipharm 1 mg tablets (Vipharm S.A.) and Azilect® (rasagiline) 1 mg tablets (marketing authorisation holder: Teva Pharma GmbH, Germany) in healthy, non-smoking (for at least 6 months prior to first drug administration), male and female volunteers under fasting conditions according to the bioequivalence guideline in force (*CPMP/EWP/QWP/1401/98/rev 1/Corr** 2010*).

All the study sites of the bioequivalence study were inspected by an EU competent authority in the period of 2010-2014 years. The study was performed according to the Good Clinical Practice (GCP) guideline (CPMP/ICH/135/95).

The design of this investigation was a pivotal, single-centrum, single-dose, randomized, open-label, laboratory blind, crossover, two-period, two-treatment, two-sequence, bioequivalence study of rasagiline with a suitable washout period between the two periods.

The subjects were dosed in both periods according to the randomization scheme after at least 10-hour fast with 240 ml of ambient temperature water at their scheduled time points: 1 tablet (1 mg rasagiline) Test- or Reference product.

Blood samples were collected by direct venipuncture or by indwelling catheter into prechilled 6 ml K_2EDTA Vacutainer® tubes, then centrifuged under refrigerated conditions.

The plasma samples of subjects were analysed using validated LC-MS/MS method for rasagiline.

ISR (incurred sample reanalysis): in order to assess the reproducibility of bio-analytical results incurred samples were selected (>5% of total samples as the sample size was greater than 1000 in the study). Samples were selected close to C_{max} and end of terminal/elimination phase in order to cover the entire range of concentration. The incurred samples should be reanalysed in singlet. The % difference for at least 67% of the total incurred samples must be within the range of ± 20%. Results of the performed ISR experiment met the acceptance criteria. The reanalysis using incurred samples confirms reproducibility of study samples used in validated bioanalytical method.

Statistical methods used in the evaluation of bioequivalence were, as follows:

- descriptive statistics of pharmacokinetic parameters: arithmetic mean, standard deviation, minimum, maximum, median, CV%, geometric LS (least squares) means for test (T) and reference (R) pharmacokinetic data;
- log-transformation of AUC_{inf}, AUC_t and C_{max} data;

- evaluation of data using a linear mixed-effects model (SAS® 9.4, SAS Inst. Inc., USA), with the main effects of *treatment*, *period*, *sequence* and *subjects nested within sequence* in ANOVA;
- calculation of 90% confidence intervals for the difference between the least square means (LSM) for primary parameters (LSMEANS, ESTIMATE procedures of ANOVA in SAS® 9.4);
- applying non-parametric analysis of T_{max} on untransformed data (Wilcoxon test);
- descriptive statistics of safety data collected during the whole study period.

Bioequivalence criteria: the Test product can be considered bioequivalent to the Reference product, when the ln-transformed Test/Reference LS (least-squares) mean ratios and their 90% confidence intervals of the primary pharmacokinetic parameters fall entirely within the acceptance interval of 80.00 - 125.00% for rasagiline.

Results:

Pharmacokinetic Parameter	Test/Reference Ratio of Geometric Means (90% Confidence Interval)	Intra-Subject CV (%)
AUC_t	99.44% (94.66% - 104.46%)	13.96
AUC_{inf}	99.47% (94.73% - 104.46%)	13.86
C_{max}	99.18% (89.46% - 109.95%)	29.74

Conclusion on the bioequivalence study: the above results support that single dose of Test product is bioequivalent with single dose of Reference product in healthy adult subjects under fasting condition.

No death or serious adverse events were reported during conduct of the study. No adverse events associated with clinical laboratory tests were experienced by the subjects at post-study. Both study drugs were well tolerated by all subjects involved.

IV.3 Pharmacodynamics

Clinical pharmacology studies to evaluate the pharmacodynamics of Rasagiline Vipharm 1 mg tablets were not performed and none are required for applications of this type.

IV.4 Clinical efficacy

No new efficacy or safety data have been submitted and none are required. The applicant has provided an adequate review of clinical trials published in the literature, describing the efficacy and safety profile of rasagiline.

IV.5 Clinical safety

With the exception of the data generated during the bioequivalence studies, no new safety data were submitted and none were required for this application. No new or unexpected safety issues were raised by the bioequivalence data. The applicant has provided an adequate review of clinical trials published in the literature, describing the efficacy and safety profile of rasagiline.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant Good Vigilance Practice module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

Summary of 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 •Malignant Melanoma •Concomitant use with pethidine or sympathomimetics
Missing information	•Pregnant and lactating women

Pharmacovigilance Plan: routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to Rasagiline Vipharm 1 mg tablets. No additional activities are proposed.

Risk Minimisation Measures: routine measures (i.e. wording in SmPC, package leaflet and classification as a prescription-only medicine) are considered sufficient

to manage all of the safety concerns connected to Vipharm S.A.'s product of rasagiline 1 mg tablets. No additional activities are proposed. For any further information on risk minimisation, please refer to the product information.

IV.6.3 Periodic Safety Update Reports

The requirements for submission of periodic safety update reports (PSURs) 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.

Currently, no routine PSUR reporting is required for generic products containing rasagiline.

IV.7 Discussion on the clinical aspects

The application concerns a generic product. Abridged applications avoid the need for repetitive tests on animals and humans. For these application the bioequivalence studies described in section IV.2 are pivotal.

To support the application the Applicant has adequately demonstrated bioequivalence between Rasagiline Vipharm 1 mg tablets and the reference product Azilect 1 mg tablets.

There is no objection against granting the marketing authorization from a clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present applications concern Rasagiline Vipharm 1 mg tablets, generic versions of rasagiline. The applicant and the future holder of authorisation is Vipharm S.A.

The indication is 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 according to Article 10(1) of Directive 2001/83/EC (generic application). The applicant has adequately demonstrated bioequivalence between Rasagiline Vipharm 1 mg tablets and the reference product Azilect 1 mg tablets (Teva).

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised.

The therapeutic benefit/risk assessment is, therefore, positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Rasagiline Vipharm 1 mg tablets.

V.2 Classification

Prescription-only medicine.

V.3 Package Leaflet and 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 patient information leaflet was Hungarian.

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. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached