PART VI SUMMARY OF ACTIVITIES IN THE RISK MANAGEMENT PLAN BY PRODUCT

This public summary applies to all products in this Risk Management Plan (Rasagiline 1 mg tablets).

1. Elements for summary tables in the EPAR

1.1 Summary table of safety concerns

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	• Malignant melanoma • Hypertension • Concomitant treatment with pethidine or sympathomimetics
Missing information	• Pregnant and lactating women

1.2 Table of ongoing and planned additional PhV studies/activities in the Pharmacovigilance Plan

NA

1.3 Summary of post authorisation efficacy development plan

NA

1.4 Summary table of risk minimisation measures

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,	None proposed

	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 behavior. POM	
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 or 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	None proposed

	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	
Concomitant use with pethidin 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.	None proposed

	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	
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
Hypertension	Information in section 4.8 of the SPC:	None proposed

	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	
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

2. Elements for a public summary

2.1 Overview of disease epidemiology

PD is a progressive neurodegenerative disorder that is characterized by the symptoms of resting shiverslow movements, stiffness, and postural instability. After Alzheimer's disease, it is the second most common neurodegenerative disease, affecting approximately 1-2% of the European population over the age of 65 years. The incidence of PD increases with age. (Hoy and Keating 2012; Oldfield et al. 2007)

2.2 Summary of treatment benefits

Restoration of the dopaminergic coverage forms the central strategy for the treatment of PD. Thus, levodopa forms the backbone of therapy of PD. Other antiparkinsonian substances, such as dopamine agonists and MAO-B inhibitors are used as monotherapy or in addition to levodopa in patients with moderate to advanced disease. (Martindale 2014; Oldfield et al. 2007)

MAO-B is the major enzyme responsible for the degradation of dopamine in the human brain. Therefore, selective MAO-B inhibitors, such as rasagiline are an important therapeutic option for patients with PD. (Hoy and Keating 2012; Oldfield et al. 2007)

2.3 Unknowns relating to treatment benefits

The safety and efficacy of rasagiline in children and adolescents have not been established. No data are available.

2.4 Summary of Safety Concerns

Important identified risks

Risk	**What is known**	**Preventability**
Decreased blood pressure when used together with levodopa	Decrease in blood pressure when rising to a standing position, with symptoms such as dizziness/light-headedness may occur by concomitant use with levodopa.	Patients should be informed and monitored. They should tell their physician if symptoms occur.
Obsessive thoughts or impulsive behavior (impulse control disorders)	There have been cases of patients who, while taking medications for the treatment of Parkinson's disease, were unable to resist the impulse, urges or cravings to carry out harmful activities to themselves or others.	Patients or caregivers should tell the doctor if the patient develops unusual behavior or were unable to resist the impulse to perform potentially harmful actions.
Severe side effects with with other antidepressive drugs (serotonin syndrome)	Severe side effects such as excitement, confusion, increased body temperature, have been observed	Patients should be monitored carefully
Concomitant use of drugs used for the treatment of depression (selective	Serious adverse effects have been observed with concomitant use of	Concomitant use with other antidepressants or CYP1A2 inhibitors should

serotonin reuptake inhibitors (SSRI), selective noradrenaline reuptake inhibitors (SNRI), or tricyclic or tetracyclic antidepressants), inhibitors of CYP1A2, (enzyme for the degradation of rasagiline) or other drugs which are used for the treatment of depression or Parkinson's disease (inhibitors of MAO)	rasagiline and SSRIs, SNRIs, or tricyclic/tetracyclic antidepressants. Combination of rasagiline with other MAO inhibitors may lead to a critical increase in blood pressure.	be done with caution. Rasagiline should not be used together with other MAO inhibitors. There should be at least 14 days between stopping rasagiline and starting a MAO inhibitor.

Important potential risks

Risk	**What is known**
Risk of melanoma	Skin cancer has been reported in around 1% of patients in controlled clinical trials. The data collected from trials indicate that Parkinson's disease and not any medicine in particular is associated with a higher risk of melanoma.
Elevated blood pressure	A few cases of elevated blood pressure have been reported during marketing of the drug
Concomitant use of a potent pain killer (pethidine) or substances present in eye or nasal drops or cold medicines (sympathomimetics)	Combination of rasagiline with a potent pain killer pethidine may result in serious adverse effects. Interactions (increased MAO activity) have been observed between rasagiline and sympathomimetics.

Missing information

Risk	**What is known**
Use during pregnancy and breast-feeding	There is no information on safety and efficacy of rasagiline in pregnant or breast-feeding women. Therefore, rasagiline should not be used during pregnancy and breast-feeding.

2.5 Summary of additional risk minimisation measures by safety concern

No additional risk minimization measures are planned.

2.6 Planned post-authorisation development plan

NA

2.7 Summary of changes to the risk management plan over time

NA