4.3 Part V.3. Summary table of risk minimization measures

Table 4-2 Summary table of Risk Minimization Measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Impulse control disorder (including pathological gambling, hypersexuality, increased libido, compulsive spending or buying, binge eating, and compulsive eating)	Guidance is provided in sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects of the SmPC.	None
Orthostatic hypotension	Guidance is provided in sections 4.4 Special warnings and precautions for use, 4.8 Undesirable effects and 4.9 Overdose of the SmPC.	None
Serotonin syndrome	Guidance is provided in sections 4.8 Undesirable effects and 4.9 Overdose of the SmPC.	None
Concomitant use with Antidepressants (SSRI, SnRI, tricyclic and tetracyclic antidepressants), CYP1A2 inhibitors or MAO inhibitors	Guidance is provided in sections 4.5 Interactions with other medicinal products and other forms of interaction and 4.8 Undesirable effects of the SmPC.	None
Malignant melanoma	Guidance is provided in sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects of the SmPC.	None
Hypertension	Guidance is provided in 4.4 Special warnings and precautions for use, 4.5 Interactions with other medicinal products and other forms of interaction, 4.8 Undesirable effects and 4.9 Overdose of the SmPC.	None
Concomitant use with pethidine or sympathomimetics	Guidance is provided in sections 4.3 Contraindications, 4.4 Special warnings and precautions for use, 4.5 Interactions with other medicinal products and other forms of interaction and 4.8 Undesirable effects of the SmPC.	None
Use in pregnant and breast-feeding women	Guidance is provided in section 4.6 Fertility, pregnancy and lactation of the SmPC.	None

5 Part VI: Summary of activities in the risk management plan by product

5.1 Part VI.1 Elements for summary tables in the EPAR

Table 5-1 Part VI.1.1 Summary table of safety concerns

Important identified risks	Impulse control disorder (including pathological gambling, hypersexuality, increased libido, compulsive spending or buying, binge eating, and compulsive eating)
	Orthostatic hypotension
	Serotonin syndrome
	Concomitant use with Antidepressants (SSRI, SnRI, tricyclic and tetracyclic antidepressants), CYP1A2 inhibitors or MAO inhibitors
Important potential risks	Malignant melanoma
	Hypertension
	Concomitant use with pethidine or sympathomimetics
Missing information	Pregnant and lactating women

Table 5-2 Part VI.1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

None

Table 5-3 Part VI.1.3 Summary of Post authorization efficacy development plan

None

Table 5-4 Part VI.1.4 Summary table of risk minimization measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Impulse control disorder (including pathological gambling, hypersexuality, increased libido, compulsive spending or buying, binge eating, and compulsive eating)	Guidance is provided in sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects of the SmPC.	None
Orthostatic hypotension	Guidance is provided in sections 4.4 Special warnings and precautions for use, 4.8 Undesirable effects and 4.9 Overdose of the SmPC.	None
Serotonin syndrome	Guidance is provided in sections 4.8 Undesirable effects and 4.9 Overdose of the SmPC.	None

Concomitant use with Antidepressants (SSRI, SnRI, tricyclic and tetracyclic antidepressants), CYP1A2 inhibitors or MAO inhibitors	Guidance is provided in sections 4.5 Interactions with other medicinal products and other forms of interaction and 4.8 Undesirable effects of the SmPC.	None
Malignant melanoma	Guidance is provided in sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects of the SmPC.	None
Hypertension	Guidance is provided in 4.4 Special warnings and precautions for use, 4.5 Interactions with other medicinal products and other forms of interaction, 4.8 Undesirable effects and 4.9 Overdose of the SmPC.	None
Concomitant use with pethidine or sympathomimetics	Guidance is provided in sections 4.3 Contraindications, 4.4 Special warnings and precautions for use, 4.5 Interactions with other medicinal products and other forms of interaction and 4.8 Undesirable effects of the SmPC.	None
Use in pregnant and breast-feeding women	Guidance is provided in section 4.6 Fertility, pregnancy and lactation of the SmPC.	None

5.2 Part VI.2 Elements for a Public Summary

5.2.1 Part VI.2.1 Overview of disease epidemiology

Parkinson disease (PD) is one of the most common disorders of the nervous system, affecting approximately 1% of people older than 60 years and causing progressive disability that can be slowed, but not halted, by treatment. The cardinal signs are resting twitching, increased muscle tone with increased resistance to passive stretch and slowness of movement. It was estimated that every year 4.5-21 new cases of PD per 100,000 people arise and 18 to 328 cases per 100,000 people currently have PD (most studies report about approximately 120 cases per 100,000 people). Both numbers face a wide variation globally, may be due to a number of factors including the way data are collected, differences in population structures and patient survival, case ascertainment, and the methodology used to define cases. The older people the more PD cases occur, the average age of onset is approximately 60 years. Onset in persons younger than 40 years is relatively uncommon. Parkinson disease is about 1.5 times more common in men than in women [Hauser RA, 2015].

5.2.2 Part VI.2.2 Summary of treatment benefits

Rasagiline tartrate is a 'monoamine-oxidase-B inhibitor'. It blocks the enzyme monoamine oxidase type B, which breaks down the neurotransmitter dopamine in the brain. Neurotransmitters are chemicals that allow nerve cells to communicate with one another. In patients with Parkinson's disease, the cells that produce dopamine begin to die and the amount of dopamine in the brain decreases. The patients then lose their ability to control their movements reliably. By increasing levels of dopamine in the parts of the brain that control movement and coordination, Rasagiline tartrate improves the signs and symptoms of Parkinson's disease, such as stiffness and slowness of movement.

5.2.3 Part VI.2.3 Unknowns relating to treatment benefits

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. It is not known whether rasagiline is excreted in human milk. There is a lack of data on safety and efficacy in children and adolescents.

5.2.4 Part VI.2.4 Summary of safety concerns

Table 5-5 Important identified risks

Risk	What is known	Preventability
Failure to resist a temptation, urge or impulse that may harm self or others (Impulse control disorder (including pathological gambling, hypersexuality, increased libido, compulsive spending or buying, binge eating, and compulsive	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,

Risk	What is known	Preventability
eating))		obsessive thoughts, pathological gambling, increased libido, hypersexuality, impulsive behaviour and compulsive spending or buying.
Low blood pressure including sudden blood pressure decrease after standing up or stretching (Orthostatic hypotension)	There have been reports of hypotensive effects when rasagiline is taken concomitantly with levodopa. Approximately 1 out of 10-100 patients experienced low blood pressure in combination with levodopa. Patients with Parkinson's disease are particularly vulnerable to the adverse effects of hypotension due to existing gait issues.	Rasagiline should be given cautiously to patients who are taking other medicinal products which may cause orthostatic hypotension.
Excessive stimulation of the central nervous system (Serotonin syndrome)	Cases of serotonin syndrome have been reported in patients that were treated with antidepressants in combination with rasagiline.	Antidepressants should only be prescribed and administered with caution in patients taking rasagiline.
Concomitant use with other medication for depression and medication that inhibit degradation of rasagiline in the liver (Concomitant use with Antidepressants (SSRI, SnRI, tricyclic and tetracyclic antidepressants), CYP1A2 inhibitors or MAO inhibitors)	Serious side effects have been reported when patients have been treated with rasagiline in combination with any of the mentioned other medication, e.g. concomitant use with other MAO inhibitors can lead to excessive blood pressure and use with antidepressants may lead to excessive stimulation of the central nervous system (serotonin syndrome).	Concomitant use with other MAO inhibitors is contraindicated. Antidepressants may be used with caution only.

Table 5-6 Important potential risks

Risk	What is known
Malignant melanoma	During the clinical development program, the occurrence of cases of melanoma (skin cancer which forms from pigment-containing cells in the skin) prompted the consideration of a possible association with rasagiline. About 1 out of 10-100 patients experienced a skin carcinoma. However, the data collected suggests that Parkinson's disease, and not any medicinal products in particular, is associated with a higher risk of skin cancer (not exclusively melanoma). Any suspicious skin lesion should be evaluated by a specialist.
High blood pressure (Hypertension)	Use of rasagiline in combination with other MAO inhibitors has been reported to lead to excessive blood pressure. A crisis due to high blood pressure has been reported in 1 out of 1,000-10,000 patients. Furthermore, ingestion of tyramine-rich food (e.g. spoiled and pickled, aged, fermented or smoked meat and fish, chocolate, alcoholic beverages, fermented food, such as most cheese) in combination with rasagiline has been reported to increase

Risk	What is known
	blood pressure.
Concomitant use with pethidine (pain medication) and medication that stimulate the central nervous system (Concomitant use with pethidine or sympathomimetics)	Serious adverse reactions have been reported with the concomitant use of pethidine. There have also been reports of side effects when rasagiline was used in combination with medication used for colds and congestion of nose and mouth. Concomitant use with pethidine is contraindicated. The use of rasagiline together with cold medicines and medication against congestion is not recommended.

Table 5-7 Missing information

Risk	What is known
Pregnant and lactating women	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. It is not known whether rasagiline is excreted in human milk. Caution should be exercised when rasagiline is administered to a breast-feeding mother.

5.2.5 Part VI.2.5 Summary of additional risk minimization measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

5.2.6 Part VI.2.6 Planned post authorization development plan

None

5.2.7 Part VI.2.7 Summary of changes to the Risk Management Plan over time

Major Changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
2.0	05 Aug 2015	Important potential risk: Falling asleep during activities of daily living	Deleted following the day100 Assessment report of Hungary in DE/H/4364-4387/001/DC executed by AET (in alignment with BfArM)
2.1	12 Aug 2015		Changes according to AET-RMP requirements in DE/H/4364-

Version	Date	Safety Concerns	Comment
			4387/001/DC (in alignment with BfArM)
		Important identified risks: - Exacerbation of dopaminergic side effects and worsening of pre-existing dyskinesia when used in combination with levodopa - Use in patients with hepatic impairment	Deleted
		Important identified risks: - Concomitant use with pethidine or sympathomimetics	Changed to important potential risk
		- Malignant melanoma and other skin cancers	Changed to “Malignant melanoma”