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

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of 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

VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Not applicable.

VI.1.3 Summary of Post authorisation efficacy development plan

Not applicable.

VI.1.4 Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risks		
Concomitant use with antidepressants (SSRI, SNRI, tricyclic and tetracyclic antidepressants), CYP1A2 inhibitors or MAO inhibitors	Overview of proposed text as included in the SmPC: Section 4.3: "*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*". Section 4.4: "*The concomitant use of rasagiline and fluoxetine or fluvoxamine should be avoided. At least five weeks should elapse between discontinuation of fluoxetine and initiation of treatment with rasagiline. At least 14 days should elapse between discontinuation of rasagiline and initiation of treatment with fluoxetine or fluvoxamine*".	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Section 4.5: "*Rasagiline must not be administered along with other MAO inhibitors (including medicinal and natural products without prescription e.g. St. John's Wort) as there may be a risk of non-selective MAO inhibition that may lead to hypertensive crises.* *Serious adverse reactions have been reported with the concomitant use of pethidine and MAO inhibitors including another selective MAO-B inhibitor*"; "*The concomitant use of rasagiline and fluoxetine or fluvoxamine should be avoided.* *For concomitant use of rasagiline with selective serotonin reuptake inhibitors (SSRIs)/selective serotoninnorepinephrine reuptake inhibitors (SNRIs) in clinical trials, see section 4.8.* *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*"; "*In vitro metabolism studies have indicated that cytochrome P450 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*". Section 4.8: "*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.* *Rasagiline clinical trials did not allow concomitant use of fluoxetine or fluvoxamine with rasagiline, but the following antidepressants and doses were allowed in the rasagiline trials: amitriptyline ≤ 50 mg/daily, trazodone ≤ 100 mg/daily, citalopram ≤ 20 mg/daily, sertraline ≤ 100 mg/daily, and paroxetine ≤ 30 mg/daily. There were no cases of serotonin syndrome in the rasagiline clinical program in which 115 patients*	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	were exposed concomitantly to rasagiline and tricyclics and 141 patients were exposed to rasagiline and SSRIs/ SNRIs". Overview of proposed text as included in the PL: Section 2: "*Do not take the following medicines while taking [Product name]:* *- **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. St. John's Wort [...]*"; "*Ask your doctor for advice before taking any of the following medicines together with [Product name]:* *- Certain **antidepressants** (selective serotonin reuptake inhibitors, selective serotonin-norepinephrine reuptake inhibitors, tricyclic or tetracyclic antidepressants) [...]*"; "*The use of [Product name] together with the antidepressants containing fluoxetine or fluvoxamine should be avoided. If you are starting treatment with [Product name], you should wait at least 5 weeks after stopping fluoxetine treatment. If you are starting treatment with fluoxetine or fluvoxamine, you should wait at least 14 days after stopping [Product name] treatment*".	
Impulse-control disorders	Overview of proposed text as included in the SmPC: Section 4.4: "*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*". Section 4.8: "*Impulse control disorders* *Pathological gambling, increased libido, hypersexuality, 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*	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	impulse control disorders has been reported post-marketing with rasagiline, which also included compulsions, obsessive thoughts and impulsive behaviour". Overview of proposed text as included in the PL: Section 2: "*Tell your doctor if you or your family/carer notices that you are developing unusual behaviours where you cannot resist the impulse, urges or cravings to carry out certain harmful or detrimental activities to yourself or others. These are called impulse control disorders. In patients taking [Product name] 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. Your doctor may need to adjust or stop your dose*". Section 4: "*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 [Product name] 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.* *Tell your doctor if you experience any of these behaviours; they will discuss ways of managing or reducing the symptoms*".	
Orthostatic hypotension	Overview of proposed text as included in the SmPC: Section 4.4: "*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*".	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Section 4.8: "*Adjunct Therapy* *[…] In parentheses is the adverse reaction incidence (% of patients) in rasagiline vs. placebo, respectively. […]* *Common: orthostatic hypotension (3.9% vs. 0.8%)*" Overview of proposed text as included in the PL: Section 4: "*The following side effects have been reported in placebo controlled clinical trials: [...]* ***Common** (may affect up to 1 in 10 people)* *[...] low blood pressure when rising to a standing position with symptoms like dizziness/light-headedness (orthostatic hypotension)*".	
Serotonin syndrome	Overview of proposed text as included in the SmPC: Section 4.4: "*The concomitant use of rasagiline and fluoxetine or fluvoxamine should be avoided. At least five weeks should elapse between discontinuation of fluoxetine and initiation of treatment with rasagiline. At least 14 days should elapse between discontinuation of rasagiline and initiation of treatment with fluoxetine or fluvoxamine*". Section 4.5: "*The concomitant use of rasagiline and fluoxetine or fluvoxamine should be avoided*". Section 4.8: "*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. Rasagiline clinical trials did not allow concomitant use of fluoxetine or fluvoxamine with rasagiline, but the following antidepressants and doses were allowed in the rasagiline trials: amitriptyline ≤ 50 mg/daily, trazodone ≤ 100 mg/daily, citalopram ≤ 20 mg/daily, sertraline ≤ 100 mg/daily, and paroxetine ≤ 30 mg/daily. There were no cases of serotonin*	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	syndrome in the rasagiline clinical program in which 115 patients were exposed concomitantly to rasagiline and tricyclics and 141 patients were exposed to rasagiline and SSRIs/ SNRIs". Section 4.9: "*Overdosage: Symptoms reported following overdose of rasagiline in doses ranging from 3 mg to 100 mg included dysphoria, hypomania, hypertensive crisis and serotonin syndrome*".	
Important potential risks		
Concomitant use with pethidine or sympathomimetics	Overview of proposed text as included in the SmPC: Section 4.3: "*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*". Section 4.4: "*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*". Section 4.5: "*Serious adverse reactions have been reported with the concomitant use of pethidine and MAO inhibitors including another selective MAO-B inhibitor. The concomitant administration of rasagiline and pethidine is contraindicated*"; "*With MAO inhibitors there have been reports of medicinal product interactions with the concomitant use of sympathomimetic medicinal products. Therefore, in view of the MAO inhibitory activity of rasagiline, concomitant administration of rasagiline and sympathomimetics such as those present in nasal and oral decongestants or cold medicinal products, containing ephedrine or pseudoephedrine, is not recommended*". Section 4.8: "*With MAO inhibitors, there have been reports of drug interactions with the concomitant use of sympathomimetic medicinal products*".	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Overview of proposed text as included in the PL: Section 2: "*Do not take the following medicines while taking [Product name]:* *- [...]* *- **pethidine** (a strong pain killer).* *You must wait at least 14 days after stopping [Product name] treatment and starting treatment with MAO inhibitors or pethidine*"; "*Ask your doctor for advice before taking any of the following medicines together with [Product name]:* *- [...]* *- sympathomimetics such as those present in eye drops, nasal and oral decongestants and cold medicine containing **ephedrine** or pseudoephedrine*".	
Hypertension	Overview of proposed text as included in the SmPC: Section 4.5: "*Rasagiline must not be administered along with other MAO inhibitors (including medicinal and natural products without prescription e.g. St. John's Wort) as there may be a risk of non-selective MAO inhibition that may lead to hypertensive crises*". Section 4.8: "*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*". Section 4.9: "*In a dose escalation study in patients on chronic levodopa therapy treated with 10 mg/day of rasagiline, there were reports of cardiovascular undesirable reactions (including hypertension and postural hypotension) which resolved following treatment discontinuation.*"	None proposed.
Malignant melanoma	Overview of proposed text as included in the SmPC: Section 4.4: "*During the clinical development program, the occurrence of cases of melanoma prompted the consideration of a possible*	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	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 skin cancer (not exclusively melanoma). Any suspicious skin lesion should be evaluated by a specialist." Section 4.8: "*Monotherapy* *The list below includes adverse reactions which were reported with a higher incidence in placebo controlled studies, in patients receiving 1 mg/day rasagiline […]* *Common: skin carcinoma (1.3% vs. 0.7%)*"; "*Adjunct Therapy* *The list below includes adverse reactions which were reported with a higher incidence in placebo controlled studies in patients receiving 1 mg/day rasagiline […]* *Uncommon: skin melanoma (0.5% vs. 0.3%)*" Section 5.3: "*Rasagiline was not carcinogenic in rats at systemic exposure, 84 – 339 times the expected plasma exposures in humans at 1 mg/day. In mice, increased incidences of combined bronchiolar/alveolar adenoma and/or carcinoma were observed at systemic exposures, 144 - 213 times the expected plasma exposure in humans at 1 mg/day.*" Overview of proposed text as included in the PL: Section 2: "***Take special care with [Product name]*** *- […] you should speak with your doctor about any suspicious* ***skin changes****.*" Section 4: "*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). You should speak with your doctor about any suspicious skin changes.*"	
Missing information		
Use in pregnant and lactating women	Overview of proposed text as included in the SmPC:	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Section 4.6: "*Pregnancy* *For rasagiline no clinical data on exposed pregnancies is available. Animals 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.* *Breast-feeding* *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.*" Section 5.3: "*Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity and reproduction toxicity.* *Rasagiline did not present genotoxic potential in vivo and in several in vitro systems using bacteria or hepatocytes. In the presence of metabolite activation rasagiline induced an increase of chromosomal aberrations at concentrations with excessive cytotoxicity which are unattainable at the clinical conditions of use.*" Overview of proposed text as included in the PL: Section 2: "***Pregnancy and breast-feeding*** *If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking any medicine.*"	

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Parkinson's disease

Parkinson's disease is a slowly progressive degenerative disorder (a disease in which the function or structure of the affected tissues or organs will increasingly deteriorate over time) of the central nervous system (brain and spinal cord). It is characterized by tremor when muscles are at rest (resting tremor), increased muscle tone (stiffness, or rigidity), slowed movements, and difficulty maintaining balance (postural instability). In many people, thinking becomes impaired, or dementia develops. It is not know what causes Parkinson's disease[4].

Usually, Parkinson's disease begins subtly and progresses gradually. In about two thirds of patients, tremors are the first symptom. In others, the first symptom is usually problems with movement or a reduced sense of smell[4].

Parkinson's disease is the second most common degenerative disorder of the central nervous system after Alzheimer's disease. It affects about one of 250 people older than 40 years, about one of 100 people older than 65, and about one of 10 people older than 80. It commonly begins between the ages of 50 and 79. Rarely, Parkinson's disease occurs in children or adolescents[4].

VI.2.2 Summary of treatment benefits

Rasagiline is used for the treatment of Parkinson's disease. Rasagiline can be used either alone, or together with levodopa (another medicine used in Parkinson's disease) in patients with Parkinson's disease who are having 'disease fluctuations' towards the end of the period between levodopa doses. Fluctuations are linked with a reduction in the effects of levodopa, when the patient experiences sudden switches between being 'on' and able to move, and being 'off' and immobile[1].

Rasagiline was more effective than placebo in three main studies involving a total of 1,563 patients with Parkinson's disease. In the study where rasagiline was taken alone, patients taking 1 mg of the medicine once a day had an average fall in a standard scale (Unified Parkinson's Disease Rating Scale, UPDRS) score of 0.13 points over the 26-week study from a starting value of 24.69. In the patients taking placebo (a 'pretend' medicine with no active ingredient), a rise of 4.07 points was observed from a starting value of 24.54. A fall in the UPDRS score indicates an improvement in symptoms, while a rise indicates a worsening of symptoms[1].

When used together with levodopa, 1 mg rasagiline reduced the time in the 'off' state more than placebo did. In both studies, patients adding rasagiline to their existing treatment spent an average of around one hour less in the 'off' state than those adding a placebo[1].

VI.2.3 Unknowns relating to treatment benefits

There are no adequate data on the use of rasagiline in women who are pregnant or breast-feeding.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Concomitant use with antidepressants (selective serotonin reuptake inhibitors, selective serotonin-norepinephrine reuptake inhibitors, tricyclic and tetracyclic antidepressants), or with other medicines (cytochrome P450 1A2 inhibitors, monoamine oxidase inhibitors)	Some patients who took rasagiline together with certain antidepressants or with monoamine oxidase inhibitors (*e.g.* for treatment of depression or Parkinson's disease, or used for any other indication) experienced serious side effects. Also, if ciprofloxacin (used against infections) is taken together with	Patients should ask their doctor for advice before taking antidepressants or the antibiotic ciprofloxacin together with rasagiline. Doctors should not prescribe rasagiline together with antidepressants such as fluoxetine or fluvoxamine. The treatment with rasagiline should start at least five

Risk	What is known	Preventability
	rasagiline, rasagiline stays active in the patient's body for longer than expected, potentially increasing the risk of side effects. This is because ciprofloxacin inhibits cytochrome P450 1A2, an enzyme present in human liver that is responsible for inactivating rasagiline after it has done its work. Other medicines that inhibit cytochrome P450 1A2 could have the same effect on rasagiline as ciprofloxacin.	weeks after stopping fluoxetine treatment. The treatment with fluoxetine or fluvoxamine should start at least 14 days after stopping rasagiline treatment. Doctors should not prescribe rasagiline together with the antibiotic ciprofloxacin or with monoamine oxidase inhibitors, including medicinal and natural products without prescription (*e.g.* St. John's Wort).
Inability to resist the impulse, drive or temptation to perform an action that could be harmful to themselves or others (impulse-control disorders)	The following symptoms have been observed with unknown frequency in patients taking rasagiline and/or other medications used to treat Parkinson's disease: • Obsessive thoughts or impulsive behaviour. • Strong impulse to gamble excessively despite serious personal or family consequences. • Altered or increased sexual interest, for example, an increased sexual drive. • Uncontrollable excessive shopping or spending.	Patients should tell their doctor if they experience any of these behaviours. The doctor will discuss ways of managing or reducing the symptoms, which may include adjusting or stopping the dose of rasagiline.
Low blood pressure that happens while standing up from sitting or from lying down (orthostatic hypotension)	Up to one in 10 patients taking rasagiline might develop low blood pressure when rising to a standing position, with symptoms like dizziness/light-headedness. There have been reports of hypotensive effects when rasagiline is taken together with levodopa.	Patients and doctors are informed about this risk.
Excessive accumulation in the body of the naturally occurring chemical serotonin (serotonin syndrome)	Serious side reactions described as 'serotonin syndrome' have been reported in patients treated with rasagiline together with certain antidepressants and in patients who took too much rasagiline. Rasagiline and certain antidepressants are known to increase serotonin levels. Serotonin	The doctor should administer antidepressants with caution in patients taking rasagiline. In particular, the use of rasagiline together with the antidepressants fluoxetine or fluvoxamine should be avoided. The treatment with rasagiline should start at least five weeks after stopping fluoxetine

Risk	What is known	Preventability
	is a chemical produced by the body which is needed for the function of nerve cells and brain. However, too much serotonin causes symptoms that can range from mild (shivering and diarrhoea) to severe (muscle rigidity, fever and seizures). Severe serotonin syndrome can be fatal if not treated.	treatment. The treatment with fluoxetine or fluvoxamine should start at least 14 days after stopping rasagiline treatment. The recommended dose of rasagiline (one tablet of 1 mg taken by mouth once daily) should not be exceeded.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Use together with the strong pain killer pethidine or with so-called sympathomimetic medicines (such as those present in eye drops, nasal and oral decongestants and cold medicine containing ephedrine or pseudoephedrine)	Some patients taking rasagiline together with pethidine had serious side effects. Therefore, these two medicines should not be taken together, and at least 14 days should pass between stopping rasagiline and starting pethidine. Some patients taking medicines of the same type as rasagiline together with sympathomimetic medicines had side effects. Therefore, to avoid possible side effects, it's better not to take rasagiline together with these medicines.
High blood pressure (hypertension)	A few patients who took rasagiline either in very high doses, or together with some types of food (tyramine-rich), or while using an eye medicine (tetrahydrozoline hydrochloride) experienced hypertension. However, further studies with rasagiline and tyramine-rich foods showed no issue when rasagiline was taken with this type of food.
Serious skin cancer (malignant melanoma)	Around 1% of people taking rasagiline during a clinical study developed skin cancer. However, evaluation of 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 part of the skin should be evaluated by a specialist.

Missing information

Risk	What is known
Use in pregnant and lactating women	No adequate information on the use of rasagiline in pregnant women is available. Studies in laboratory animals did not show reproductive toxicity. It is not known whether rasagiline is excreted in breast milk. Rasagiline may inhibit production of breast milk. Rasagiline should be used with caution in pregnant or breast-feeding women.

VI.2.5 Summary of additional risk minimisation measures by safety concern

No additional risk minimisation measures have been proposed.

VI.2.6 Planned post authorisation development plan

No post-authorization development is planned.

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

Not applicable.