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

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

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
Orthostatic hypotension	Proposed content in SPC 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. Orthostatic hypotension is listed ADR in Section 4.8 **Prescription only medicine.**	None proposed
Serotonin syndrome	Proposed content in SPC 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. There were no cases of serotonin 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. The following information is included in Section 4.9: Overdosage: Symptoms reported following overdose of rasagiline in doses ranging	None proposed

	from 3 mg to 100 mg included dysphoria, hypomania, hypertensive crisis and serotonin syndrome. **Prescription only medicine.**	

Impulse control disorder	Proposed content in SPC 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. The following information is included in 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 impulse control disorders has been reported post-marketing with rasagiline, which also included compulsions; obsessive thoughts and impulsive behaviour (see section 4.4). **Prescription only medicine.**	None proposed
Concomitant use with antidepressants (SSRI, SnRI, tricyclic and tetracyclic	Proposed content in SPC Section 4.3: Concomitant treatment with other monoamine oxidase	None proposed

antidepressants), CYP1A2 inhibitors or MAO inhibitors	(MAO) inhibitors (including medicinal and natural products without prescription e.g. St. John's Wort) or pethidine (see section 4.5). At least 14 days must elapse between discontinuation of rasagiline and initiation of treatment with MAO inhibitors or pethidine. The following information is included in Section 4.4: The concomitant use of rasagiline and fluoxetine or fluvoxamine should be avoided (see section 4.5). 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. The following information is included in Section 4.5: The concomitant use of rasagiline and fluoxetine or fluvoxamine should be avoided (see section 4.4). 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. The following information is included in 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 were exposed concomitantly to rasagiline and tricyclics and 141 patients were exposed to rasagiline and SSRIs/ SNRIs. **Prescription only medicine.**	

Hypertension	Proposed content in SPC 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 (see section 4.3). The following information is included in 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. The following information is included in 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. Overdose can be associated with significant inhibition of both MAO-A and MAO-B. In a single-dose study healthy volunteers received 20 mg/day and in a ten-day study healthy volunteers received 10 mg/day. Adverse events were mild or moderate and not related to rasagiline treatment. In a dose escalation study in patients on chronic levodopa therapy treated with 10 mg/day of	None proposed

	rasagiline, there were reports of cardiovascular undesirable reactions (including hypertension and postural hypotension) which resolved following treatment discontinuation. These symptoms may resemble those observed with nonselective MAO inhibitors. **Prescription only medicine.**	

Malignant melanoma	Proposed content in SPC The following information is included in Section 4.4: 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 skin cancer (not exclusively melanoma). Any suspicious skin lesion should be evaluated by a specialist. The following information is included in Section 4.8: Skin carcinoma (skin melanoma) is listed ADR in Section 4.8. **Prescription only medicine.**	None proposed
Concomitant use with pethidine or sympathomimetics	Proposed content in SPC 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 (see section 4.5). At least 14 days must elapse between discontinuation of rasagiline and initiation of treatment with MAO inhibitors or pethidine. The following information is included in 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	None proposed

	recommended (see section 4.5). The following information is included in 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 (see section 4.3). 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 (see section 4.4). The following information is included in Section 4.8: With MAO inhibitors, there have been reports of drug interactions with the concomitant use of sympathomimetic medicinal products. In post marketing period, there was one case of elevated blood pressure in a patient using the ophthalmic vasoconstrictor tetrahydrozoline	

	hydrochloride while taking rasagiline. **Prescription only medicine.**	
Pregnant and lactating women	Proposed content in SPC Section 4.6: 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 (see section 5.3). 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. **Prescription only medicine.**	None proposed

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Rasagiline is used to treat of Parkinson's disease. Parkinson's disease is a progressive brain disorder that causes shaking, slow movement and muscle stiffness. Rasagiline can be used either alone, or as an add-on to levodopa (another medicine used in Parkinson's disease) in patients who are having '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.

The disease affects approximately 1 percent of persons older than 60 years, and up to 4 percent of those older than 80 years. The rate of progression of Parkinson's disease, as well as the parkinsonian signs and symptoms, differs widely among individual patients.

Risk factors for Parkinson's disease include a family history, male gender, head injury, exposure to pesticides, consumption of well water and rural living.

VI.2.2 Summary of treatment benefits

Rasagiline has been studied in three main studies involving a total of 1,563 patients with Parkinson's disease. In the first study, two different doses of rasagiline taken alone were compared with placebo (a dummy treatment) in 404 patients with early-stage disease. The main measure of effectiveness was the change in symptoms over 26 weeks, as assessed on a standard scale (Unified Parkinson's Disease Rating Scale, UPDRS). The other two studies involved a total of 1,159 patients with later stage disease, where rasagiline was added to the patients' existing treatment including levodopa. It was compared with placebo or entacapone (another medicine for Parkinson's disease). The studies lasted 26 and 18 weeks, respectively. The main measure of effectiveness was the time spent in the 'off' state during the day, as recorded in patient diaries.

Rasagiline was more effective than placebo in all of the studies. In the study where rasagiline was used alone, patients taking 1 mg of the medicine once a day had an average fall in UPDRS score of 0.13 points over the 26-week study from a starting value of 24.69. When used as an add-on to levodopa, 1 mg of rasagiline reduced the time in the 'off' state more than placebo did. In both studies, patients adding rasagiline spent an average of around one hour less in the 'off' state than those adding placebo.

VI.2.3 Unknowns relating to treatment benefits

Rasagiline Krka is a generic medicine and is bioequivalent to the reference medicine, its benefits and risks are taken as being the same as the reference medicine's.

For rasagiline no clinical data on pregnancies is available. Animals studies do not show harmful effects with respect to pregnancy or foetal development. Caution should be exercised when prescribing to pregnant women.
Experimental data showed 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.

VI.2.4 Summary of safety concerns

Important identified risks:

Risk	What is known	Preventability
Orthostatic hypotension (Low blood pressure when rising to a standing position, with symptoms like dizziness/light-headedness (orthostatic hypotension)	Orthostatic hypotension is low blood pressure when rising to a standing position with symptoms like dizziness/light-headedness especially in the first two months of treatment. Orthostatic hypotension has been reported commonly (they may affect up to 1 in 10 people).	Patient should tell a doctor if she/he experiences symptoms like dizziness/light-headedness. A doctor will discuss ways of managing or reducing the symptoms.
Serotonin syndrome (A life-threatening syndrome that develops due to high levels of the chemical serotonin**)**	Cases of serotonin syndrome have been reported in patients taking rasagiline with antidepressants that increase the levels of the chemical serotonin. The possible signs and symptoms are: agitation, confusion, rigidity and fever.	Patient should tell a doctor if she/he experiences symptoms like agitation, confusion, rigidity and fever. A doctor will discuss ways of managing or reducing the symptoms.
Impulse control disorders (Developing urges or cravings to behave in ways that are unusual and it cannot resist the impulse, drive or temptation to carry out certain activities that could harm us or others. These are called impulse control disorders)	In patients taking rasagiline 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.	Patient should tell a doctor if she/he or other notice that patient is developing unusual behaviours where he/she cannot resist the impulse, urges or cravings to carry out certain harmful or detrimental activities to himself/herself or others. A doctor may need to adjust or stop his/her dose.
Concomitant use with antidepressants (SSRI, SnRI, tricyclic and tetracyclic antidepressants), CYP1A2 inhibitors or MAO inhibitors	Serious side effects have been reported with the concomitant use of certain antidepressants (selective serotonin reuptake inhibitors, selective serotonin-norepinephrine reuptake inhibitors, tricyclic or tetracyclic antidepressants).	Concomitant use of certain antidepressants (selective serotonin reuptake inhibitors, selective serotonin-norepinephrine reuptake inhibitors, tricyclic or tetracyclic antidepressants) and rasagiline should be used with caution.

Important potential risks:

Risk	What is known
Hypertension	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 hypertensive crises. Exacerbation of hypertension may occur during treatment with rasagiline. Monitor patients for new-onset hypertension or hypertension that is not adequately controlled after starting rasagiline.
Malignant melanoma (skin cancer)	People who have Parkinson's disease may have a greater risk of developing skin cancer than people who do not have Parkinson's disease. Skin cancer was reported in 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).
Concomitant use with pethidine (a strong pain killer) or **sympathomimetics** (nasal, oral decongestants or cold medicinal products (containing ephedrine or pseudoephedrine)	Pethidine is a strong pain killer and must not be used together with rasagiline. A patient must wait at least 14 days after stopping rasagiline treatment and starting treatment with pethidine. There have been reports of drug interactions between sympathomimetic medicinal products (nasal, oral decongestants or cold medicinal products containing ephedrine or pseudoephedrine) and rasagiline. This combination of drugs is not recommended. Patient should tell a doctor if she/he is planning to take pethidine. Concomitant use of rasagiline and pethidine is not allowed. Patient should not use nasal and oral decongestants or cold medicinal products (containing ephedrine or pseudoephedrine) and rasagiline.

Missing information

Risk	What is known
Pregnant and lactating women	There is no clinical data in pregnant women therefore rasagiline should be used with caution during pregnancy. It is not known whether rasagiline is excreted in human milk. Caution should be exercised when rasagiline is used in a breast-feeding mother.

VI.2.5 Summary of risk minimisation 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.

The Summary of Product Characteristics and the Package leaflet for this product can be found at the agency's EPAR page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable. No postauthorisation studies are planned.

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

Not applicable, this is the first Risk management plan.