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.