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Summary of the risk management plan (RMP) for Rasagiline ratiopharm (rasagiline)

This is a summary of the risk management plan (RMP) for Rasagiline ratiopharm, which details the measures to be taken in order to ensure that Rasagiline ratiopharm is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Rasagiline ratiopharm, which can be found on Rasagiline ratiopharm's EPAR page.

Overview of disease epidemiology

Rasagiline ratiopharm (rasagiline) is a medicine used to treat adults with Parkinson's disease.

Parkinson's disease is a progressive brain disorder that causes shaking, slow movement and muscle stiffness. The rate of progression of Parkinson's disease, as well as the array of parkinsonian signs and symptoms, differs widely among individual patients.

The disease affects about 1% of the population over the age of 55 years, with a male-to-female ratio of 3:2.

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

Summary of treatment benefits

Rasagiline ratiopharm blocks the action of an enzyme called monoamine oxidase type B, which breaks down a substance in the brain called dopamine, levels of which are lowered in Parkinson's disease; by blocking the enzyme, the medicine helps to increase the amount of dopamine in the parts of the brain that control movement and coordination, thereby improving the symptoms of the disease such as stiffness and slowness of movement.

The medicine has been shown in three studies, involving 1,563 patients, to be effective in both relieving the symptoms of Parkinson's disease and in reducing the time patients spend in their 'off' periods.

In one of the studies, a 26-week treatment with Rasagiline ratiopharm resulted in an average fall of 0.13 points in UPDRS (a standard scale for assessing symptoms of Parkinson's disease) from a starting value of 24.69 compared with a rise of 4.07 points in the patients taking placebo (dummy treatment) 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.

In the two other studies, Rasagiline ratiopharm was given as 'add-on' to patients with later stage disease who were already being treated with levodopa, and compared with placebo and another medicine entacapone (also used as add-ons). The studies included 1,159 patients and lasted 26 and 18 weeks, respectively. In both studies, patients taking Rasagiline ratiopharm spent an average of around

one hour less in the 'off' state than those taking placebo. Similar reductions in time spent in the 'off' state were seen in patients taking entacapone.

Unknowns relating to treatment benefits

Post-marketing experience in the therapeutic practice does not indicate any sub-populations requiring further studies. All data consistently support that the safety and efficacy is the same across races.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Low blood pressure when rising to a standing position, with symptoms like dizziness/light-headedness (orthostatic hypotension)	Orthostatic hypotension is a common side effect of rasagiline (may affect up to 1 in 10 people)	Healthcare professionals and patients should be aware of this risk.
High levels of serotonin in the body (serotonin syndrome)	Serotonin syndrome is a condition caused by excess serotonin in the body. Symptoms can range from mild (shivering and diarrhoea) to severe (muscle rigidity, fever and seizures). Severe serotonin syndrome can be fatal if not treated. Rasagiline belongs to the class of 'monoamine oxidase (MAO) B inhibitor' which are known to increase serotonin levels in the body. Using MAO inhibitors with other medicines known to increase serotonin levels such as antidepressants (tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors [SNRIs], selective serotonin reuptake inhibitors [SSRIs]) may cause serotonin syndrome. There were no cases of serotonin syndrome in the rasagiline clinical program in which 115 patients were exposed concomitantly to rasagiline and tricyclic antidepressants and 141 patients were exposed to rasagiline and SSRIs/ SNRIs. However, in the	Healthcare professionals should avoid using Rasagiline ratiopharm together with the SSRI antidepressants fluoxetine or fluvoxamine. In addition, healthcare professionals should wait until the antidepressant is completely cleared form the body before starting rasagiline, or vice versa. Treatment with rasagiline should only be started 5 weeks after stopping fluoxetine treatment. Treatment with fluoxetine or fluvoxamine should only be started 14 days after stopping rasagiline treatment. Other antidepressants should be used with caution when using Rasagiline ratiopharm.

Risk	What is known	Preventability
	post-marketing period, cases of serotonin syndrome have been reported by patients treated with antidepressants including SNRIs together with rasagiline.	
Temptation to carry out certain activities such as addictive gambling, excessive spending, and impulsive behaviour and an abnormally high sex drive (impulse control disorders).	There have been cases of patients who, while taking one or more medications for Parkinson's disease, were unable to resist the temptation to perform an action that could be harmful or detrimental to themselves or others.	Doctors should monitor patients regularly for the development of impulse control disorders and should consider dose adjustments or stopping treatment in case they occur. Patients should tell their doctor if they notice that unusual behaviours where they cannot resist the temptation to carry out certain harmful or detrimental activities to themselves or others.
Concomitant use with other medications (antidepressants, CYP1A2 inhibitors, MAO inhibitors)	Rasagiline is removed from the body predominantly by certain enzymes in the liver. Other medicines that affect the same liver enzymes can increase the side effects or reduce the therapeutic effects of rasagiline.	Doctors should avoid prescribing these medicines together. Patients should tell their doctor if they are taking or have recently taken any other medicines, including medicines obtained without prescription.

Important potential risks

Risk	What is known
High blood pressure (Hypertension)	In the post-marketing period, cases of elevated blood pressure, including rare cases of hypertensive crisis (dangerously high blood pressure) associated with ingestion of foods rich in tyramine (e.g. aged cheeses, cured meats) have been reported in patients taking Rasagiline ratiopharm. However, results of five clinical studies, together with results of home monitoring of blood pressure after meals (of 464 patients treated with 0.5 or 1 mg/day of rasagiline or placebo along with levodopa for six months without tyramine restrictions) showed no interaction and support that rasagiline can be used safely without dietary tyramine restrictions. In addition there no reports of tyramine/rasagiline interaction in clinical studies conducted without tyramine restriction.
Skin cancer (Malignant melanoma)	Skin cancer was reported in around 1% of patients in the placebo-controlled clinical trials. Nevertheless, scientific evidence suggests that Parkinson's disease itself is associated with a risk of cancer in general and that this risk is not specific to a particular medicine.
Concomitant use with	Serious adverse reactions have been reported with the concomitant use of

Risk	What is known
other medications (pethidine, sympathomimetics)	pethidine and MAO inhibitors including products that work in a similar way to rasagiline). There have been reports of interactions between MAO inhibitors and sympathomimetic medicines (such as nasal and oral decongestants containing ephedrine and pseudoephedrine) when used at the same time.

Missing information

Risk	What is known
Limited information on use in pregnant and breastfeeding women	For Rasagiline ratiopharm no clinical data on use during pregnancy are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy. It is not known whether rasagiline is excreted in human milk.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Rasagiline ratiopharm can be found on Rasagiline ratiopharm's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Registry-based study: risk of melanoma among PD patients (TVP-1012/401 study)	1) To estimate and compare the incidence rate of melanoma in patients with Parkinson's disease who start treatment with rasagiline and those who start treatment with other anti-Parkinson's medicines. 2) To examine the association between use of rasagiline and malignant	Safety concern: malignant melanoma	Planned	Final study report June 2015

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	melanoma among Parkinson's disease patients. 3) To compare the incidence rate of melanoma in patients with Parkinson's disease not treated with rasagiline with the rate in subjects without Parkinson's disease. In addition, the incidence rates of other (non-melanoma) malignant neoplasms of the skin will be evaluated to examine the presence of reporting bias secondary to potential increased monitoring of users of rasagiline.			

Studies which are a condition of the marketing authorisation

None

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 12-2014.