RASAGILINE ORION 1 MG TABLETS

PUBLIC SUMMARY OF RISK MANAGEMENT PLAN

DATE: 08-07-2015, VERSION 1.1

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Parkinson's disease (PD) is a progressive brain disease affecting mainly elderly people. The classical motor symptoms of PD are slowness of movements, muscle stiffness and tremor at rest. Also balance problems are relatively common in later disease. Although not usually present at the time of diagnosis, some patients will develop for example cognitive problems, excessive daytime sleepiness and hallucinations after many years into the disease. Also constipation, urinary incontinense, drop in blood pressure upon standing with subsequent dizziness and various pains may be related to PD.

The occurrence of PD is increasing with increasing age and PD is rare before age of 50 years. 0.3% of the entire population and 1% of people over 60 years of age have PD. It is estimated that approximately 10-20 out of a population of 100 000 people will develop PD in every year. There are no significant differences in the occurrence of PD between men and women or between different races. In general, geographical differences are not known either and PD is equally common in different European countries.

Long and excessive exposure to herbicides, pesticides and heavy metals may increase the risk of PD. On the other hand, smoking and coffee are known to decrease the risk of PD. Genetic mutations causing PD are relatively rare.

VI.2.2 Summary of treatment benefits

Rasagiline, 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 improves the signs and symptoms of Parkinson's disease, such as stiffness and slowness of movement.

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.

Rasagiline has been more effective than placebo in clinical studies. In a study where two different doses of rasagiline were used alone, patients with early-stage disease taking 1 mg of the medicine once a day had an average fall in the Unified Parkinson's Disease Rating Scale (UPDRS) score of 0.13 points over the 26-week study from a starting value of 24.69. This was compared with a rise of 4.07 points in the patients taking placebo (a 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 studies where rasagiline was used as an add-on to pre- existing levodopa treatment in patients with later stage disease, 1 mg rasagiline reduced the time in the 'off' state more than placebo did. In these 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

For rasagiline, no clinical data on exposed pregnancies is available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development.

Experimental data indicated that rasagiline inhibits prolactin secretion and thus, may inhibit lactation. It is not known whether rasagiline is excreted in human milk.

VI.2.4 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)	There have been reports of decrease in blood pressure when rasagiline is taken concomitantly with levodopa. Patients with Parkinson's disease are particularly vulnerable to the adverse effects of too low blood pressure due to existing issues with body movement.	Changes in posture should be made slowly avoiding quick and hasty changes in posture. When patient rises up from lying, it is recommended first to sit up for a while before standing up. This way cardiovascular system has time to adapt to changes in the posture and decrease in blood pressure is diminished.

Risk	What is known	Preventability
Serotonin syndrome	Serious adverse reactions are known to occur with the concomitant use of certain drugs called selective serotonin reuptake inhibitors (SSRIs), selective serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic or tetracyclic antidepressants and monoamine oxidase (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.	Patients should tell doctor or pharmacist if they are taking, have recently taken or might take any other medicines. Patients must not take the following medicines while taking rasagiline: · 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. · Pethidine (a strong pain killer). Patients must wait at least 14 days after stopping rasagiline treatment and starting treatment with MAO inhibitors or pethidine. Patients should ask their doctor for advice before taking SSRIs,

Risk	What is known	Preventability
		SNRIs, tricyclic or tetracyclic antidepressants.

Risk	What is known	Preventability
Impulse control disorders	In patients taking rasagiline and/or other medications used to treat Parkinson's disease, unusual 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.	Patients should tell their doctor if they or their family/carer notices that patients are developing unusual behaviours where they cannot resist the impulse, urges or cravings to carry out certain harmful or detrimental activities to themselves or others. Doctor may need to adjust the dose or stop rasagiline.

Risk	What is known	Preventability
Concomitant use with antidepressants (SSRI, SNRI, tricyclic and tetracyclic antidepressants), CYP1A2 inhibitors or MAO inhibitors	Use of rasagiline together with certain medicinal and natural products may cause serious side effects such as unsafe rise in blood pressure and condition called serotonin syndrome.	Patients should tell doctor or pharmacist if they are taking, have recently taken or might take any other medicines and if they are smoking or intend to stop smoking. Patients must not take the following medicines while taking rasagiline: · 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. Patients must wait at least 14 days after stopping rasagiline treatment and starting treatment with MAO inhibitors. Patients should ask their doctor for advice before taking any of the following medicines together with rasagiline: · Certain antidepressants (selective serotonin reuptake inhibitors, selective serotonin-norepinephrine reuptake inhibitors, tricyclic or

Risk	What is known	Preventability
		tetracyclic antidepressants). · The antibiotic ciprofloxacin used against infections. The use of rasagiline together with the antidepressants containing fluoxetine or fluvoxamine should be avoided. If patients are starting treatment with rasagiline, they should wait at least 5 weeks after stopping fluoxetine treatment. If patients are starting treatment with fluoxetine or fluvoxamine, they should wait at least 14 days after stopping rasagiline treatment.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
High blood pressure (Hypertension)	Rasagiline must not be administered along with other MAO inhibitors (including medicinal and natural products without prescription e.g. St. John's Wort) since this may lead to unsafe rise in blood pressure. Patients should ask their doctor for advice before taking sympathomimetics such as those present in eye drops, nasal and oral decongestants and cold medicine containing ephedrine or pseudoephedrine.

Risk	What is known (Including reason why it is considered a potential risk)
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, and not any medicine in particular, is associated with a higher risk of skin cancer (not exclusively melanoma). Patients should speak with their doctors about any suspicious skin changes.

Risk	What is known (Including reason why it is considered a potential risk)
Concomitant use with pethidine or sympathomimetics	Use of rasagiline together with pethidine may cause serious condition called serotonin syndrome. Patients must not take pethidine while taking rasagiline. Patients must wait at least 14 days after stopping rasagiline treatment and starting treatment with pethidine. Use of rasagiline together with sympathomimetics (such as those present in eye drops, nasal and oral decongestants and cold medicine

Risk	What is known (Including reason why it is considered a potential risk)
	containing ephedrine or pseudoephedrine) may lead to unsafe rise in blood pressure. Patients should ask their doctor for advice before taking sympathomimetics.

Missing information

Risk	What is known
Use during pregnancy and lactation	For rasagiline, no clinical data on exposed pregnancies is available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development. Experimental data indicated that rasagiline inhibits prolactin secretion and thus, may inhibit lactation. It is not known whether rasagiline is excreted in human milk. If patient is pregnant or breast-feeding, think she may be pregnant or is planning to have a baby, she should ask doctor or pharmacist for advice before taking rasagiline.

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 [invented name] can be found in the national authority's web page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan (if applicable)

Not applicable.

VI.2.7 Summary of changes to the risk management plan over time

Not applicable.