Pentiro

31.7.2014, Version 1.3

PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Entacapone/levodopa/carbidopa is a medicine that contains the active substance entacapone. It is available as tablets and is used to treat patients with Parkinson's disease. Parkinson's disease is a progressive brain disorder that causes shaking, slow movement and muscle stiffness. Entacapone is used together with levodopa (either a combination of levodopa and benserazide or a combination of levodopa and carbidopa) when the patient is having 'fluctuations' towards the end of the period between two doses of their medication.

Parkinson's disease is one of the most common neurologic disorders, affecting approximately 1% of individuals older than 60 years. The incidence of Parkinson disease has been estimated to be 4.5-21 cases per 100,000 population per year, and estimates of prevalence range from 18 to 328 cases per 100,000 population. The incidence and prevalence of Parkinson disease increase with age, and the average age of onset is approximately 60 years. Onset in persons younger than 40 years is relatively uncommon. Parkinson disease is about 1.5 times more common in men than in women.

VI.2.2 Summary of treatment benefits

Entacapone has been tested in several clinical trials worldwide to be effective in the indication stated above.

Entacapone has been studied in a total of 376 patients with Parkinson's disease, in two six-month studies that measured the effects of adding entacapone or placebo (a dummy medicine) to the patient's combination of levodopa and carbidopa or levodopa and benserazide. The main measure of effectiveness was the time spent in the 'on' state (the time when levodopa is controlling the symptoms of Parkinson's disease) after the first levodopa dose of the morning in the first study, and over one day in the second study.

Entacapone was more effective than placebo in both studies. In the first study, adding Entacapone increased the 'on' time by 1 hour and 18 minutes more than adding placebo. In the second study, the 'on' time was increased by 35 minutes compared with placebo.

VI.2.3 Unknowns relating to treatment benefits

Not applicable

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Urges or cravings to behave unusual or unable to resist temptation (Impulse control disorders)	Urges or cravings to behave in ways that are unusual or unable to resist the impulse, drive or temptation to carry out certain activities that could harm a patient or	Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control

Risk	What is known	Preventability
	others may occur. These behaviours are called impulse control disorders and can include addictive gambling, excessive eating or spending, an abnormally high sex drive or a preoccupation with an increase in sexual thoughts or feelings	disorders including 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 containing levodopa. Review of treatment is recommended if such symptoms develop Urges or cravings to behave unusual or unable to resist temptation
Rhabdomyolysis (breakdown of muscle fibres)	Rhabdomyolysis has been reported during treatment. Signs may include rigid muscles, violent jerking, tremors, agitation, confusion, fever, rapid pulse, or wide fluctuations in blood pressure.	This medication should be used with caution in patients with a previous history of rhabdomyolysis. Any abrupt dose reduction or withdrawal of levodopa should be carefully observed, particularly in patients at risk.
Neuroleptic malignant syndrome (a dangerous nervous-system disorder)	Neuroleptic malignant syndrome has been reported during treatment. Signs may include rigid muscles, violent jerking, tremors, agitation, confusion, fever, rapid pulse, or wide fluctuations in blood pressure.	This medication should be used with caution in patients with a previous history of neuroleptic malignant syndrome. Any abrupt dose reduction or withdrawal of levodopa should be carefully observed, particularly in patients at risk.
Use in patients with liver problems (Liver and biliary system disorders and liver laboratory abnormalities)	In patients with liver impairment, the process through which the body alters the medication may be slower which can cause increase amounts of the medication in the blood. Inflammation of the liver (hepatitis) has been reported during treatment. Abnormal liver function tests may affect up to 1 in 100 people. Signs of liver disease may include weight loss in a short period of time, weakness and exhaustion.	In patients with a liver problem, the dose may need to be adjusted. If signs of liver problems occur, a general medical evaluation including liver function tests should be considered.
Use in patients with pre-existing heart problems (Myocardial infarction and other ischemic heart disease)	Ischaemic heart disease, abnormal heart rhythms and heart attacks have been reported during treatment, as well as shortness of breath.	It is not recommended to use in patients with a heart attack or any other diseases of the heart including cardiac arrhythmias, or of the blood vessels, asthma or any other disease of the lungs, kidney or hormone-related diseases, stomach ulcers or convulsions. Cardiac function should be monitored with particular care during the period of initial dose adjustments.

Risk	What is known	Preventability
Use in patients with depression with suicidal behaviour (Depression with suicidal tendencies)	Depression as well as suicidal behaviour have been reported during treatment.	Patients should be monitored carefully for the development of mental changes, depression with suicidal tendencies, and other serious antisocial behaviour. Patients with past or current issues with their mental state should be treated with caution.
Gastrointestinal bleeding (Gastrointestinal haemorrhage)	Gastrointestinal bleeding has been reported during treatment.	Report any symptoms of gastrointestinal bleeding to your doctor.
Inflammation of the colon (Colitis)	Inflammation of the colon has been reported during treatment. Prolonged or persistent diarrhoea may be a sign of inflammation of the colon.	Treatment should be stopped if prolonged or persistent diarrhoea occurs and this should be reported to a doctor.
Decreased numbers of platelets in the blood (Thrombocytopenia)	Thrombocytopenia has been reported during treatment. Changes in the blood cell count may result in bleeding. Symptoms of thrombocytopenia can include bruising, purpura, petechia, nosebleeds, and bleeding of the gums. If patients develop these symptoms they should consult their physician.	The patient should consult a doctor prior to taking this medication if they suffer from thrombocytopenia or if they have any of the symptoms associated with thrombocytopenia.
Blood pressure suddenly falling when standing up or stretching (Orthostatic hypotension)	Decreased blood pressure has been reported during treatment and particularly when this medication is given in combination with other medication which may cause orthostatic hypotension. Symptoms of orthostatic hypotension may affect the patient's ability to drive or operate machinery.	Patients should use this medication cautiously if being treated with other mediation which may cause a decreased blood pressure. If patients develop dizziness, they should not drive and should consult their physician.

Important potential risks

Risk	What is known
Severe skin and severe allergic reactions	This medication is known to cause rash, angioedema and urticarial. This medication should not be used by patients with a known allergy to the this medication, soya, peanut or to any of the

	ingredients within this product
Prostate cancer	No known risk for prostate cancer.
Medication error	No known risk of medication error.

Important missing information

Risk	What is known
Pregnancy	There are no adequate data from the use of the combination of levodopa/carbidopa/entacapone in pregnant women. Studies in animals have shown reproductive toxicity of the separate compounds. The potential risk for humans is unknown. This should not be used during pregnancy unless the benefits for the mother outweigh the possible risks to the foetus.

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

No additional risk minimisation activities are required. Routine pharmacovigilance activities are considered sufficient to monitor the benefit-risk profile of the product and detect any safety concerns.

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

There are no studies in the post authorisation development plan.

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

Table 1. Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
Version 1	Under review	Use in patients with hepatic impairment	N/A
		Use in patients with chronic underlying disease (cardiac, pulmonary, renal, endocrine, epilepsy)	
		Mental changes and depression with suicidal tendencies	
		Concomitant administration of monoamine oxidase inhibitors (MAOI, selective and non-selective)	
		Use in patients with glaucoma (narrow-angle/chronic wide-angle)	
		Orthostatic hypotension	
		Somnolence/sudden sleep onset	

Version	Date	Safety Concerns	Comment
		Dyskinesia Rhabdomyolysis Diarrhoea Impulse control disorders Use in renal impairment Use in pregnancy and breastfeeding	
Version 1.1	Under review	*Important identified risks* • Impulse control disorders (Pathological gambling, increased libido, hypersexuality, compulsive buying and spending, compulsive and binge eating) • Rhabdomyolysis • Neuroleptic malignant syndrome • Liver and biliary system disorders and liver laboratory abnormalities • Myocardial infarction and other ischemic heart disease *Important potential risks* • Use in pregnancy and breastfeeding	Comments received from the RMS
Version 1.2	Under review	*Important identified risks* • Impulse control disorders (Pathological gambling, increased libido, hypersexuality, compulsive buying and spending, compulsive and binge eating) • Rhabdomyolysis • Neuroleptic malignant syndrome • Liver and biliary system disorders and liver laboratory abnormalities • Myocardial infarction and other ischemic heart disease *Important potential risks* Use in pregnancy and breastfeeding	Comments received from the RMS

Version	Date	Safety Concerns	Comment
Version 1.3	Under review	*Important identified risks* • Depression with suicidal tendencies • Gastrointestinal haemorrhage • Colitis • Thrombocytopenia • Orthostatic hypotension Important potential risks • Severe skin and severe allergic reactions • Prostate cancer • Medication error Important missing information • Pregnancy	Comments received from the RMS