VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Parkinson's disease affects individuals globally (WHO 2006). It is the most common serious movement disorder, including speech and 'body language' (WHO 1998; Samii et al. 2004) in the world, affecting about 1% of adults older than 60 years. Although the incidence is higher in the elderly population, more than one in ten sufferers is diagnosed by the age of 50 (WHO 1998). The disease is attributed to selective loss of neurons in the midbrain (substantia nigra), and its cause is puzzling in most individuals.

Like many other neurological illnesses, Parkinson's disease is chronic, progressive and, at the moment, incurable (WHO 1998).

VI.2.2 Summary of treatment benefits

Levodopa/carbidopa/entacapone is used for the treatment of Parkinson's disease.

Parkinson's disease is caused by low levels of a substance called dopamine in the brain. Levodopa increases the amount of dopamine and hence reduces the symptoms of Parkinson's disease. Carbidopa and entacapone improve the antiparkinson effects of levodopa.

The standard symptomatic therapy for Parkinson's disease for more than 30 years has been levodopa. This is the precursor of dopamine which is deficient in Parkinson's disease. Levodopa is readily transformed into dopamine by dopa decarboxylase. To reduce peripheral metabolism (transformation) of levodopa, it is combined with a peripheral dopa decarboxylase inhibitor (ie carbidopa). This increases the amount of levodopa that crosses the blood-brain barrier. Entacapone inhibits the COMT

(catechol-O-methyl transferase) enzyme, which degrades dopamine, thereby prolonging the effects of levodopa and it has been used to complement levodopa (NCC-CC 2006).

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
Rhabdomyolysis *(Damage of muscle fibres)*	Damage of muscle fibres secondary to severe movement disorders (dyskinesias) or neuroleptic malignant syndrome (NMS) has been observed rarely in patients with Parkinson's disease.	Contact your doctor immediately if your muscles get very rigid or jerk violently, you get tremors, agitation, confusion, fever, rapid pulse, or wide fluctuations in your blood pressure. These can be symptoms of neuroleptic malignant syndrome (NMS), or rhabdomyolysis. Do not stop taking Levodopa/carbidopa/entacapone unless your doctor tells you to. In such a case your doctor may need to adjust your other antiparkinson medicines, especially levodopa, to give sufficient control of your symptoms. If you suddenly stop taking Levodopa/carbidopa/entacapone and other antiparkinsonian medicines it may result in unwanted side effects. Any abrupt dose reduction or discontinuation of levodopa should be carefully observed, particularly in patients who are also receiving neuroleptics.
Neuroleptic malignant syndrome *(NMS –a rare reaction to medicines used to treat severe mental disorders)*	NMS is a rare severe reaction to medicines used to treat disorders of the central nervous system. If NMS occurs, muscles may get rigid or jerk violently, patient could get tremors, be agitated, or confused, could get fever, rapid pulse, or wide fluctuations in blood pressure. A syndrome resembling the NMS has been reported with the abrupt withdrawal of drugs used to treat Parkinson's disease.	Do not take levodopa/carbidopa/entacapone if you have ever had neuroleptic malignant syndrome (NMS) or non-traumatic rhabdomyolysis (a rare severe muscle disorder). Do not stop taking levodopa/carbidopa/entacapone unless your doctor tells you to. In such a case your doctor may need to adjust your other antiparkinson medicines, especially levodopa, to give sufficient control of your

Risk	What is known	Preventability
		symptoms. If you suddenly stop taking Levodopa/carbidopa/entacapone and other antiparkinsonian medicines it may result in unwanted side effects. Any abrupt dose reduction or discontinuation of levodopa should be carefully observed, particularly in patients who are also receiving neuroleptics. Contact your doctor immediately if your muscles get very rigid or jerk violently, you get tremors, agitation, confusion, fever, rapid pulse, or wide fluctuations in your blood pressure. These can be symptoms of neuroleptic malignant syndrome (NMS), or rhabdomyolysis. The early diagnosis is important for the appropriate management of NMS.
Liver and biliary system disorders and liver laboratory abnormalities	Abnormal liver function test may occur in up to 1 in 100 people and hepatitis (inflammation of the liver) may also occur in some patients.	Do not take levodopa/carbidopa/entacapone if you have a severe liver disease. Talk to your doctor or pharmacist before taking Levodopa/carbidopa/entacapone if you have or have ever had: a liver problem, because your dose may need to be adjusted. Consult your doctor if during the treatment with Levodopa/carbidopa/entacapone you experience progressive anorexia, asthenia (weakness, exhaustion) and weight decrease within a relatively short period of time. If this happens, a general medical evaluation including liver function should be considered.
Impulse control disorders (pathological gambling, increased libido, hypersexuality, compulsive buying and spending, compulsive and	Patients may experience the development of impulse control disorders (inability to resist the impulse to perform an action that could be harmful) which may include behavioural symptoms of impulse control disorders including strong impulse to gamble excessively despite serious or personal family consequences; altered or increased	Patients and carers should be made aware that behavioural symptoms may occur. Tell your doctor if you or your family/carer notices you are developing urges or cravings to behave in ways that are unusual for you or you cannot resist the impulse, drive or temptation to carry out

Risk	What is known	Preventability
binge eating) *(Inability to resist the impulse to perform an action that could be harmful)*	sexual interest and behaviour of significant concern to you or to others, for example, an increased sexual drive; uncontrollable excessive shopping or spending; and binge eating (eating large amounts of food in a short time period) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger).	certain activities that could harm yourself or others. These behaviours are called impulse control disorders and can include addictive gambling, excessive eating or shopping/spending, an abnormally high sex drive or a preoccupation with an increase in sexual thoughts or feelings. Your doctor may need to review your treatments.
Dyskinesia *(uncontrolled movements)*	More than 1 in 10 patients may be affected by uncontrolled movements. These side effects may be increased of levodopa/carbidopa/entacapone is used with certain medicines used to treat depression.	Consult your doctor if during the treatment with Levodopa/carbidopa/entacapone you notice that uncontrolled movements begin or get worse after you started to take Levodopa/Carbidopa/Entacapone. If this happens, your doctor may need to change the dose of your antiparkinson medicine.
Sudden onset of sleep	Drowsiness may affect up to 1 in 10 people.	Consult your doctor if during the treatment with Levodopa/carbidopa/entacapone you find yourself suddenly falling asleep. If you feel very drowsy, or if you sometimes find yourself suddenly falling asleep, wait until you feel fully awake again before driving or doing anything else that requires you to be alert. Otherwise, you may put yourself and others at risk of serious injury or death.
Mental changes (including depression with suicidal tendencies, and other serious antisocial behaviour)	There is a possibility of development of mental changes, depression with suicidal tendencies, and other serious antisocial behaviour in patients treated with levodopa/carbidopa/entacapone.	Talk to your doctor or pharmacist before taking Levodopa/carbidopa/entacapone if you have or have ever had any form of severe mental disorder like psychosis. Tell your doctor if you experience mental changes – including psychotic symptoms, problems with memory, anxiety and depression (possibly with thoughts of suicide). Patients should be monitored carefully and patients with past or current psychosis should be treated with caution.

Risk	What is known	Preventability
Severe skin and severe allergic reactions	Allergic reactions to the active substances or to any of the other constituents of the product may occur. The signs may include hives (nettle rash), itching, rash, swelling of your face, lips, tongue or throat. This may cause difficulties in breathing or swallowing.	Contact your doctor immediately if you notice an allergic reaction like hives (nettle rash), itching, rash, swelling of your face, lips, tongue or throat. Do not take Levodopa/carbidopa/entacapone if you previously had allergic reactions to levodopa/carbidopa/entacapone or to any other constituents of the product.
Myocardial infarction and other ischaemic heart disease	Levodopa/carbidopa/entacapone therapy should be administered cautiously to patients with heart problems (ischemic heart disease, severe cardiovascular disease), or patients with history of heart attack (myocardial infarction) and consequential irregularities in heart functions (atrial nodal or ventricular arrhythmias) as adverse reactions may include ischemic heart disease events other than myocardial infarction (e.g. angina pectoris), irregular heart rhythm, myocardial infarction, orthostatic hypotension and hypertension.	Talk to your doctor or pharmacist before taking Levodopa/carbidopa/entacapone if you have or have ever had a heart attack or any other diseases of the heart including cardiac arrythmias, or of the blood vessels or if you are taking a medicine which may cause low blood pressure when rising from a chair or bed as Levodopa/carbidopa/entacapone may make these reactions worse. Periodic evaluation of cardiovascular function is recommended during extended therapy with levodopa/carbidopa/entacapone.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Prostate cancer	Potential effect of levodopa/carbidopa/entacapone on occurrence of prostate cancer is being reviewed; however, no new conclusions or recommendations about the use of this drug have been made.

Missing information

Risk	What is known
Use in pregnant and lactating women	No adequate data from the use of the combination of levodopa/carbidopa/entacapone in pregnant women is available and the potential risk for humans is unknown. Therefore, the product should not be used during pregnancy unless the benefits for the mother outweigh the possible risks to the foetus. Levodopa is excreted in human breast milk, however, is not known whether carbidopa or entacapone are excreted in human breast milk. The safety of levodopa, carbidopa or entacapone in the infant is not

Risk	What is known
	known and women should not breast-feed during treatment with Levodopa/Carbidopa/Entacapone.
Use in patients with mild to moderate hepatic impairment *(Use in patients with mild to moderate liver failure)*	Levodopa/carbidopa/entacapone should be administered with caution to patients with mild to moderate liver failure. The metabolism of entacapone is slowed in patients with mild to moderate liver failure leading to an increased blood concentration of entacapone.
Use in patients with renal impairment *(Use in patients with kidney failure)*	Kidney failure does not affect the pharmacokinetics of entacapone and no particular studies are reported on the pharmacokinetics of levodopa and carbidopa. However caution and longer dosing interval is advised in patients with severe kidney failure including those receiving dialysis therapy.

VI.2.5 Summary of risk minimisation measures by safety concern

No additional risk minimisation measures are proposed.

VI.2.6 Planned post authorisation development plan

Not applicable.

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

Table 2. Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	04 October 2013	**Important identified risks** • Impulse control disorders • Mental changes (including depression with suicidal tendencies, and other serious antisocial behaviour) • Rhabdomyolysis secondary to severe dyskinesias or neuroleptic malignant syndrome (NMS) • Hypersensitivity reactions including angioedema • Cardiovascular disorders **Important potential risks** • Worsening of parkinsonian symptoms (concomitant administration of antipsychotics with dopamine receptor-blocking properties) • Changes in intra-ocular pressure **Missing information** • Use in pregnant and lactating women	Not applicable.

Version	Date	Safety Concerns	Comment
1.1	19 March 2014	**Important identified risks** • Rhabdomyolysis • Neuroleptic malignant syndrome • Liver and biliary system disorders and liver laboratory abnormalities • Impulse control disorders (pathological gambling, increased libido, hypersexuality, compulsive buying and spending, compulsive and binge eating) • Mental changes (including depression with suicidal tendencies, and other serious antisocial behaviour) • Dyskinesia • Sudden onset of sleep • Severe skin and severe allergic reactions • Myocardial infarction and other ischaemic heart disease **Important potential risks** • Prostate cancer **Missing information** • Use in pregnant and lactating women • Use in patients with mild to moderate hepatic impairment • Use in patients with renal impairment	Safety concerns were updated according to the RMS Day 70 Preliminary Assessment Report (DE/H/4021/001-007/DC)