7.2 Part VI.2 Elements for a Public Summary

7.2.1 Part 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 may develop for example cognitive problems, excessive daytime sleepiness and hallucinations after many years into the disease. Also constipation, urinary incontinence, 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 of100,000 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.

7.2.2 Part VI.2.2 Summary of treatment benefits

All the currently used medicinal treatments are symptomatic in nature and there are no treatments that are known to slow down the progression of PD. The goal for the treatment of PD is to improve and maintain patients´ quality of life and functioning in everyday life. Medicinal treatment of PD is usually "taylor-made" case by case depending for example on patient's age and other diseases and treatments. According to widely accepted treatment guidelines and clinical practice, treatment of PD is often started with MAO-B inhibitors (selegiline or rasagiline) or dopamine agonists (e.g. ropinirole or pramipexole), except in the elderly (app. >70-75 years) when medicinal therapy is commonly started with levodopa preparations. Usually MAO-B inhibitors and/ or dopamine agonists are providing adequate symptom relief in early PD. When MAO-B inhibitors and/or dopamine agonists do not provide satisfactory response any longer, levodopa is usually started. Levodopa remains the most effective symptomatic treatment for PD and is therefore often regarded as "golden standard" in the treatment of PD. The long-term problems associated with levodopa are so called response fluctuations (also called as wearing-off) when the response to levodopa varies during the day between "ON" (time when there is a satisfactory response to levodopa with relatively minor parkinsonian symptoms) and "OFF" (time when the good response has disappeared and parkinsonian symptoms are negatively affecting normal daily activities). In addition, involuntary movements (dyskinesia) may occur during "ON"-periods in patients

with wearing-off symptoms and these purposeless movements are sometimes troublesome and compromising normal functioning. When wearing-off symptoms have developed, modifications to the treatment regimen are needed. At this stage, the number of daily doses of levodopa is 3-4 or higher. Changes in individual doses or dosing frequency of levodopa may be done and also COMT-inhibitors (entacapone or tolcapone) may be added to levodopa treatment in order to decrease treatment fluctuations. Also MAO-B inhibitors or dopamine agonists remain as treatment options in some patients at this stage of the disease, if these drugs have not been used before. Several well-controlled studies have demonstrated that entacapone or the combination tablet of levodopa/carbidopa/entacapone decrease response fluctuations improving patients' quality of life and ability to cope with normal daily activities.

7.2.3 Part VI.2.3 Unknowns relating to treatment benefits

Controlled clinical studies and clinical practice have shown that the efficacy of entacapone or levodopa/carbidopa/entacapone is similar in adults of different ages and between men and women and different races. There is limited experience with entacapone or levodopa/carbidopa/entacapone in patients with liver or kidney impairment. In addition, metabolism and elimination of levodopa, carbidopa or entacapone are either changed or unknown in these patients compared with normal liver and kidney function. Therefore, levodopa/carbidopa/entacapone should be used cautiously in patients with severe renal impairment or mild to moderate liver impairment. Levodopa/carbidopa/entacapone is contraindicated in severe liver impairment. There is no or very limited experience of levodopa/carbidopa/entacapone during pregnancy or in children.

7.2.4 Part VI.2.4 Summary of safety concerns

Table 7-5 Important identified risks

Risk	What is known	Preventability
Rhabdomyolysis A condition, which typically consists of muscular pain and may be associated with fever, confusion and decreased consciousness. This condition causes skeletal muscle tissue damage and break down, which is associated with release of muscular break down products (such as muscular protein called myoglobin) into the blood stream. These breakdown products may be especially harmful for kidneys and lead to impaired function of the kidneys.	Rhabdomyolysis is mainly associated with severe dyskinesias or neuroleptic malignant syndrome (see below) and it has been observed rarely in patients with Parkinson's disease.	If the dose of drugs used for Parkinson's disease is abruptly reduced or the treatment is withdrawn, the patient should be carefully observed. Special attention should be given to patients who are also receiving neuroleptics (drugs used for treatment of certain neurological and psychiatric conditions). The early diagnosis is important for the appropriate treatment of this condition. With appropriate treatment prognosis for recovery is good and kidney function can normally be restored.
Neuroleptic malignant syndrome (NMS) A rare severe reaction to medicines used to treat disorders of the central nervous system, which typically consists of high fever, muscle rigidity, tremor, agitation, confusion, rapid pulse and/or wide fluctuations in blood pressure as well as changes in specific muscular enzyme in the blood stream (creatine phosphokinase).	Neuroleptic malignant syndrome has not been reported in association with entacapone treatment in clinical trials in which entacapone was discontinued abruptly. However, after acceptance of marketing authorization, isolated cases of neuroleptic malignant syndrome have been reported, especially following abrupt reduction or discontinuation of drugs used for treatment of Parkinson's disease.	Any abrupt dose reduction or withdrawal of drugs used for treatment of Parkinson's disease should be carefully observed. Special attention should be given to patients who are also receiving neuroleptics (drugs used for treatment of certain neurologic and psychiatric conditions).The early diagnosis is important for the appropriate treatment of this syndrome. If the patient's muscles get very rigid or jerk violently, or if he/she get tremors, agitation, confusion, high fever, rapid pulse, or wide fluctuations in blood pressure, the patient should be admitted immediately to medical care.
Liver and biliary system disorders and liver laboratory abnormalities	Serious hepatitis with mainly cholestatic features may occur during treatment although no cases have been identified from the clinical trial data. Abnormalities in hepatic function tests and hepatitis with mainly cholestatic features are described adverse events in association with	Periodic evaluation of hepatic function is recommended during extended therapy. Levodopa-carbidopa-entacapone products should not be used in patients with severely impaired liver function and it is advised that they should be administered cautiously to patients with mild to

Risk	What is known	Preventability
	levodopa-carbidopa-entacapone treatment.	moderately impaired liver function. Reduction of dose may be needed in these patients.
Impulse control disorders (i.e. pathological gambling, increased libido, hypersexuality, compulsive buying and spending, compulsive and binge eating)	Impulse control disorders like 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.
Depression with suicidal tendencies	Depression has been observed commonly in patients with Parkinson's disease.	All 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 psychosis should be treated with caution.
Gastrointestinal haemorrhage	Serious events of gastrointestinal haemorrhage (uncommon) have been identified from the clinical trials.	In the event of gastrointestinal haemorrhage, the drug should be discontinued and appropriate medical therapy and investigations considered.
Colitis	Prolonged or persistent diarrhoea appearing during use of entacapone may be a sign of colitis.	In the event of prolonged or persistent diarrhoea, the drug should be discontinued and appropriate medical therapy and investigations considered.
Thrombocytopenia	Thrombocytopenia has been observed uncommonly.	In the event of thrombocytopenia, the drug should be discontinued and appropriate medical therapy and investigations considered.
Orthostatic hypotension	Levodopa/Carbidopa/Entacapone may induce orthostatic hypotension.	Levodopa/Carbidopa/Entacapone should be given cautiously to patients who are taking other medicinal products which may cause orthostatic hypotension.
Myocardial infarction and other ischaemic heart disease	Levodopa/Carbidopa/Entacapone may increase the risk of heart or artery disease events (e.g. chest pain), irregular heart rate or rhythm.	Therapy with Levodopa/Carbidopa/Entacapone should be administered cautiously to patients with ischemic heart disease. In patients with a history of myocardial infarction who have residual atrial nodal or ventricular arrhythmias, cardiac function should be monitored with particular care during the period of initial dose adjustments.

Table 7-6 Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Severe skin and severe allergic reactions	Serious events with angioedema have been identified from the clinical trials. In addition, isolated cases of severe skin reactions have been reported. However, the evidence of the role of levodopa-carbidopa-entacapone in these reactions is currently sparse.
Prostate cancer	In only one clinical trial it was reported more cases of prostate cancer in levodopa-carbidopa-entacapone treated patients. However, when the whole data from clinical trials and adverse reaction reports received were evaluated, no difference in this risk has been seen.
Medication error	Currently available data do not support the need for risk minimization.

Table 7-7 Missing information

Risk	What is known
Pregnancy and lactation	There are no data of the use of levodopa-carbidopa-entacapone products during pregnancy and lactation. Carbidopa and entacapone are excreted in milk in animals but is not known whether they are excreted in human breast milk.

7.2.5 Part VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a 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.

This medicine has no additional risk minimisation measures.

7.2.6 Part VI.2.6 Planned post authorisation development plan

None

7.2.7 Part VI.2.7 Summary of changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.1	17.03.2014	**The product brand names has been placed on the front page of the RMP.** **All relevant tables within the RMP have been revised in line with the comment on the table for the**	The RMP is updated to address the requests of the D70 Assessment report of procedure NL/H/3064-3065/001-007/DC (dated 10 Feb 2014)

Version	Date	Safety Concerns	Comment
		Summary of the safety concerns **The following risks have been added to the section " Important Identified risks":** *- "Impulse control disorders"* *- "Depression with suicidal tendencies"* *- "Gastrointestinal haemorrhage"* *- "Colitis"* *- "Thrombocytopenia"* *- "Orthostatic hypotension"* **This risk has been moved from Important Potential Risks to Important Identified Risks:** - "Myocardial infarction and other ischaemic heart disease" **These risks have been reworded:** **FROM;** **"Medication residue"** **TO:** **"Medication Error"** **FROM:** **"Pregnancy"** **TO:** **"Pregnancy and lactation"**	
1.2	05.08.2014	**The pack size and legal status of the product was included in Part V** **The version number was up-dated**	Changes have been made according to the RMS Day 120 Draft Assessment Report, dated 27.06.2014

Version	Date	Safety Concerns	Comment
1.3	28 May 2015	The risk Impulse control disorder has been amended with the different types of disorders: (i.e. pathological gambling, increased libido, hypersexuality, compulsive buying and spending, compulsive and binge eating) The risk "orthostatic hypotension and myocardial infarction and other ischemic disease has been split into two separate risks	Changes have been made according to RMS Day 70 Preliminary Assessment report, NL/H/3399-3401/001-007/DC, dated 30 Apr 2015
1.4	13 Oct 2015	Effect on fertility has been added to "missing information"	Changes have been made according to CMS Day 145 comment
1.5	20 Nov 2015	Missing Information: Pregnancy and lactation, effect on fertility	According to RMS NL AR in agreement with CMS FR, "effect on fertility" was deleted as missing information
		N/A	According to RMS NL AR, the brand names were added at the cover page and in 1.1 For each product.