VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Parkinson's disease (PD) is a degenerative disorder of the central nervous system. The motor symptoms of Parkinson's disease result from the death of dopamine-generating cells in the substantia nigra, a region of the midbrain; the cause of this cell death is unknown. Early in the course of the disease, the most obvious symptoms are movement-related; these include shaking, rigidity, slowness of movement and difficulty with walking and gait. Later, thinking and behavioral problems may arise, with dementia commonly occurring in the advanced stages of the disease, whereas depression is the most common psychiatric symptom. Other symptoms include sensory, sleep and emotional problems.

PD is the second most common neurodegenerative disorder after Alzheimer's disease and affects approximately seven million people globally and one million people in the United States. The prevalence (proportion in a population at a given time) of PD is about 0.3% of the whole population in industrialized countries. PD is more common in the elderly and prevalence rises from 1% in those over 60 years of age to 4% of the population over 80. The mean age of onset is around 60 years, although 5–10% of cases, classified as young onset, begin between the ages of 20 and 50. Some studies have proposed that it is more common in men than women, but others failed to detect any differences between the two sexes. The incidence of PD is between 8 and 18 per 100,000 person–years.

VI.2.2 Summary of treatment benefits

PD is slowly progressive. Severe disability or death may be expected in 25% of the patients within 5 years, in 65% of the patients within 10 years and in 80% of the patients within 15 years of onset.

Modern treatments are effective at managing the early motor symptoms of the disease, mainly through the use of levodopa and dopamine agonists. As the disease progresses and dopaminergic neurons continue to be lost, these drugs eventually become ineffective at treating the symptoms and at the same time produce a complication called dyskinesia, marked by involuntary writhing movements.

In general, a patient with early stages PD will start with dopamine-agonists, for example with ropinirole. If symptoms are insufficiently controlled levodopa is added during the course of the disease. In advanced PD most patients will receive both levodopa and a dopamine-agonist. When ropinirole is used as an adjunct to levodopa in advanced Parkinson's disease patients with motor fluctuations, it reduces off-time and allows a reduction in the levodopa dose.

Ropinirole is a well examined medicinal product. Efficacy was demonstrated in several studies, safety was monitored over many years and sufficient safety data were gathered in these studies. Ropinirole has been shown to be effective in controlling motor symptoms in patients with early PD and is generally well tolerated. Ropinirole has a broader therapeutic range than other dopamine agonist, so that an increase in dose is likely to lead to an increase in therapeutic response. Widespread information exists concerning the optimal dose range and dosage regimes of ropinirole, its efficacy and safety of subpopulations, interactions with other medicinal products and adverse events. Ropinirole is a medicinal product that meanwhile has been used in several European countries for more than ten years. The overall benefit/risk ratio can therefore be judged "positive".

VI.2.3 Unknowns relating to treatment benefits

There are insufficient data available on safety of use of the product when used over a long period of time.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Seeing things that are not really there (hallucinations)	The common factors associated with visual hallucinations in Parkinson's disease include greater age and duration of illness, cognitive impairment, and depression and sleep disturbances. Fortunately, many people with PD retain insight and quickly realize that the hallucination is not real and that their mind is "playing tricks" on them.	Yes, by monitoring for early symptoms.
Hypotension (postural/orthostatic)	Hypotension, especially orthostatic hypotension, occurs at a greater rate in patients treated with a dopamine agonist compared to similar patients not treated with a dopamine agonist.	Yes, by monitoring of the patient. Patients should be warned of this effect and advised of the symptoms such as light-headedness, dizziness, general malaise, and an increased risk of

Risk	What is known	Preventability
	The effect is known to occur with all of the dopamine agonist drugs and there is no suggestion that it is more or less prominent with any one of them. It is more common when treatment is initiated.	falls. Patients that are considered at risk of hypotension, for example due to other medication, should have their dopamine agonist therapy titrated more cautiously.
Fainting (syncope)	Very common adverse drug reaction concerning nervous system.	Yes, by monitoring for early symptoms.
Sleep attacks/sudden oneset of sleep	Sleepiness and excessive somnolence is a feature of Parkinson's disease and many of the drugs that are used to treat it. However, the sudden onset of sleep without any prior symptoms is a rare effect associated with all dopamine agonist drugs.	Yes, by monitoring for early symptoms of somnolence. Patients should be warned about the nature of excessive daytime sleepiness. They should be educated to recognize the warning symptoms and the associated risks of these episodes occurring while driving, and about the importance of never driving when sleepy. Finally, patients should be asked regularly during follow-up visits about symptoms that suggest daytime sleepiness or sudden onset of sleep.
Unusual urges and/or behaviours (such as excessive gambling or excessive sexual behaviour) /Impulse control and compulsive disorder	There is evidence to suggest that impulsive behaviour, often expressed as pathological gambling or increased libido including hypersexuality, may be a rare class effect of dopamine agonists. The effects may be dose related and are generally reversible upon reduction of the dose or treatment discontinuation. Patients should be warned about these possible side-effects and should be advised to seek help from their doctor if they, their family, or their carer(s), notice unusual behaviour.	Yes, by monitoring for early symptoms of unusual urges and/or behaviours.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Fibrotic organ-based changes (fibrotic complications)	Retroperitoneal and pleuropulmonary fibrosis are well known but rare complications of the treatment of Parkinson's disease with ergolinic dopamine agonists. Hovewer, ropinirole, a non-ergot derived dopamine agonist, is considered a safe substance in terms of fibrotic complications, including retroperitoneal fibrosis. World literature reports, a very few cases of fibrotic complications, mainly related to an overdose of ropinirole.
An abnormal variation from the normal heartbeat (cardiac rhythm disorders or effect of cardiac repolarisation)	In spite of the great number of patients treated with ropinirole, the number of reported cardiac side effects is really low. The available clinical data from a thorough QT study do not indicate a risk of QT prolongation at doses of ropinirole up to 4 mg/day. Unfortunately, there are no sufficient clinical data to support the appearance of cardiac side effects in higher doses of ropinirole.
Type of skin cancer, which form from melanocytes (melanoma)	Epidemiologic studies have shown that patients with Parkinson's disease have a higher risk of developing melanoma than the general population. The evaluation of this risk ended in a recommendation to perform periodic dermatological examinations in patients as follow-up measure of their treatment.
Medication errors relating to prescribing, dispensing and switching	In order to avoid medical errors associated with the administration of the correct dose of the drug to the patient, caution should be paid to the correct prescription of appropriate formulations of the medicine product to avoid confusion between immediate and prolonged-release formulations. There is a caveat toward the need to carefully titrate dopamine-agonists even in case of switching from immediate to prolonged-release formulation.
Other medication errors: tablet robustness, crushing, chewing or dividing of tablets	Mistakes can occur when people have trouble swallowing a tablet and they try to chew, crush, break or mix the tablet in food or drink. The reason is certain medications have a special release mechanism designed to slowly release a certain amount of medication over a given extended time. If the medication is altered or destroyed in any way, the medication can be released too fast and cause a bad effect. The prolonged release tablets should be administered in its entirety and should never be broken into halves.
Disorder of the process of blood cell production and homeostasis (haematopoiesis disorders)	Unknown frequency. Adverse drug reactions observed during the premarketing evaluation and all placebo-controlled adjunct therapy studies of Requip® (originator).

Missing information

Risk	What is known
Long-term safety data	There are no adequate data to show long-term safety data of ropinirole prolonged-release tablets usage.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPCs) 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.

VI.2.6 Planned post authorisation development plan

Not applicable.

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

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	06.11.2014		First approved version
2.0	28.07.2016		Updated in accordance with RMP tamplete for generic medicinal products. New medicinal products added: Aropilos 2, 3, 4, 6, 8 mg prolonged-release tablets in new countries: Slovakia and Czech Republic.