Risk Management Plan (RMP) Summary

for

Ongentys® (opicapone)

50 mg hard capsules

Final Version 2.0 (14 May 2020)

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Ongentys® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisation.

Please note that the reference document which is valid and relevant for the effective and safe use of Ongentys® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic.

Bial, S.A. is fully responsible for the accuracy and correctness of the content of the published summary RMP of Ongentys®.

This RMP summary is based on Part VI of the EU RMP for Ongentys® (opicapone) version 3.0, dated 15 October 2015

1 Elements for Summary Tables in the EPAR

1.1 Summary Table of Safety Concerns

Summary of safety concerns	
Important identified risks	
	Dyskinesia
	Hallucinations
Important potential risks	
	Ischaemic heart disease
	Neuroleptic malignant syndrome
	Impulse control disorders and other related behaviours
	Drug-related hepatic injury
	Interactions with drugs metabolised by CYP2C8 (e.g. hypoglycaemia risk with repaglinide)
Missing information	
	Use in patients with moderate/severe hepatic impairment
	Use in pregnancy and lactation
	Long-term safety
	Very elderly population

1.2 Table of On-Going and Planned Studies in the Post-Authorisation Pharmacovigilance Development Plan

No category 1-3 studies are planned.

1.3 Summary of Post Authorisation Efficacy Development Plan

No post-authorisation efficacy studies are planned in the target indication.

1.4 Summary Table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Dyskinesia	SmPC* section 4.2 provides instructions for reducing the levodopa dosage within the first days to first weeks after initiating Ongentys® treatment according to the clinical condition of the patient. SmPC* section 4.4 includes a warning about levodopa-related dopaminergic adverse reactions (e.g. dyskinesia, hallucinations, nausea, vomiting and orthostatic hypotension). SmPC* section 4.8 Undesirable effects Dyskinesia included as a very common (≥1/10) adverse reaction.	None proposed.
Hallucinations	SmPC* section 4.2 provides instructions for reducing the levodopa dosage within the first days to first weeks after initiating Ongentys® treatment according to the clinical condition of the patient. SmPC* section 4.4 includes a warning about levodopa-related dopaminergic adverse reactions (e.g. dyskinesia, hallucinations, nausea,	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	vomiting and orthostatic hypotension). SmPC* section 4.8 Undesirable effects Hallucination – common (≥1/100 to <1/10) Hallucination visual – common (≥1/100 to <1/10) Hallucination auditory – uncommon (≥ /1,000 to <1/100)	
Ischaemic Heart Disease	None proposed.	None proposed.
Neuroleptic malignant syndrome	SmPC* section 4.3 includes a contra-indication for patients with a history of neuroleptic malignant syndrome and/or non-traumatic rhabdomyolysis.	None proposed.
Impulse control disorders and other related behaviours	SmPC* section 4.4 contains a warning about impulse control disorders occurring in patients treated with dopamine agonists and/or other dopaminergic treatments. Advises that patients should be monitored regularly for the development of impulse control disorders and that treatment should be reviewed if symptoms develop.	None proposed.
Drug-related hepatic injury	SmPC* section 4.4 warns that increases in liver enzymes were reported in studies with nitrocatechol COMT inhibitors. Advises that an evaluation of liver function	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	should be considered.in patients who experience progressive anorexia, asthenia and weight decrease within a relatively short period of time.	
Interactions with drugs metabolised by CYP2C8 (e.g. hypoglycaemia risk with repaglinide)	SmPC* Section 4.4 warn that concomitant use of opicapone may increase the blood glucose-lowering effect of repaglinide and thus increase the risk of severe hypoglycaemia. SmPC section 4.5 of the SmPC advises that concomitant use of medicinal products specifically metabolised by CYP2C8 must be avoided.	None proposed.
Use in patients with moderate/severe hepatic impairment	SmPC* section 4.2 advises that no dose adjustment of Ongentys® is necessary in patients with mild hepatic impairment. Caution must be exercised in patients with moderate hepatic impairment and dose adjustment may be necessary. Ongentys® is not recommended in patients with severe hepatic impairment as there is no clinical experience.	None proposed.
Use in pregnancy and lactation	SmPC* section 4.6 advises that there is no data from the use of opicapone in pregnant women and it is not known whether opicapone or its metabolites are excreted in human milk. Therefore, it is preferable to avoid the use of Ongentys® during pregnancy.	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Breast-feeding should be discontinued during treatment with Ongentys®.	
Long-term safety	None proposed	None proposed
Very elderly population	SmPC* section 4.2 advises that caution must be exercised in patients ≥ 85 years of age as there is limited experience in this age group.	None proposed.

** SmPC: refers to the European Summary of Product Characteristics*

2 Elements for a Public Summary

2.1 Overview of Disease Epidemiology

Parkinson's disease is a progressive disorder in which the cells in the brain that produce a chemical messenger called dopamine begin to be lost and the amount of dopamine in the brain decreases. This causes patients to lose their ability to control movement reliably. The main symptoms of Parkinson's disease are shaking, slow movement and muscle rigidity. Medicines to treat Parkinson's disease (levodopa and benserazide or/ levodopa and carbidopa) restore the levels of dopamine in the brain. However, patients can experience fluctuations in the effectiveness of their medications towards the end of the period between doses due to a decrease in the amount of dopamine. These "motor fluctuations" mean that the patient may have sudden switches between being 'on' and able to move, and being 'off' and immobile. Approximately half of the patients, who have taken levodopa for five years or more, experience motor fluctuations.

2.2 Summary of Treatment Benefits

Ongentys® has been studied in a total of 1027 subjects with Parkinson's disease in two main clinical studies with an initial treatment duration of 14 to 15 weeks. The effects of adding Ongentys, entacapone (a marketed drug similar to Ongentys®) or placebo (an inactive medicine) to the patient's standard medications (levodopa and carbidopa or/ levodopa and benserazide) were measured. The main measure of effectiveness was the change in time spent in the "off" state (the time when levodopa is not controlling the symptoms of Parkinson's disease) from the baseline assessment to the end of the treatment period. The 50 mg dose of Ongentys was more effective than placebo in both studies with a reduction in the amount of "off" time in each study of 116.8 minutes and 118.8 minutes respectively. Placebo decreased the "off" time by 56.0 minutes and 64.5 minutes in these studies. Ongentys® 50 mg was as effective as entacapone in reducing "off" time with a reduction of 116.8 minutes compared with 96.3 minutes for entacapone.

2.3 Unknowns Relating to Treatment Benefits

In the main studies most of the patients were Caucasians and approximately 10% were Asian. There is no evidence to suggest that results would be any different in non-white patients.

2.4 Summary of Safety Concerns

Important identified risks

Risk	What is known	Preventability
Unintended, involuntary and uncontrollable movements e.g. twitches, jerking, twisting and restlessness (Dyskinesia)	Dyskinesia was reported in more than 10 % of patients receiving Ongentys® in the clinical studies. This can happen because Ongentys® increases the effects of levodopa.	It may be necessary to decrease the dosage of levodopa within the first days to first weeks after starting treatment with Ongentys® in order to prevent dyskinesia.
Hallucinations (visual image or sound with no cause)	Visual hallucinations occur in approximately one quarter to one third of the patients with Parkinson's disease. The reason that this happens is not clearly understood but it is thought to be caused by both the disease itself together with drugs used to treat the disease. However, it is thought that levodopa and drugs that work in the same way as Ongentys® are less likely to cause this to happen than some other drugs used to treat Parkinson's disease.	It may be necessary to decrease the dosage of levodopa within the first days to first weeks after starting treatment with Ongentys® in order to prevent hallucinations.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Blockage or interruption of the blood and oxygen supply to the heart caused by a build-up of fatty substances in the coronary arteries that can lead to angina (chest pain) and heart attacks (Ischaemic Heart Disease)	Side effects such as chest pain (angina) are common in patients taking a marketed drug that works in a similar way to Ongentys® but heart attacks are uncommon for that drug. At present there is no information to suggest that Ongentys® causes side effects like angina.
A potentially life threatening nervous condition that can occur when drugs used to treat Parkinson's disease are stopped abruptly. Symptoms include high fever, sweating, unstable blood pressure, muscular rigidity, and near unconsciousness (Neuroleptic Malignant Syndrome)	Neuroleptic malignant syndrome is a rare but life-threatening side effect which can occur when drugs used to treat Parkinson's disease such as levodopa are stopped too suddenly. Symptoms include high fever, sweating, unstable blood pressure, muscular rigidity, and near unconsciousness. There have been no cases confirmed as Neuroleptic malignant syndrome with Ongentys® in the clinical studies but the number of patients who have taken Ongentys® is limited. Patients must not use Ongentys® if they have had neuroleptic malignant syndrome or a muscle disorder known as rhabdomyolysis in the past.
Failure to resist an impulsive act or behaviour that may be harmful to self or others e.g. pathological gambling, increased sex drive, compulsive spending or compulsive eating. (Impulse control disorders)	Behavioural symptoms of impulse control disorders including pathological gambling, increased sex drive, hypersexuality, compulsive spending of buying, binge eating and compulsive eating can occur in patients treated with some drugs to treat Parkinson's disease. Reports of impulse control disorders were uncommon (0.4%) in the patients who took Ongentys® in the clinical studies but there were none reported in patients who took the inactive medication.
Drug-related liver injury	A drug that is similar to Ongentys® is known to cause serious and severe liver problems. In the Ongentys® clinical studies liver problems were reported more frequently in the patients receiving inactive medicine (placebo) than in patients taking Ongentys®. None of the liver problems reported in patients receiving Ongentys were like the ones reported for the drug that is known to cause severe problems.
Use of Ongentys® together with other drugs, such as repaglinide, that are broken	Ongentys® has been shown to increase the amount of another drug repaglinide in the blood. Repaglinide lowers the amount of glucose in the blood and patients taking these 2 drugs

Risk	What is known (Including reason why it is considered a potential risk)
down in the liver by an enzyme called CYP2C8	together need to make sure that they check blood glucose levels to avoid them becoming too low.

Missing information

Risk	What is known
Use in patients with moderate/severe liver impairment	No dose adjustment of Ongentys® is necessary in patients with mild liver impairment. Care must be taken in patients with moderate liver impairment and the dose may need to be adjusted. Patients with severe liver disease were not included in the clinical studies and so there is no experience in these patients. Ongentys® should not be used in patients with severe liver disease.
Use in pregnancy and whilst breast-feeding	There is limited data from the use of Ongentys® in pregnant women and it is preferable to avoid the use of Ongentys® during pregnancy. It is not known whether Ongentys® or its metabolites are excreted in human milk. Breast-feeding should be stopped during treatment with Ongentys®.
Long-term safety	There is limited clinical trial data in patients who have received Ongentys® for more than 15 months.
Very elderly patients	There is limited clinical trial data in very elderly patients (85 years and older).

2.5 Summary of Risk Minimisation Measures by Safety Concern

All medicines have an Information for Professionals (also known as 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 Information for Patients (also known as Package Leaflet - PL). The measures in these documents are known as routine risk minimisation measures.

The SmPC and the PL for Ongentys® can be found on www.swissmedicinfo.ch.

This medicine has no additional risk minimisation measures.

2.6 Planned Post Authorisation Development Plan

No post-authorisation studies are planned.

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	20/11/2014	**Identified Risks** Dyskinesia **Potential Risks** Psychotic and Psychotic disorders (e.g. hallucinations) Orthostatic hypotension Ischaemic heart disease Neuroleptic malignant syndrome Impulse control disorders and other related behaviours Hepatic disorders Interactions with drugs metabolised by CYP2C8 (e.g. hypoglycaemia risk with repaglinide) Interactions with other anti-Parkinson's disease drugs leading to enhanced dopaminergic undesirable effects	

Version	Date	Safety Concerns	Comment
		Missing Information Use in patients with severe hepatic impairment Use in pregnancy and lactation Concomitant use with Tricyclic antidepressants, MAO-A inhibitors or noradrenaline re-uptake Inhibitors Concomitant use with drugs metabolised by COMT	
2.0	17/7/2015	**Identified Risks** Dyskinesia Hallucinations **Potential Risks** Ischaemic heart disease Neuroleptic malignant syndrome Impulse control disorders and other related behaviours Drug-related hepatic injury Interactions with drugs metabolised by CYP2C8 (e.g.	The following changes were made in response to the Day 120 Questions. Psychotic and Psychotic disorders deleted as a potential risk and Hallucinations upgraded to an identified risk. The following potential risks was deleted: Orthostatic hypotension and Interactions with other anti-Parkinson's disease drugs leading to

Version	Date	Safety Concerns	Comment
		hypoglycaemia risk with repaglinide) **Missing information** Use in patients with severe hepatic impairment Use in pregnancy and lactation Long-term safety (> 15 months)	enhanced dopaminergic undesirable effects. Potential risk "Hepatic disorders" changed to "Drug-related hepatic injury". The following missing information was deleted: Concomitant use with Tricyclic antidepressants, MAO-A inhibitors or noradrenaline re-uptake Inhibitors and Concomitant use with drugs metabolised by COMT. Long-term safety was added as missing information.
3.0	15/10/2015	**Identified Risks** Dyskinesia Hallucinations **Potential Risks** Ischaemic heart disease Neuroleptic malignant syndrome Impulse control disorders and other related behaviours	The following changes were made in response to the Day 180 Questions. Patients with moderate hepatic impairment and the very elderly population were added as missing information.

Version	Date	Safety Concerns	Comment
		Drug-related hepatic injury Interactions with drugs metabolised by CYP2C8 (e.g. hypoglycaemia risk with repaglinide) **Missing information** Use in patients with moderate/severe hepatic impairment Use in pregnancy and lactation Long-term safety (> 15 months) Very elderly population	