Core/EU Risk Management Plan for Levodopa/Carbidopa Intestinal Gel (LCIG)

AbbVie Inc. (AbbVie)

Version 7.2

January 2017

Active substance(s) (INN or common name):	Levodopa/carbidopa
Pharmaco-therapeutic group (ATC Code):	Anti-Parkinson drugs, dopaminergic agents (N04BA02)
Name of Marketing Authorisation Holder or Applicant:	AbbVie Inc.
Number of medicinal product(s) to which this RMP refers:	1
Product(s) concerned (brand name(s)):	Duodopa®

Data lock point for this RMP:	26 May 2015
Version number:	7.2
Date of final sign off:	January 2017

VI.2 Elements for a Public Summary

Duodopa Intestinal Gel (levodopa/carbidopa)

All medicines have some risks – a risk is something unwanted that may happen when you take a medicine. A medicine is approved when there is enough evidence that, for the average patient, the benefits of taking the medicine should be greater than the risks. However, even though the benefits outweigh the risks, those possible risks remain.

- This public summary explains how those possible other risks will be managed for this medicine.
- The risks AbbVie knows about are in the patient leaflet that comes with the medicine. Read this leaflet if you are having Duodopa Intestinal Gel (or are caring for someone who does).

If you have any questions about the information in this summary, talk to your doctor or healthcare professional.

Duodopa Intestinal Gel is available in 1 concentration:

- 20 mg/mL levodopa + 5 mg/mL carbidopa

VI.2.1 Overview of Disease Epidemiology (About Parkinson's Disease)

Parkinson's disease (PD) is an illness of the nervous system which gradually gets worse over time. It affects how a person moves – it happens when nerve cells in the brain do not make enough of a messenger called 'dopamine.'

How many people are affected by Parkinson's disease?

Across the world in any 1 year, PD affects between about 10 and 14 out of every 100,000 people.

- PD may be partly inherited in some people. It may also be partly caused by things in the environment.
- The illness usually begins when people are in their early 60s. It is more likely to happen the older you get, but can also happen as early as in the 20s.

- The World Health Organization (WHO) estimates that in 2015 there are 6 million people worldwide living with PD, 2.1 million of those live in Europe.
- If not treated, the illness will get worse. Over time there is an increasing effect on a person being able to move, which affects daily living activities. Ten percent of PD patients without treatment are living with advanced disease and are unable to walk without assistance, have to use a wheelchair or are forced to stay in bed.
- People with PD are more likely to die compared to people of a similar age. This is mainly due to complications of the illness.

VI.2.2 Summary of Treatment Benefits

About Duodopa Intestinal Gel

This document is about a medicine called Duodopa Intestinal Gel. It contains 2 active substances:

- levodopa
- carbidopa

It is used in advanced Parkinson's disease.

How does Duodopa work?

- Levodopa is turned into dopamine in the brain. This replaces the lack of dopamine which causes PD. This treats the symptoms of Parkinson's disease.
- However, when levodopa gets into the body, it is quickly turned into dopamine before it gets to the brain. Carbidopa works by stopping this change, making more levodopa available to the brain.

How does Duodopa Intestinal Gel work?

In this medicine, levodopa and carbidopa are put into something called an 'intestinal gel.' This is a gel which goes through a tube into the gut (the 'small intestine'). The gel is pumped into the gut continuously. This helps to improve the 'on' time (the time when movement is improved) and reduce the 'off' time (the time when movement is not helped), for people with advanced Parkinson's disease.

What have studies shown about the benefits of Duodopa Intestinal Gel?

There have been 4 main studies using the Duodopa Intestinal Gel 20 mg/mL levodopa + 5 mg/mL carbidopa concentration. They have been used to look at the benefit of the gel. They have also been used to look at how effective and safe it is in the long term. Results from the main study are shown below.

Study 1

This was a study of 71 patients who had advanced Parkinson's disease. It compared 2 treatments:

- Duodopa Intestinal Gel.
- Levodopa/carbidopa tablets taken by mouth ('immediate release' tablets).

After 12 weeks the results showed the gel:

- decreased the 'off' time (when patients could not function because of their Parkinson's disease associated with poor mobility, slowness, and stiffness) significantly more than the tablets. The difference was nearly 2 hours (1.9 hours) each day – this means with the gel there were 2 hours less 'off' time than with tablets.
- increased the 'on' time (when patients could function well) significantly more than the tablets. The difference was nearly 2 hours (1.9 hours) each day – this means that with the gel there were 2 hours more 'on' time than with tablets.

VI.2.3 Unknowns Relating to Treatment Benefits (Groups of People Where AbbVie Has Less Information)

The treatment benefit for patients with earlier Parkinson's disease was not investigated in the studies above. These studies only looked at people with advanced Parkinson's disease.

VI.2.4 Summary of Safety Concerns

Important Identified Risks (Important Risks that Are Known)

Risk	What Is Known	Preventability (How it Can Be Stopped)
Risks of gastrointestinal, gastrointestinal device, and gastrointestinal procedure related events • Problems putting in the stomach tube and intestinal tube • Long term problems with the intestinal tube	Putting in the tubes involves surgery and this may lead to problems Common problems include: • pain or redness • drainage from the hole into the stomach • movement of the tube inside the gut Less common or rare complications include: • infections in the stomach area (abdomen), ulcers or holes in the stomach or gut • collections of food that attach to the inside of the gut Rarely these may become life threatening and require surgery	Tube and procedure related events can be reduced by set procedures by the healthcare professionals: • before inserting the tubes • while inserting the tubes • after inserting the tubes
Risks of dyskinesia Dyskinesia is uncontrollable muscle spasms or involuntary movements affecting your eyes, head, neck and/or body.	Dyskinesia is common in Parkinson's disease and in Parkinson's disease patients treated with a medicine like Duodopa that contains levodopa/carbidopa.	Do not take more Duodopa than is needed to manage symptoms of Parkinson's disease. Ask your healthcare professional before taking other medicines with your Duodopa.
Risks of psychosis associated events Psychosis associated events include seeing, hearing or feeling things that are not there (hallucinations), confusion, nightmares, feeling sleepy, fatigue, sleeplessness, euphoria (abnormal elation), loss of memory, and other mental problems.	Psychosis associated events are commonly observed in Parkinson's disease patients treated with levodopa/carbidopa.	Do not take more Duodopa than is needed to manage symptoms of Parkinson's disease. Ask your healthcare professional before taking other medicines with your Duodopa. Notify your healthcare professional if you or your family thinks that you have any psychosis related events.
Risks of impulse control disorders (ICDs) Impulse control disorders include pathological gambling (failure to resist gambling impulses despite serious personal or family consequences), increased sex	Impulse control disorders are commonly observed in Parkinson's disease patients treated with levodopa/carbidopa.	Do not take more Duodopa than is needed to manage symptoms of Parkinson's disease. Notify your healthcare professional if you or your family thinks that you have any impulse control disorders.

Risk	What Is Known	Preventability (How it Can Be Stopped)
drive, binge eating, and hypersexuality (altered sexual interest and behavior of significant concern to the patient or to others).		
Risks of orthostatic hypotension Orthostatic hypotension includes feeling dizzy, especially when you stand up. This may lead to falls.	Orthostatic hypotension is commonly observed in Parkinson's disease patients treated with levodopa/carbidopa.	Be careful when you stand up while taking Duodopa.
Risks of sudden onset of sleep/somnolence Feeling very sleepy, falling asleep suddenly. If this happens, you should not drive or operate machinery.	Sudden onset of sleep/somnolence is commonly observed in Parkinson's disease patients treated with levodopa/carbidopa.	Duodopa may cause you to feel dizzy, sleepy, or to fall asleep suddenly. Do not drive or use any tools or machines until you are sure how the medicine affects you.
Risks of neuroleptic malignant syndrome (NMS) Suddenly stopping or lowering your Duodopa dose may result in a serious problem called 'Neuroleptic Malignant Syndrome.' The signs may include: • Fast heartbeat, changing blood pressure and sweating followed by fever • Faster breathing, muscle stiffness, lower consciousness and coma • Higher levels of a protein in your blood (an enzyme called creatine phosphokinase).	A sudden stop or lowering the dose of levodopa/carbidopa can cause Neuroleptic malignant syndrome. This problem is more likely to happen if you are also taking a medicine called an 'antipsychotic.'	It is important that you do not stop having Duodopa or lower your dose until told to do so by your doctor. If you have signs of Neuroleptic malignant syndrome seek medical attention immediately. If you have any further questions on the use of this product, ask your doctor or pharmacist.

Important Potential Risks (Possible Other Risks Which Are Important)

Risk	What Is Known (Including Reason Why It Is Considered a Potential Risk)
Weight loss	Many patients with Parkinson's disease lose weight. • It is possible that some of this weight loss may be related to levodopa/carbidopa.
Polyneuropathy Where nerves do not work properly – which affects how you feel things or how you control your muscles.	Many patients with Parkinson's disease get 'polyneuropathy.' • It is possible that some of this is caused by a lack of vitamins seen in some people with Parkinson's disease – before starting the gel. • The lack of vitamins could be from poor diet or difficulty swallowing. It might also be due to taking levodopa/carbidopa pills. However, it is also possible that these nerve problems may be related to the Duodopa medicine.

Missing Information (Areas Where Little Information Is Available)

Risk	What Is Known
Hydrazine Effect of hydrazine from the breakdown of carbidopa	Hydrazine is formed from carbidopa in the body. Hydrazine has been shown to cause some harm in animals if given in high doses. • At this time it is unknown if the hydrazine in the gel could cause problems in humans. • Hydrazine at high doses can cause cancer and liver or kidney problems in animals. However, after 10 years of treating humans with the gel, AbbVie has not seen any increase in these problems in patients. This is compared to people of the same age who are not using the gel.
Cardiovascular deaths Deaths from heart disease	Deaths from heart disease are very common in the elderly. They are also very common in patients with Parkinson's disease. • It is not known if levodopa/carbidopa or the gel could increase the number of patients who die from heart disease. However, after 10 years of treating humans with the gel, AbbVie has not seen any increase in these heart-related deaths. This is compared to people of the same age who are not using the gel.

VI.2.5 Summary of Risk Minimisation Measures by Safety Concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists, and other health care professionals with details on how to use the medicine. It also lists the risks and recommendations for minimising them. A shorter version of this in everyday language is provided in the form of the package leaflet. The measures in these documents are called 'routine risk minimisation measures.'

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). These additional risk minimisation measures are for problems putting in the stomach tube and intestinal tube.

Safety Concern in Lay Terms (Medical Term):

Side effects and complications from the use of stomach tubes for a long time to deliver the medication to the gut ('small intestine') (gastrointestinal, gastrointestinal device, and gastrointestinal procedure related events):

Risk Minimisation Measure(s):

- Slides and video on critical aspects of preparing stomach and gut tubes and how they are placed – to make sure healthcare professionals know the best way to prevent the risks when putting in the tubes
- Aftercare Guideline for the tubes
- Best Practice Patient Aftercare Guidance
- Slide presentation on Duodopa safety, placing the gut tubes, aftercare, and Duodopa system use and pump operations
- Patient Pump Pocket Guide

Reasons: To inform and educate healthcare professionals and patients. This relates to better understanding of the risks of long-term use of tubes that deliver the gel to the gut, how these tubes are put into the body, and aftercare procedures.

Proposed actions: The educational materials will be provided directly or through AbbVie Duodopa Specialists to dedicated centers for healthcare professionals (i.e., Gastroenterologists, Neurologists and Nurses) in direct patient care. Patients and their caregivers will receive a Pump Pocket Guide from their centers through their healthcare professionals or AbbVie Duodopa Specialists.

VI.2.6 Planned Post-Authorisation Development Plan

List of Studies in Post-Authorisation Development Plan

The following studies are happening now.

Name of the study	What the study is looking at
Study M12-920 • Study happening now • Advanced Parkinson's disease patients • Lasts for 12 weeks • In the United States	This study is looking at the effect of the gel on Parkinson's disease symptoms which are not related to movement (such as feeling dizzy, sleeping problems, or mood). • This is measured by a special scale called 'the Non-Motor Symptom Scale.'
Study M12-927 • Study happening now • Advanced Parkinson's disease patients • Lasts for 26 weeks • Worldwide	This study is looking at the effect of the gel compared to something called 'optimized medical therapy' (OMT) on symptoms not related to movement. • This is measured by a special scale called 'the Non-Motor Symptom Scale.' • It is also measured by a sleep scale called 'the Modified Parkinson's disease sleep scale.'

Studies Which Are a Condition of the Marketing Authorisation

None of the above studies are conditions of the marketing authorisation.

VI.2.7 Summary of Changes to the Risk Management Plan Over Time

Major Changes to the Risk Management Plan Over Time

Version	Date[a]	Safety Concerns	Comments
1	27 February 2008	<u>Important identified risks</u> • PEG insertion – Perforation and injury of internal organs incl. bleedings • PEG insertion – infection including peritonitis • Long-term therapy – Stoma complications • Long-term therapy – PEG tube complications <u>Important potential risks</u> • Cardiovascular fatalities • Respiratory problems – Aspiration (pneumonia) • Long-term therapy – Gastrointestinal emergencies <u>Missing information</u> • None identified	

2	16 March 2009	<u>Important identified risks</u>
		• Risks of PEG insertion:
		  ○ Perforation and injury of internal organs incl. bleeding
		  ○ Infection including peritonitis
		• Long-term complications of PEG:
		  ○ Stoma complications during long-term therapy
		  ○ PEG tube complications during long-term therapy
		<u>Important potential risks</u>
		• Device-associated gastrointestinal disorders
		• Cardiovascular fatalities
		<u>Missing information</u>
		• None identified
			• "Perforation and injury of internal organs incl. bleedings" and "PEG insertion – infection including peritonitis" were merged and renamed as "Risks of PEG insertion."
			• "Stoma complications during long-term therapy" and "PEG tube complications during long-term therapy" were merged and renamed as "Long-term complications of PEG."

Version	Date[a]	Safety Concerns	Comments
2 (cont.)			• "GI emergencies" was reworded to "Device-associated gastrointestinal disorders." • The important potential risk, "Respiratory problems – Aspiration (pneumonia)" was removed from the RMP.

3	21 December 2009	<u>Important identified risks</u>
		• Risks of PEG insertion:
		  ○ Perforation and injury of internal organs incl. bleeding
		  ○ Infection including peritonitis
		• Long-term complications of PEG:
		  ○ Stoma complications during long-term therapy
		  ○ PEG tube complications during long-term therapy
		<u>Important potential risks</u>
		• Device-associated gastrointestinal disorders
		• Cardiovascular fatalities
		<u>Missing information</u>
		• Polyneuropathy/Guillain-Barré syndrome
			• Polyneuropathy/ Guillain-Barré syndrome was added to missing information.

4	20 December 2010	<u>Important identified risks</u>
		• Risks of PEG insertion:
		  ○ Perforation and injury of internal organs incl. bleeding
		  ○ Infection including peritonitis
		• Long-term complications of PEG:
		  ○ Stoma complications during long-term therapy
		  ○ PEG tube complications during long-term therapy
		<u>Important potential risks</u>
		• Device-associated gastrointestinal disorders
		• Cardiovascular fatalities
		• Polyneuropathy
		<u>Missing information</u>
		• Clinical relevance of hydrazine content
			• Polyneuropathy was reclassified as an important potential risk.
			• Clinical relevance of hydrazine content was added to missing information.

5	December 2011	<u>Important identified risks</u> • Risks of PEG insertion:	• Weight loss was added as an important

Version	Date[a]	Safety Concerns	Comments
		○ Perforation and injury of internal organs incl. bleeding ○ Infection including peritonitis • Long-term complications of PEG: ○ Stoma complications during long-term therapy ○ PEG tube complications during long-term therapy • Weight loss <u>Important potential risks</u> • Device-associated gastrointestinal disorders • Cardiovascular fatalities • Polyneuropathy <u>Missing information</u> • Clinical relevance of hydrazine content	identified risk.
6	December 2012	<u>Important identified risks</u> • Gastrointestinal and gastrointestinal procedure related events <u>Important potential risks</u> • Weight loss • Polyneuropathy <u>Missing information</u> • Clinical relevance of hydrazine content • Cardiovascular fatalities	• Because of the extensive overlap of the PTs in the risks of PEG insertion, long-term complications of PEG, and device-associated gastrointestinal disorders, it was decided to elevate device-associated gastrointestinal disorders to the Important Identified Risk category and then to combine these 3 groups into a new risk group entitled "Gastrointestinal and Gastrointestinal Procedure Related Events." • With the addition of the new clinical trial data (Studies S187.3.003, S187.3.004, and S187.3.005), weight loss could not be supported as an Important Identified Risk and was moved into the Important Potential Risk category.

Version	Date[a]	Safety Concerns	Comments
6 (cont.)			• With the addition of the pivotal trial data and additional postmarketing experience, it was determined that there is no clear evidence of a causal relationship between LCIG and cardiovascular fatality. This potential signal has been followed for 5 years. It is the sponsor's opinion that this potential signal has not been validated, therefore, this risk was moved to the Missing Information category and the sponsor will continue to monitor cardiovascular fatalities through routine pharmacovigilance.
7	October 2015	<u>Important identified risks</u> • Gastrointestinal and gastrointestinal procedure related events <u>Important potential risks</u> • Weight loss • Polyneuropathy <u>Missing information</u> • Clinical relevance of hydrazine content • Cardiovascular fatalities	• No change in safety concerns from Edition 6. • The RMP was revised to conform to the current template. As a consequence, there were organizational changes throughout and content was updated accordingly.

Version	Date[a]	Safety Concerns	Comments
7.1	June 2016	Important identified risks • Gastrointestinal, gastrointestinal device, and gastrointestinal procedure related events • Dyskinesia • Psychosis associated events • Impulse control disorders (ICDs) • Orthostatic hypotension • Sudden onset of sleep/somnolence • Neuroleptic malignant syndrome (NMS) Important potential risks • Weight loss • Polyneuropathy Missing information • Clinical relevance of hydrazine content • Cardiovascular fatalities	• Request from Reference Member State to add gastrointestinal devices to gastrointestinal and gastrointestinal procedures related risks and to add dyskinesia, psychosis associated events, impulse control disorders (ICDs), orthostatic hypotension, sudden onset of sleep/somnolence, and neuroleptic malignant syndrome (NMS) to the Important Identified Risks.
7.2	January 2017	Important identified risks • Gastrointestinal, gastrointestinal device, and gastrointestinal procedure related events • Dyskinesia • Psychosis associated events • Impulse control disorders (ICDs) • Orthostatic hypotension • Sudden onset of sleep/somnolence • Neuroleptic malignant syndrome (NMS) Important potential risks • Weight loss • Polyneuropathy Missing information • Clinical relevance of hydrazine content • Cardiovascular fatalities	• Removed references to the 40 mg/mL levodopa + 10 mg/mL carbidopa formulation except for the Study M14-595 summary and subject exposure numbers.

a. Issue date.