VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Parkinson's disease is the second most common neurodegenerative disorder and the most common movement disorder. It is characterized by progressive loss of muscle control, which leads to trembling of the limbs and head while at rest, stiffness, slowness, and impaired balance. As symptoms worsen, it may become difficult to walk, talk, and complete simple tasks.

The progression of Parkinson's disease and the degree of impairment vary from individual to individual. Many people with Parkinson's disease live long productive lives, whereas others become disabled much more quickly. Premature death is usually due to complications such as falling-related injuries or pneumonia.

Worldwide about 5 million people are affected by Parkinson's disease. Most individuals who develop Parkinson's disease are 60 years of age or older. Parkinson's disease occurs in approximately 1% of individuals aged 60 years and in about 4% of those aged 80 years. Since overall life expectancy is rising, the number of individuals with Parkinson's disease will increase in the future. Adult-onset Parkinson's disease is most common, but early-onset Parkinson's disease (onset between 21-40 years), and juvenile-onset Parkinson's disease (onset before age 21) also exist.

VI.2.2 Summary of treatment benefits

Apomorphine is a medication made for "off" seasons in Parkinson's disease.

The "On-off" phenomenon occurs during treatment of Parkinson's disease. It describes the fluctuation in benefit of the medications used to treat Parkinson's disease.

To be "on" describes the time when the patients feel that their medications work and the symptoms are well controlled. To be "off" describes the time when the patients feel that their medications are not working well and the symptoms return. The "on/off" phenomenon can occur very fast. The switch from "on" to "off" or "off" to "on" can occur just as suddenly. The speed of this shift can be so dramatic that patients have likened this effect to a light switch being turned on and off.

Apomorphine is a medicinal product to treat an "off" episode, which can occur despite optimal therapy. This helps the patients in "off" episodes to control movements and so help them to walk, talk and move easier.

VI.2.3 Unknowns relating to treatment benefits

Experiences are limited concerning the effect on plasma range of other medicinal products (especially those with a narrow therapeutic range). Therefore all medications taken by the patient should be known by the physician.

As the experiences concerning children and adolescents is limited, apomorphine is contraindicated in these patient groups.

There is no experience of apomorphine usage in pregnant woman. Therefore apomorphine should not be used during pregnancy unless clearly necessary.

It is not known whether apomorphine is excreted in breast milk. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with apomorphine should be made taking into account the benefit of breast-feeding to the child and the benefit of apomorphine to the woman.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Prolongation of the QT interval with combined use of domperidone and apomorphine	QT prolongation is a known and serious event that can occur during apomorphine therapy. The QT interval, which is the traditional measurement for assessing the duration of ventricular de- and repolarization, is measured in milliseconds (ms) on the body surface electrocardiogram (ECG) from the Q-top, the beginning of the QRS complex, until the end of the T wave. Both pharmacodynamic and pharmacokinetic drug effects may lead to QT prolongation. A pharmacodynamic interaction of concomitantly used drugs can lead to a prolonged QT interval if the individual QT prolonging drugs have an additive or potentiating effect. A pharmacokinetic effect may occur if a drug reduces the clearance of a concomitantly used QTc prolonging drug, leading to increased plasma and tissue concentrations. Pharmacokinetic interactions often involve drugs which are both metabolized by specific CYP iso-enzymes. Patients using two or more drugs concomitantly metabolized by CYP3A4 or CYP2D6, can develop QTc prolongation due to increased plasma concentrations [28].	It is recommended to avoid the administration of apomorphine with other drugs known to prolong the QT interval [a]. Caution should be exercised when treating patients at risk for torsades de pointes arrhythmia [a]. An ECG (electrocardiogram) should be performed: - prior to treatment with domperidone - during the treatment initiation phase - as clinically indicated thereafter The patient should be instructed to report possible symptoms which may come from the heart, e.g. palpitations, fainting, or near-fainting.

Risk	What is known	Preventability
Blood disorder that occurs when red blood cells are destroyed faster than the bone marrow can make them (Haemolytic anaemia)	Haemolytic anaemia is a known and uncommon event that can occur during apomorphine therapy. Haemolytic anaemia is a condition in which red blood cells are destroyed and removed from the bloodstream before their normal lifespan is over. Red blood cells carry oxygen to your body. They also remove carbon dioxide (a waste product) from your body. Red blood cells are made in the bone marrow—a sponge-like tissue inside the bones. They live for about 120 days in the bloodstream and then die [3]. Haemolytic anaemia and thrombocytopenia have been reported in patients treated with apomorphine.	Haematology tests should be undertaken at regular intervals as with levodopa, when given concomitantly with apomorphine [a].
Decrease in platelet count (Thrombocytopenia)	Thrombocytopenia is a known and uncommon event that can occur during apomorphine therapy. Thrombocytopenia is a condition in which the blood has a lower than normal number of blood cell fragments called platelets. Platelets are made in the bone marrow along with other kinds of blood cells. They travel through the blood vessels and stick together (clot) to stop any bleeding that may happen if a blood vessel is damaged. Platelets also are called thrombocytes because a clot also is called a thrombus [4].	Yes, haematology tests should be undertaken at regular intervals as with levodopa, when given concomitantly with apomorphine [a].
Inability to resist impulses to perform actions that are harmful to oneself or others (Impulse control disorders, incl. pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive	Impulsive control disorders (incl. pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating) are known events that can occur during apomorphine therapy. The frequency of	Yes, patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido,

Risk	What is known	Preventability
eating)	occurrence is not known. Impulse control disorders are common psychiatric conditions in which affected individuals typically report significant impairment in social and occupational functioning, and may incur legal and financial difficulties as well [6]	hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including apomorphine. Dose reduction/tapered discontinuation should be considered if such symptoms develop [a].
Local subcutaneous effects	Local subcutaneous effects, injection site necrosis and ulceration are known and uncommon events that can occur during apomorphine therapy. Necrosis is a kind of cell injury that results in the premature death of cells in living tissue. It can be caused by infection, toxins or traumata that result in the unregulated digestion of cell components. A skin ulcer is a crater-like formation on the skin that is caused by any number of reasons, from an infection to cancer or inflammation. Ulcers are sores that typically do not heal properly or keep returning. Ulcers may or may not cause pain. Many people with skin ulcers experience a burning or itching around the area of the wound as well as discomfort from the swelling that usually accompanies an ulcer. Ulcers also may be accompanied by a red rash, a brown discoloration around the sore and dry, flaky skin [7].	Yes, subcutaneous access and administration of apomorphine should only be made by professionals with relevant experience.
Drop of blood pressure (Postural hypotension)	Postural hypertension is a known and uncommon event that can occur during apomorphine therapy. Orthostatic hypotension — also called postural hypotension — is a form of low blood pressure	Yes, by giving extra caution during initiation of therapy in elderly patients and patients with pre-existing postural hypotension [a].

Risk	What is known	Preventability
	that happens when the patient stands up from sitting or lying down. Orthostatic hypotension can make the patient feel dizzy or lightheaded, and maybe even faint. Orthostatic hypotension is often mild, lasting a few seconds to a few minutes after standing [8]	
Near-sleep condition (Somnolence)	Somnolence is a known and common event that can occur during apomorphine therapy. Somnolence is a near-sleep condition with a strong desire for sleep or sleeping for an unusual period of time.	Patients must be informed of this risk and advised to exercise caution while driving or operating machines during treatment with apomorphine. Patients who have experienced somnolence must refrain from driving or operating machines. Furthermore, a reduction of dosage or termination of therapy may be considered.
Neuropsychiatric disturbances	Neuropsychiatric disturbances are known and common events that can occur during apomorphine therapy. Neuropsychiatric disorders are any illness with a psychological origin manifested either in symptoms of emotional distress or in abnormal behaviour [9].	There is evidence that for some patients neuropsychiatric disturbances may be exacerbated by apomorphine. Special care should be exercised when apomorphine is used in these patients [a].
Abnormal involuntary movements (Dyskinesia)	Dyskinesia is a known and uncommon event that can occur during apomorphine therapy. Dyskinesias are abnormal, involuntary movements that occur in response to repeated dopamine-replacement therapy. Sometimes, they can be debilitating. These motor complications are typically "choreiform". Chorea comes from the Greek word meaning "to dance", so the dyskinesias looks similar to dance-like, constant writhing or wriggling movements of the arms, legs, trunk, and sometimes even facial muscles. However, dyskinesias can also be dystonic	Apomorphine hydrochloride must not be administered to patients who have an "on" response to levodopa which is marred by severe dyskinesia or dystonia.

Risk	What is known	Preventability
	(prolonged twisting of body parts), or myoclonic (rapid and random twitching of isolated muscle groups) or other movement disorders, and can become progressively more severe with increasing duration of treatment [10].	
Wrong dose due to technical malfunction of mini-pump or syringe-driver	Errors include the wrong rate of infusion caused by inaccurate measurement of fluid length or miscalculation or incorrect rate setting of the device. Dose errors also occur because of different models using mm per hour or mm per 24 hours. Other issues include syringes becoming dislodged, inadequate device alarms and lack of internal memory (a technical issue which makes establishing the reason for any over or under-infusion difficult) [11].	EVER Neuro Pharma is aware of this possible technical defect and therefore provides a continuous communication between Pharmacovigilance and quality assurance. A harmonised European Standard, BS EN 60601-2-24 19981 identifies technical features for ambulatory syringe drivers that aim to reduce the risk of serious incidents in practice. It stipulates mechanisms that only allow the infusion to begin if the syringe is properly fitted and alarms that activate if the syringe is removed before the infusion is stopped. Many older ambulatory syringe drivers do not provide these features. More modern ambulatory syringe drivers with these safer design features and with rate settings in millilitres (ml) per hour are now available.
Off-label use in restless legs syndrome	Restless legs syndrome (RLS) is a disorder that causes a strong urge to move your legs. This urge to move often occurs with strange and unpleasant feelings in your legs. Moving your legs relieves the urge and the unpleasant feelings. People who have RLS describe the unpleasant feelings as creeping, crawling, pulling, itching, tingling, burning, aching, or electric shocks. Sometimes, these feelings also	Off-label use in restless legs syndrome cannot be avoided by EVER Neuro Pharma. SmPC and PIL do clearly not mention restless legs syndrome as an indication for apomorphine.

Risk	What is known	Preventability
	occur in the arms. The urge to move and unpleasant feelings happen when you're resting and inactive. Thus, they tend to be worse in the evening and at night [12].	
Medication error (e.g. use of morphine instead of apomorphine)	Both apomorphine and morphine are administered as continuous subcutaneous infusion and may therefore be mixed up. As morphine is chemically similar to apomorpine the same adverse reactions can occur when treated with these substances.	Use of morphine instead of apomorphine can be avoided by verification of the correct treatment prescription. Treatment should not be discontinued abruptly and signs of intoxication should be treated accordingly.
Hypersensitivity to substance or excipients (sodium metabisulphite)	Hypersensitivity reactions are known but rare events that can occur during apomorphine therapy. They can either be caused by the active substance apomorphine [14] or by an excipient such as sodium metabisulphite. Sodium metabisulphite is used as a preservative in some drinks, foods and medicinal products and is known to cause allergic reactions, most commonly asthma symptoms in those with underlying asthma, sometimes allergic rhinitis like reactions, occasionally urticaria and very rarely, anaphylaxis (severe allergic reaction) [15].	Yes, by initiating apomorphine treatment in the controlled environment of a specialist clinic and by being supervised by a physician experienced in the treatment of Parkinson`s disease.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Off-label use in erectile dysfunction	Erectile dysfunction is also known as impotence and describes the inability to achieve or sustain an erection for satisfactory sexual activity.
Wrong dose due to technical malfunction of the pen	The possibility exists that the apomorphine-cartridge is used in combination with a mechanically compatible pen that is specified for the use with other substances, e.g. insulin, thus having a different dosing scale as required for apomorphine. However, in order to avoid incorrect dosing the product information

Risk	What is known (Including reason why it is considered a potential risk)
	clearly states that the product should only be administered using the dedicated D-mine-Pen which is clearly labelled with the corresponding product name. Additionally, the product information clearly describes that the appropriate dose for each patient is to be established by incremental dosing schedules taking the clinical response of the patient into account and putting appropriate time intervals between succeeding injections until a satisfactory motor response is obtained. Taking the incremental dosing schedule and a maximum of 0,6mg apomorphine per single dose step into account the administered dosage does not reach a dosage range with a risk for overdose even if another dosage scale is used by mistake. Therefore routine risk minimisation measures are considered sufficient and no additional risk minimisation measures are proposed.
Wrong dose due to a handling error of the pen	The possibility exists that a wrong dose is administered because of a handling error (e.g. the remaining air in the catridge is not removed before injection, the incorrect dosage is set, error due to a switch from a pen of another brand). However, each patient/user receives clear instructions and appropriate training before using the pen. Besides, as the technically possible maximum single dose of the pen is 6 mg, there is no risk for overdose and no hazardousness is given as the allowed maximum single dose of 10 mg is not exceeded. The risk of under-dosing is only theoretical, because the effect of apomorphine is variable among patients. Any potential loss of effect caused by underdosing certainly leads to immediate correction in the next bolus dosage (by increasing the dose).
QT prolongation	QT prolongation is a known and serious event that can occur during apomorphine therapy. The QT interval, which is the traditional measurement for assessing the duration of ventricular de- and repolarization, is measured in milliseconds (ms) on the body surface electrocardiogram (ECG) from the Q-top, the beginning of the QRS complex, until the end of the T wave. Both pharmacodynamic and pharmacokinetic drug effects may lead to QT prolongation. A pharmacodynamic interaction of concomitantly used drugs can lead to a prolonged QT interval if the individual QT prolonging drugs have an additive or potentiating effect. A pharmacokinetic effect may occur if a drug reduces the clearance of a concomitantly used QTc prolonging drug, leading to increased plasma and tissue concentrations. Pharmacokinetic interactions often involve drugs which are both metabolized by specific CYP iso-enzymes. Patients using two or more drugs concomitantly metabolized by CYP3A4 or CYP2D6, can develop QTc prolongation due to increased plasma concentrations [28].

Risk	What is known (Including reason why it is considered a potential risk)
Dopamine dysregulation syndrome including punding and dopamine withdrawal syndrome	Dopamine dysregulation syndrome may be caused by long-term dopaminergic replacement therapy. Even if levodopa is considered the most potent trigger for dopamine dysregulation syndrome, subcutaneous apomorphine and oral dopamine agonists may also be responsible. Discontinuation or reduction of dopaminergic drug, levodopa particularly, should be the first adjustment, which may however induce severe motor disorder, depression or anxiety.

Missing information

Risk	What is known
Effect on plasma range of other medicinal products (especially those with a narrow therapeutic range)	Apomorphine is a type of dopaminergic agonist, a morphine derivative which primarily affects the hypothalamic region of the brain. The precise mechanism of action of apomorphine as a treatment for Parkinson's disease is unknown, although it is believed to be due to stimulation of post-synaptic dopamine D2-type receptors within the brain. Apomorphine has been shown to improve motor function in an animal model of Parkinson's disease. In particular, apomorphine attenuates the motor deficits induced by lesions in the ascending nigrostriatal dopaminergic pathway with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in primates [13]. The possible effects of apomorphine on the plasma concentrations of other medicinal products have not been studied. Therefore caution is advised when combining apomorphine with other medicinal products, especially those with a narrow therapeutic range.
Pregnancy and lactation	There is no experience of apomorphine usage in pregnant woman. Therefore apomorphine should not be used during pregnancy unless clearly necessary. It is not known whether apomorphine is excreted in breast milk. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with apomorphine should be made taking into account the benefit of breast-feeding to the child and the benefit of apomorphine to the woman.

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, 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.

The Summary of Product Characteristics and the Package leaflet for apomorphine can be found in the apomorphine's EPAR page.

Additionally, the medical devices delivered in combination with apomorphine have corresponding Instructions for Use which provide physicians, pharmacists and other health care professionals with details on how to use the medicine in combination with the medical device, the risks and recommendations for minimising them. The measures in this document are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

N/A

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

Version	Date	Safety Concerns	Comment
2.0	31. August 2013	Haemolytic anaemia	This safety concern has been added to the important identified risks.
2.0	31. August 2013	Thrombocytopenia	This safety concern has been added to the important identified risks.
2.0	31. August 2013	Eosinophilia	This safety concern has been added to the important identified risks.
2.0	31. August 2013	Impulse control disorders (incl. pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating)	This safety concern has been added to the important identified risks.
2.0	31. August 2013	Injection site necrosis and ulceration	This safety concern has been added to the important identified risks.
2.0	31. August 2013	Postural hypotension	This safety concern has been added to the important identified risks.
2.0	31. August 2013	Somnolence	This safety concern has been added to the important identified risks.
2.0	31. August 2013	Neuropsychiatric disturbances	This safety concern has been added to the important identified risks.
2.0	31. August 2013	Dyskinesia	This safety concern has been added to the important identified risks.
2.0	31. August 2013	Wrong dose due to technical malfunction of mini-pump or syringe-driver	This safety concern has been added to the important identified risks.
2.0	31. August 2013	Off-label use restless legs syndrome	This safety concern has been added to the important potential risks.
2.0	31. August 2013	Off-label use erectile dysfunction	This safety concern has been added to the important potential risks.
2.0	31. August 2013	Effect on plasma range of other medicinal products (especially those with a narrow therapeutic range)	This safety concern has been added to the missing information.
2.0	31. August 2013	Children and adolescents	This safety concern has been added to the missing information.
3.0	09. October 2014	Use of morphine instead of apomorphine	This safety concern has been added to the important identified risks.
4.0	27. May 2015	Local subcutaneous effects	This safety concern has been renamed (Injection site necrosis and ulceration -> Local subcutaneous effects)

4.0	27. May 2015	Eosinophilia	This safety concern has been deleted from the important identified risks.
4.0	27. May 2015	Medication error (e.g. use of morphine instead of apomorphine)	This safety concern has been renamed [Use of morphine instead of apomorphine -> Medication error (e.g. use of morphine instead of apomorphine)]
4.0	27. May 2015	Hypersensitivity to substance or excipients (sodium metabisulphite)	This safety concern has been added to the important identified risks.
4.0	27. May 2015	Pregnancy and lactation	This safety concern has been added to the missing information.
4.0	27. May 2015	Children and adolescents	This safety concern has been deleted from the missing information.
4.0	27. May 2015	Wrong dose due to technical malfunction of the pen	This safety concern has been added to the important potential risks for apomorphine 10mg/ml solution for injection in cartridge
4.3	15. February 2016	Wrong dose due to a handling error of the pen	This safety concern has been added to the important potential risks for apomorphine 10mg/ml solution for injection in cartridge
4.3	15. February 2016	Risk of contamination	This safety concern has been added to the important potential risks for apomorphine 10mg/ml solution for injection in cartridge
4.3	15. February 2016	Prolongation of the QT interval with combined use of domperidone and apomorphine	This safety concern has been added to the important identified risks
4.3	15. February 2016	Prolongation of the QT interval	This safety concern has been added to the important potential risks
4.3	15. February 2016	Dopamine dysregulation syndrome including punding and dopamine withdrawal syndrome	This safety concern has been added to the important potential risks
4.4	01. March 2016	Risk of contamination	This safety concern has been deleted