Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Apomorphine hydrochloride 5 mg/ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 5 mg apomorphine hydrochloride hemihydrate.
One 20 ml vial contains 100 mg apomorphine hydrochloride hemihydrate.

Excipient with known effect: Sodium metabisulfite 1 mg per ml.

Contains sodium 3.3mg per ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion
Clear and practically colourless solution
pH 2.6 – 4.0

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of motor fluctuations ('on-off' phenomena) in patients with Parkinson's disease which are not sufficiently controlled by oral anti-Parkinson medication.

4.2 Posology and method of administration

Posology

Patients Suitable for Apomorfin PharmSwed
Patients selected for treatment with Apomorfin PharmSwed should be able to recognise the onset of their 'off' symptoms and be capable of inserting the needle s.c. themselves or else have a responsible carer able to insert the needle s.c. for them when required.

Patients treated with apomorphine will usually need to start domperidone at least two days prior to initiation of therapy. The domperidone dose should be titrated to the lowest effective dose and discontinued as soon as possible. Before the decision to initiate domperidone and apomorphine treatment, risk factors for QT interval prolongation in the individual patient should be carefully assessed to ensure that the benefit outweighs the risk (see section 4.4).

Apomorphine treatment should be initiated in a controlled environment of a specialist clinic. The treatment should be managed by a physician experienced in the treatment of Parkinson's
disease (e.g. neurologist). The patient's treatment with levodopa, with or without dopamine agonists, should be optimised before starting Apomorfin PharmSwed treatment.

Establishment of treatment
Alterations in dosage may be made according to the patient's response.

The optimal dosage of apomorphine hydrochloride varies between individuals but, once established, it remains relatively constant for the individual patient.

Precautions on continuing treatment
The daily dose of Apomorfin PharmSwed varies widely between patients, typically within the range of 3-30 mg.

The total daily dose of apomorphine hydrochloride should not exceed 100 mg.

In clinical studies it has usually been possible to make a slight reduction in the dose of levodopa. This varies however considerably between patients and must be carefully managed by an experienced physician.

Once treatment has been established domperidone therapy may be gradually reduced in some patients. Only in a few patients domperidone may be completely discontinued without any vomiting or hypotension as a result.

Paediatric population
Apomorfin PharmSwed 5 mg/ml, solution for infusion, is contra-indicated for children and adolescents under 18 years of age (see Section 4.3).

Elderly
The elderly are well represented in the population of patients with Parkinson's disease and constitute a high proportion of those studied in clinical trials of apomorphine hydrochloride. The treatment with apomorphine hydrochloride has been the same in elderly and younger patients. Special caution is however recommended during initiation of therapy in elderly patients due to the risk of postural hypotension.

Renal impairment
A dose schedule similar to that recommended for adults and the elderly can be followed for patients with renal impairment (see Section 4.4).

Method of administration
Apomorfin PharmSwed 5 mg/ml, solution for infusion, is intended for use without dilution as a continuous subcutaneous infusion by minipump and / or syringe pump (infusion pump).

Apomorphine must not be used via the intravenous route.

Do not use if the solution has turned green. The solution should be visually inspected prior to use. Only clear and particle free solutions should be used. See Section 6.6.

Continuous Infusion

Patients who have shown a good 'on period' response during an initial apomorphine injection, but whose overall control remains unsatisfactory using intermittent injections, or who require many and frequent injections (more than 10 per day), may be commenced on or transferred to continuous subcutaneous infusion by minipump and / or syringe pump as follows:

The choice of which minipump and / or syringe pump to use, and dosage settings required will be determined by the physician in accordance with the particular needs of the patient.

The threshold dose for continuous infusion should be determined as follows:
Continuous infusion is started at a rate of 1 mg apomorphine hydrochloride (0.2 ml) per hour. The dose can thereafter be increased according to the patient's response during that particular day. Increases in the infusion rate should not exceed 0.5 mg at intervals of not less than 4 hours. Hourly infusion rates may range between 1 mg and 4 mg (0.2 ml and 0.8 ml), equivalent to 0.014 - 0.06 mg/kg/hour. Infusions should run for waking hours only. Unless the patient is experiencing severe night-time problems, 24 hour infusions are not recommended. Tolerance to the therapy does not seem to occur as long as there is an overnight period without treatment of at least 4 hours. The infusion site should be changed every 12 hours.

Where appropriate and as advised by a physician, the continuous infusion may need to be supplemented with intermittent bolus doses.

A reduction in dosage of other dopamine agonists may be considered during continuous infusion treatment.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Respiratory depression, dementia, psychotic diseases or hepatic insufficiency.

Apomorphine hydrochloride treatment must not be administered to patients who develop severe dyskinesia or dystonia as response to levodopa.

Apomorfin PharmSwed must not be given to children and adolescents under 18 years of age.

4.4 Special warnings and precautions for use

Apomorphine hydrochloride should be given with caution to patients with renal, pulmonary or cardiovascular disease and persons prone to nausea and vomiting.

Special caution is recommended during initiation of therapy in elderly and/or debilitated patients.

Since apomorphine may produce hypotension, even when given with domperidone, care should be exercised in patients with cardiac disease or in patients taking vasoactive medicinal products such as antihypertensives, and especially in patients with a history of postural hypotension.

Since apomorphine, especially at high dose, may have the potential for QT prolongation, caution should be exercised when treating patients at risk for torsades de pointes arrhythmia.

When used in combination with domperidone, risk factors in the individual patient should be carefully assessed. This should be done before treatment initiation, and during treatment. Important risk factors include serious underlying heart conditions such as congestive cardiac failure, severe hepatic impairment or significant electrolyte disturbance. Also medication possibly affecting electrolyte balance, CYP3A4 metabolism or QT interval should be assessed. Monitoring for an effect on the QTc interval is advisable. An ECG 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 cardiac symptoms including palpitations, syncope, or near-syncope. They should also report clinical changes that could lead to hypokalaemia, such as gastroenteritis or the initiation of diuretic therapy.

At each medical visit, risk factors should be revisited.

Apomorphine is associated with local subcutaneous reactions. These may sometimes be reduced by switching injection site or possibly by using ultra-sound (if this is available) on areas with nodularity and induration.

Haemolytic anaemia has been reported in patients treated with levodopa and apomorphine.

Haematology tests should be undertaken at regular intervals as with levodopa when given concomitantly with apomorphine.

Caution is advised when combining apomorphine with other medicinal products, especially those with a narrow therapeutic range (see Section 4.5).

Neuropyschiatric problems co-exist in many patients with advanced Parkinson's disease.

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.

Apomorphine has been associated with somnolence, and other dopamine agonists can be associated with sudden sleep onset episodes, particularly in patients with Parkinson's disease.

Patients must be informed of this 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.

Impulse control disorders

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 and hyper sexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including Apomorfin PharmSwed. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

Dopamine dysregulation Syndrome (DDS) is an addictive disorder resulting in excessive use of the product seen in some patients treated with apomorphine. Before initiation of treatment, patients and caregivers should be warned of the potential risk of developing DDS.

Apomorfin PharmSwed 5 mg/ml, solution for infusion, contains sodium metabisulfite which may rarely cause severe hypersensitivity reactions and bronchospasm.

This medicinal product contains 3.3 mg sodium per ml of solution, equivalent to 0.17 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interactions

Patients selected for treatment with apomorphine hydrochloride are almost certain to be taking concomitant medicinal products for their Parkinson’s disease. In the initial stages of apomorphine hydrochloride therapy the patient should be monitored for unusual undesirable effects or signs of potentiation of effect.

Neuroleptic medicinal products may have an antagonistic effect if used with apomorphine.
There is a potential interaction between clozapine and apomorphine. Clozapine may however also be used to reduce the symptoms of neuropsychiatric complications.

If neuroleptics have to be used in patients with Parkinson’s disease treated by dopamine agonists, a gradual reduction in apomorphine dose may be considered when administration is by minipump and / or syringe pump (symptoms suggestive of neuroleptic malignant syndrome have been reported rarely with abrupt withdrawal of dopaminergic therapy).

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.

Antihypertensive and cardiac active medicinal products
Even when co-administered with domperidone, apomorphine may potentiate the antihypertensive effects of these medicinal products (see Section 4.4).

It is recommended to avoid the administration of apomorphine with other drugs known to prolong the QT interval.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is no experience of apomorphine usage in pregnant women.

Reproduction studies in animals do not indicate any teratogenic effect, but in rats, dosages that are toxic to the mother may cause respiratory failure in the newborn offspring. The potential risk for humans is unknown. Apomorfin PharmSwed should therefore be used during pregnancy only when considered absolutely necessary.

Breast-feeding
It is not known whether apomorphine is excreted in breast milk. Decision whether breast -feeding should be continued/ discontinued or if Apomorfin PharmSwed treatment should be continued/discontinued should be taken after consideration of the advantages of breast-feeding the child and the advantages of Apomorfin PharmSwed treatment for the mother.

4.7 Effects on ability to drive and use machines

Apomorphine hydrochloride has minor or moderate influence on the ability to drive and use machines.

Patients being treated with apomorphine and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities (e.g. operating machines) where impaired alertness may put themselves or others at risk of serious injury or death until such recurrent episodes and somnolence have resolved (see also Section 4.4).

4.8 Undesirable effects

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Blood and lymphatic system disorders Uncommon Rare	 Haemolytic anaemia, thrombocytopenia Eosinophilia
Immune system disorders Rare	Allergic reactions due to the presence of sodium metabisulfite (including anaphylaxis and bronchospasm)
Psychiatric disorders Very common Common Not known	Hallucinations Neuropsychiatric disturbances (including transient mild confusion and visual hallucinations) Impulse control disorders: pathological gambling, increased libido and hyper sexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including Apomorfin PharmSwed (see Section 4.4) Aggression, agitation
Nervous system disorders Common Uncommon Not known	 Transient sedation with each dose of apomorphine hydrochloride at the start of therapy may occur. This usually resolves over the first few weeks. Somnolence. Dizziness / lightheadedness Apomorphine may induce dyskinesia during 'on periods', which can be

	severe in some cases, and in a few patients may result in cessation of therapy. Syncope, headache
Vascular disorders Uncommon	Postural hypotension (see Section 4.4).
Respiratory, thoracic and mediastinal disorders Common Uncommon	Yawning Breathing difficulties
Gastrointestinal disorders Common	Nausea and vomiting, particularly when apomorphine treatment is first initiated, usually as a result of not using domperidone (see Section 4.2).
Skin and subcutaneous tissue disorders Uncommon	Local and generalised rash
General disorders and administration site conditions Very common Uncommon Not known	In most patient's injection site reactions develop, particularly with continuous use. These may include subcutaneous nodules, induration, erythema, tenderness and panniculitus. A number of other local reactions (such as irritation, pruritus, bruising and pain) may also occur. Necrosis and ulceration at the injection site Periferal edema
Investigations Uncommon	Positive Coombs' tests for patients receiving levodopa and apomorphine

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website: www.hpra.ie, e-mail: medsafety@hpra.ie

4.9 Overdose

There is limited clinical experience of overdose with apomorphine by subcutaneous administration. Symptoms of overdose may be treated empirically as suggested below:

Excessive emesis may be treated with domperidone.
Respiratory depression may be treated with naloxone.
Hypotension: appropriate measures should be taken, e.g. raising the foot of the bed.
Bradycardia may be treated with atropine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dopamine agonists, ATC code: N04BC07

Apomorphine is a direct stimulant of dopamine receptors. Even if it is possessing both D1 and D2 receptor agonist properties it does not share transport or metabolic pathways with levodopa.

Although in intact experimental animals, administration of apomorphine suppresses the rate of firing of nigro-striatal cells and in low dose has been found to produce a reduction in locomotor activity (thought to represent pre-synaptic inhibition of endogenous dopamine release) its actions on parkinsonian motor disability are likely to be mediated at post-synaptic receptor sites. This biphasic effect is also seen in humans.

5.2 Pharmacokinetic properties

After subcutaneous injection of apomorphine its pharmacokinetics can be described by a two-compartment model, with a distribution half-life of 5 (±1.1) minutes and an elimination half-life of 33 (±3.9) minutes. Clinical response correlates well with levels of apomorphine in the cerebrospinal fluid. Apomorphine is rapidly and completely absorbed from subcutaneous tissue, correlating with the rapid onset of clinical effects (4-12 minutes). The brief duration of clinical action of apomorphine (about 1 hour) is explained by its rapid clearance. The metabolism of apomorphine is by glucuronidation and sulphonation to at least ten per cent of the total; other pathways have not been described.

5.3 Preclinical safety data

Repeat dose subcutaneous toxicity studies reveal no special hazard for humans, beyond the information included in other sections of the SmPC.

In vitro genotoxicity studies demonstrated mutagenic and clastogenic effects, most likely due to products formed by oxidation of apomorphine. However, apomorphine was not genotoxic in *in vivo* studies.

The effect of apomorphine on reproduction has been studied in rats. Apomorphine was not teratogenic in this species, but it was observed that toxic doses to the mother can result in impaired maternal attention and respiratory failure in the newborn offspring.

No carcinogenicity studies have been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium metabisulfite (E223)
Hydrochloric acid (for pH adjustment)
Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.
After opening and filling the drug product in syringes attached with infusion sets: chemical and physical in-use stability has been demonstrated for 96 hours (4 days) at 30-35°C. In-use storage times and conditions are the responsibility of the user due to risk of microbial contamination when opening and handling the product.

6.4 Special precautions for storage

Keep in the outer carton in order to protect from light.
Do not store above 25 ºC.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Vial (type I glass) with bromobutyl rubber stopper and aluminum seal, containing 20 ml.

Pack sizes: 1 vial, 5 vials or 30 (6x5) vials (bundled pack)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only.

Do not use if the solution has turned green. The solution should be visually inspected prior to use. Only clear and particle free solutions should be used. See Section 4.2.

After use, vials and syringes and any unused contents should be discarded.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Evolan Pharma AB
PO Box 120
182 12 Danderyd
Sweden

8 MARKETING AUTHORISATION NUMBER

PA2262/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26th October 2012
Date of last renewal: 16th July 2015

10 DATE OF REVISION OF THE TEXT

March 2022