

Public Assessment Report
Mutual Recognition Procedure

**APO-go PFS 5mg/ml Solution
for infusion in pre-filled Syringe**

Apomorphine Hydrochloride

UK/H/0342/03/MR

Applicant: Forum Products Limited

LAY SUMMARY

The Medicines Healthcare products Regulatory Agency (MHRA) granted Forum Products Limited a Marketing Authorisation (national licence) for the medicinal product APO-go PFS 5mg/ml Solution for infusion in pre-filled Syringe on 15th September 2004. This is a prescription-only medicine (POM) used to treat Parkinson's disease. It helps to reduce the amount of time spent in an "off" or immobile state in people who have previously been treated for Parkinson's disease with levodopa and/or other dopamine agonists.

Completion of first wave Mutual Recognition Procedure (UK/H/0464/002/MR) was approved on 20th December 2007 in the following countries: Austria, Denmark, Finland, Germany, Greece, Ireland, Norway, The Netherlands, Spain and Sweden.

Apomorphine hydrochloride is the active ingredient in this medicinal product and is a morphine derivative with structural similarities to dopamine. It is a potent agonist and is used in the diagnosis and management of Parkinsonism.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking APO-go PFS 5mg/ml Solution for Infusion in Pre-Filled Syringe outweigh the risks; hence a Marketing Authorisation has been granted.

TABLE OF CONTENTS

Module 1: Information about initial procedure	Page 4
Module 2: Summary of Product Characteristics	Page 5
Module 3: Product Information Leaflets	Page 12
Module 4: Labelling	Page 13
Module 5: Scientific Discussion	Page 14
1 Introduction	Page 14
2 Quality aspects	Page 16
3 Non-clinical aspects	Page 18
4 Clinical aspects	Page 19
5 Overall conclusions	Page 23
Module 6: Steps taken after initial procedure	Page 24

Module 1

Product Name	APO-go PFS 5mg/ml Solution for infusion in pre-filled Syringe
Type of Application	Known active substance, Article 8.3
Active Substance	Apomorphine hydrochloride
Form	Solution for infusion
Strength	5 mg/ml
MA Holder	Forum Products Limited
Reference Member State (RMS)	UK
CMS	Austria, Denmark, Germany, Greece, Spain, Finland, Ireland, Norway, The Netherlands and Sweden
Procedure Number	UK/H/0342/03/MR
Timetable	Day 90 – 18 th December 2007

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

APO-go PFS 5mg/ml Solution for Infusion in Pre-filled Syringe (United Kingdom/Ireland)
APO-go 5mg/ml Infusionslösung in einer Fertigspritze (Austria/Germany)
APO-go til pumpe (Denmark)
APO-go PFS 5mg/ml (Greece)
APO-go 5mg/ml oplossing voor infusie in een voorgevulde spuit (the Netherlands)
APO-go för Pump (Sweden)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1ml contains 5mg apomorphine hydrochloride.
Each 10ml pre-filled syringe contains 50mg apomorphine hydrochloride.

Excipient:
Sodium metabisulphite 0.5 mg per ml

For a full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM

Solution for Infusion, pre-filled syringe
Solution is clear and colourless
pH3.0-4.0

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

Selection of Patients Suitable for APO-go:

Patients selected for treatment with APO-go should be able to recognise the onset of their 'off' symptoms and be capable of injecting themselves or else have a responsible carer able to inject for them when required.

It is essential that the patient is established on domperidone, usually 20 mg three times daily for at least two days prior to initiation of therapy.

Apomorphine should be initiated in the controlled environment of a specialist clinic. The patient should be supervised 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 APO-go treatment.

Administration

APO-go PFS 5mg/ml Solution for Infusion in Pre-filled Syringe is a pre-diluted pre-filled syringe intended for use without dilution as a continuous subcutaneous infusion by minipump and / or syringe-driver. It is not intended to be used for intermittent injection.

Apomorphine must not be used via the intravenous route.

Do not use if the solution has turned green. The solution should be inspected visually prior to use. Only clear, colourless and particle free solution should be used.

Continuous Infusion

Patients who have shown a good 'on' period response during the initiation stage of apomorphine therapy, 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 driver as follows:-

The choice, of which minipump and / or syringe-driver to use, and the 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 HCl (0.2 ml) per hour then increased according to the individual response each 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 advised. Tolerance to the therapy does not seem to occur as long as there is an overnight period without treatment of at least 4 hours. In any event, the infusion site should be changed every 12 hours.

Patients may need to supplement their continuous infusion with intermittent bolus boosts, as necessary, and as directed by their physician.

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

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, remains relatively constant for each patient.

Precautions on continuing treatment

The daily dose of APO-go varies widely between patients, typically within the range of 3-30 mg.

It is recommended that the total daily dose of apomorphine HCl should not exceed 100 mg.

In clinical studies it has usually been possible to make some reduction in the dose of levodopa; this effect varies considerably between patients and needs to be carefully managed by an experienced physician.

Once treatment has been established domperidone therapy may be gradually reduced in some patients but successfully eliminated only in a few, without any vomiting or hypotension.

Children and adolescents

APO-go PFS 5mg/ml Solution for Infusion in Pre-filled Syringe 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 APO-go. The management of elderly patients treated with APO-go has not differed from that of younger patients. However

extra caution is recommended during initiation of therapy in elderly patients because of 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).

4.3 Contraindications

In patients with respiratory depression, dementia, psychotic diseases or hepatic insufficiency.

Apomorphine HCl treatment must not be administered to patients who have an 'on' response to levodopa which is marred by severe dyskinesia or dystonia.

APO-go should not be administered to patients who have a hypersensitivity to apomorphine or any excipients of the medicinal product.

APO-go is contra-indicated for children and adolescents under 18 years of age.

Pregnancy and lactation (see Section 4.6)

4.4 Special warnings and precautions for use

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

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

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

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)

Neuropsychiatric 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.

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including apomorphine.

APO-go PFS 5mg/ml Solution for Infusion in Pre-filled Syringe contains sodium metabisulphite which may rarely cause severe allergic reactions and bronchospasm.

This medicinal product contains less than 1 mmol sodium (23 mg) per 10 ml, i.e. essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Patients selected for treatment with apomorphine HCl are almost certain to be taking concomitant medicinal products for their Parkinson's disease. In the initial stages of apomorphine HCl 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, however clozapine may also be used to reduce the symptoms of neuropsychiatric complications.

If neuroleptic medicinal products 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- driver (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).

4.6 Pregnancy and lactation

Animal reproduction studies have not been conducted with apomorphine HCl.

There is no experience of apomorphine usage in pregnant women. Therefore, apomorphine HCl must not be used in women of child-bearing potential (see Section 4.3).

It is not known whether apomorphine is excreted in breast milk. Women must not breast-feed during apomorphine HCl therapy (see Section 4.3).

4.7 Effects on ability to drive and use machines

Apomorphine HCl 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 ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($< 1/10,000$)

Not known (cannot be estimated from the available data)

Blood and lymphatic system disorders

Uncommon:

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

Rare:

Eosinophilia has rarely occurred during treatment with apomorphine HCl.

Immune system disorders

Rare:

Due to the presence of sodium metabisulphite, allergic reactions (including anaphylaxis and bronchospasm) may occur.

Psychiatric disorders

Common:

Neuropsychiatric disturbances are common in parkinsonian patients. APO-go should be used with special caution in these patients. Neuropsychiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine HCl therapy.

Not known:

Patients treated with dopamine agonists for treatment of Parkinson's disease, including apomorphine, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation.

Nervous system disorders

Common:

Transient sedation with each dose of apomorphine HCl at the start of therapy may occur; this usually resolves over the first few weeks.

Apomorphine is associated with somnolence.

Uncommon:

Apomorphine may induce dyskinesias during 'on' periods, which can be severe in some cases, and in a few patients may result in cessation of therapy.

Vascular disorders

Uncommon:

Postural hypotension is seen infrequently and is usually transient (See Section 4.4).

Respiratory, thoracic and mediastinal disorders

Uncommon:

Breathing difficulties have been reported.

Gastrointestinal disorders

Common:

Nausea and vomiting, particularly when apomorphine treatment is first initiated, usually as a result of the omission of domperidone (See Section 4.2).

Skin and subcutaneous tissue disorders

Very common:

Local induration and nodules (usually asymptomatic) often develop at subcutaneous sites of injection in most patients, particularly with continuous use. In patients on high doses of apomorphine HCl these may persist and give rise to areas of erythema, tenderness and induration. Panniculitis has been reported from these patients where a skin biopsy has been undertaken. Care should be taken to ensure that areas of ulceration do not become infected. Pruritus may occur at the site of injection.

These local subcutaneous effects can sometimes be reduced by rotation of injection sites or possibly by the use of ultrasound (if available) to areas of nodularity and induration.

Uncommon:

Local and generalised rashes have been reported.

Investigations

Uncommon:

Positive Coombs' tests have been reported for patients receiving apomorphine and levodopa.

4.9 Overdose

There is little clinical experience of overdose with apomorphine by this route of 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

Pharmatherapeutic group: Dopamine agonists

ATC Code: N04B C07

Apomorphine is a direct stimulant of dopamine receptors and while possessing both D1 and D2 receptor agonist properties 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 fate 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; the active substance distribution being best described by a two-compartment model. Apomorphine is rapidly and completely absorbed from subcutaneous tissue, correlating with the rapid onset of clinical effects (4-12 minutes), and the brief duration of clinical action of the active substance (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 the in vivo studies performed.

There are no data on fertility and embryo-foetal toxicity. No carcinogenicity studies have been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium metabisulphite (E223)

Hydrochloric acid (37%), (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

Once opened the pre-filled syringe should be used immediately.

From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately.

If not used immediately in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Keep the pre-filled syringe in the outer carton in order to protect from light.

For storage of the product after opening see Section 6.3.

Do not store above 25°C.

6.5. Nature and Contents of Container

Clear glass (Type I) pre-filled syringe, 10 ml with a chlorobutyl rubber stopper and tip.

Packs contain 5 Pre-filled Syringes in a cardboard tray in an outer cardboard carton.

Bundle packs of 25 and 50 Pre-filled Syringes are available in some territories:

- The 25 pre-filled syringes bundle packs consists of 5 packs each containing 5 pre-filled syringes.
- The 50 pre-filled syringes bundle packs consists of 10 packs each containing 5 pre-filled syringes.

Not all pack sizes are marketed.

6.6 Special precautions for disposal

APO-go PFS 5mg/ml Solution for Infusion in Pre-filled Syringe is for single use only. Any unused solution should be discarded.

After single use, adaptors and syringes should be discarded and disposed of in a "Sharps" bin.

7 MARKETING AUTHORISATION HOLDER

Forum Products Limited
41 - 51 Brighton Road
Redhill
Surrey
RH1 6YS
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 05928/0025

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

September 2004

10 DATE OF (PARTIAL) REVISION OF THE TEXT

May 2008

10 DATE OF REVISION OF THE TEXT

12/11/2008

Module 3

Patient Information Leaflet

Rare side effects (1 to 10 users in 10,000)

- an allergic reaction such as:
 - difficulty breathing or tightness of the chest
 - puffiness of the eyelids, face or lips
 - swelling or redness of the tongue
- Side effects with unknown frequency (frequency cannot be estimated from the available data):
 - pathological gambling (failure to resist gambling impulses despite serious personal or family consequences)
 - increased sex drive
 - hypersexuality (altered sexual interest and behaviour of significant concern to the patient or to others)

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store APO-go PFS

Keep out of the reach and sight of children.

Do not use APO-go PFS after the expiry date which is stated on the label/carton. The expiry date refers to the last day of that month.

Keep the pre-filled syringe in the outer carton in order to protect from light.

Do not store above 25°C.

Once opened APO-go PFS should be used immediately.

Do not use APO-go PFS if the solution has turned green. It should only be used if the solution is clear, colourless and free of any visible particles.

Withdraw contents immediately after opening.

Take care not to splash any of the solution onto yourself, or the carpet as it may stain green. At the end of use the glass pre-filled syringe should be discarded in a Sharp's bin as well as any used plastic syringes and the adaptor. Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further information

What APO-go PFS contains

The active substance is apomorphine hydrochloride. 1ml contains 5mg apomorphine hydrochloride. Each 10ml pre-filled syringe contains 50mg apomorphine hydrochloride.

The other ingredients are:

- Sodium metabisulphite (E223)
- Hydrochloric acid (37%)
- Water for injections

What APO-go PFS looks like and contents of the pack
APO-go PFS is a solution for infusion, pre-filled syringe. The solution is clear and colourless.

APO-go PFS is supplied in clear glass pre-filled syringes. Each pack contains 5 syringes in an outer cardboard carton. Bundle packs of 25 (5 x 5) and bundle packs of 50 (10 x 5) are available in some territories.

Marketing Authorisation Holder

Forum Products Ltd
41-51 Brighton Road
Redhill
Surrey RH1 6YS, United Kingdom

Manufacturers

Catalent Belgium S.A. Britannia Pharmaceuticals Limited
Font Saint Landry 10 41-51 Brighton Road
B-120 Brussels Redhill
Neder Over Heembeek Surrey RH1 6YS
Belgium United Kingdom

This medicinal product is authorised in the Member states of the EEA under the following names:

Austria	AP0-go 5 mg/ml Infusionslösung in einer Fertigspritze
Denmark	AP0-go Pumpfill 5 mg/ml infusionsvæske, opløsning i fyldt injektionspørefte
Germany	AP0-go 5 mg/ml Infusionslösung in einer Fertigspritze
Greece	AP0-go PFS 5mg/ml
Ireland	AP0-go PFS 5mg/ml Solution for Infusion in Pre-filled Syringe
Sweden	AP0-go Pumpfill 5 mg/ml infusionsvätska, lösning i färdfylld sprita
The Netherlands	AP0-go 5mg/ml oplossing voor infuzie in een voorgevulde spuit
United Kingdom	AP0-go PFS 5mg/ml Solution for Infusion in Pre-filled Syringe

This leaflet was last approved in 11/2008

UK/RL004

In this leaflet:

1. What APO-go PFS is and what it is used for
2. Before you use APO-go PFS
3. How to use APO-go PFS
4. Possible side effects
5. How to store APO-go PFS
6. Further information

1. What APO-go PFS is and what it is used for

Apomorphine hydrochloride belongs to a group of medicines known as dopamine agonists which are used to treat Parkinson's disease. It helps to reduce the amount of time spent in an "off" or immobile state in people who have previously been treated for Parkinson's disease with levodopa and/or other dopamine agonists. Your doctor or nurse will help you to recognise the signs of when to use your medicine.

2. Before you use APO-go PFS

Do not use APO-go PFS

- if you are under 18 years of age
- if you have breathing difficulties or suffer from asthma
- if you have dementia or Alzheimer's disease
- if you suffer from confusion, hallucinations or any other similar problems
- if you have liver problems
- if you have severe dyskinesia (involuntary movements) or severe dystonia (inability to move) on account of the treatment with levodopa
- if you are allergic to apomorphine or any of the other ingredients of APO-go PFS (for other ingredients see section 6)
- if you are pregnant, think you may be pregnant or you are planning to become pregnant
- if you are breast-feeding

Take special care with APO-go PFS

- if you have kidney problems
- if you have lung problems
- if you have heart problems
- if you have low blood pressure or feel faint and dizzy when you stand
- if you are taking any medicines to treat high blood pressure
- if you feel sick or suffer from being sick
- if you have any mental disorders when APO-go PFS is started, if you are elderly or frail

– when driving or operating machinery since apomorphine may cause sleepiness including sudden sleep onset episodes (you must not drive or operate machinery if APO-go PFS makes you sleepy)

– if you are taking levodopa (another treatment for Parkinson's disease) as well as apomorphine your doctor should check your blood regularly.

If any of the above situations applies to you, please inform your doctor or nurse.

Taking other medicines

If you take apomorphine in combination with other medicines (especially neuroleptics such as clozapine or medicines to reduce your blood pressure or other medicines for Parkinson's disease) the effect of your medicines may be altered. Your doctor will advise you if you need to adjust the dose of your apomorphine or any of your other medicines.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Using APO-go PFS with food and drink
Food and drink do not affect APO-go PFS.

Pregnancy and breast-feeding

You should not use APO-go PFS if you are pregnant, think you may be pregnant or you are planning to become pregnant.

You should not use APO-go PFS if you are breast-feeding. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Do not drive if APO-go PFS makes you sleepy. Do not use any tools or machines if APO-go PFS makes you sleepy.

Important information about some of the ingredients of APO-go PFS

Rarely sodium metabisulphite may cause a severe allergic reaction and difficulty breathing. This medicinal product contains less than 1 mmol (23mg) of sodium per 10ml, i.e. essentially sodium free.

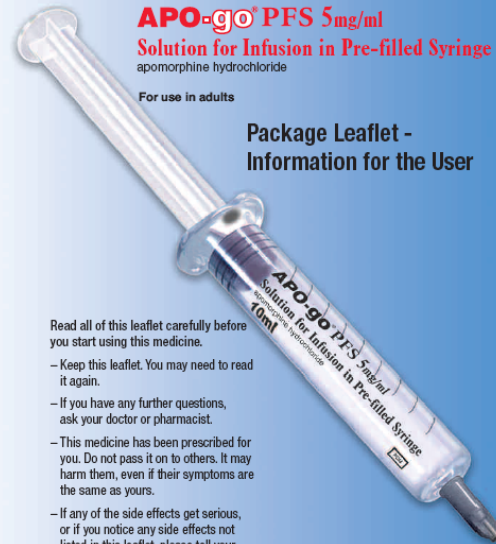
3. How to use APO-go PFS

The infusion is given subcutaneously (i.e. into the area under the skin).

AP0-go® PFS 5mg/ml
Solution for Infusion in Pre-filled Syringe
apomorphine hydrochloride

For use in adults

Package Leaflet -
Information for the User



Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Do not use a syringe if the solution has turned green. Always use APO-go PFS exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

APO-go PFS has been designed for continuous infusion with a syringe driver. It is not to be used for intermittent injection. Your doctor will decide which minipump and/or syringe-driver and which dosage settings you should use.

Both the amount of APO-go PFS that you should use and the total amount of time you should receive your medicine each day, will depend upon your personal needs. Your doctor will discuss this with you and tell you how much of your medicine you should administer. The amount that will work best will have been determined on your visit to the specialist clinic. The average infusion dose per hour is between 1mg and 4mg apomorphine hydrochloride. This is usually given when you are awake and generally stopped before sleeping. The amount of apomorphine hydrochloride that you receive each day should not exceed 100mg. Your doctor or nurse will decide which dose is best for you.

A different site for your infusion should be used every 12 hours.

This medicine should not be administered into a vein.

There is no need to dilute APO-go PFS before use. In addition, it should not be mixed with other medicines.

If you use more APO-go PFS than you should

- tell your doctor or contact your nearest hospital emergency department immediately.
- it is important to administer the correct dose of APO-go PFS and not to use more than the amount recommended by your doctor. Higher doses may cause a slow heart rate, excessive sickness, excessive sleepiness and/or difficulty breathing. You may also feel faint or dizzy particularly when you stand up, due to low blood pressure. Lying down and raising your feet will help to treat low blood pressure.

If you forget to use APO-go PFS

- take it when you next require it.
- do not take a double dose to make up for a forgotten dose.

If you stop using APO-go PFS

– contact your doctor before stopping treatment and discuss whether this is appropriate or not.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, APO-go PFS can cause side effects, although not everybody gets them. Tell your doctor if you think your medicine is making you feel unwell or if you get any of the following:

Very common side effects (more than 1 user in 10):

- lumps under the skin at the site of injection which are sore, troublesome and may be red and itchy. In order to avoid getting these lumps, it is advisable to change the site of injection every time you insert the needle.

Common side effects (1 to 10 users in 100):

- feeling sick or being sick, particularly when starting APO-go PFS. Domperidone should be started at least 2 days before APO-go PFS to stop you feeling or being sick. If you are taking domperidone and still feel sick, or if you are not taking domperidone and have sickness, tell your doctor or nurse as soon as possible.
- feeling tired or excessive sleepiness. You must take special care when you drive or operate machinery. If you experience tiredness, it is important to avoid driving or any activity where reduced alertness may put yourself or others at risk.
- confusion or hallucinations.

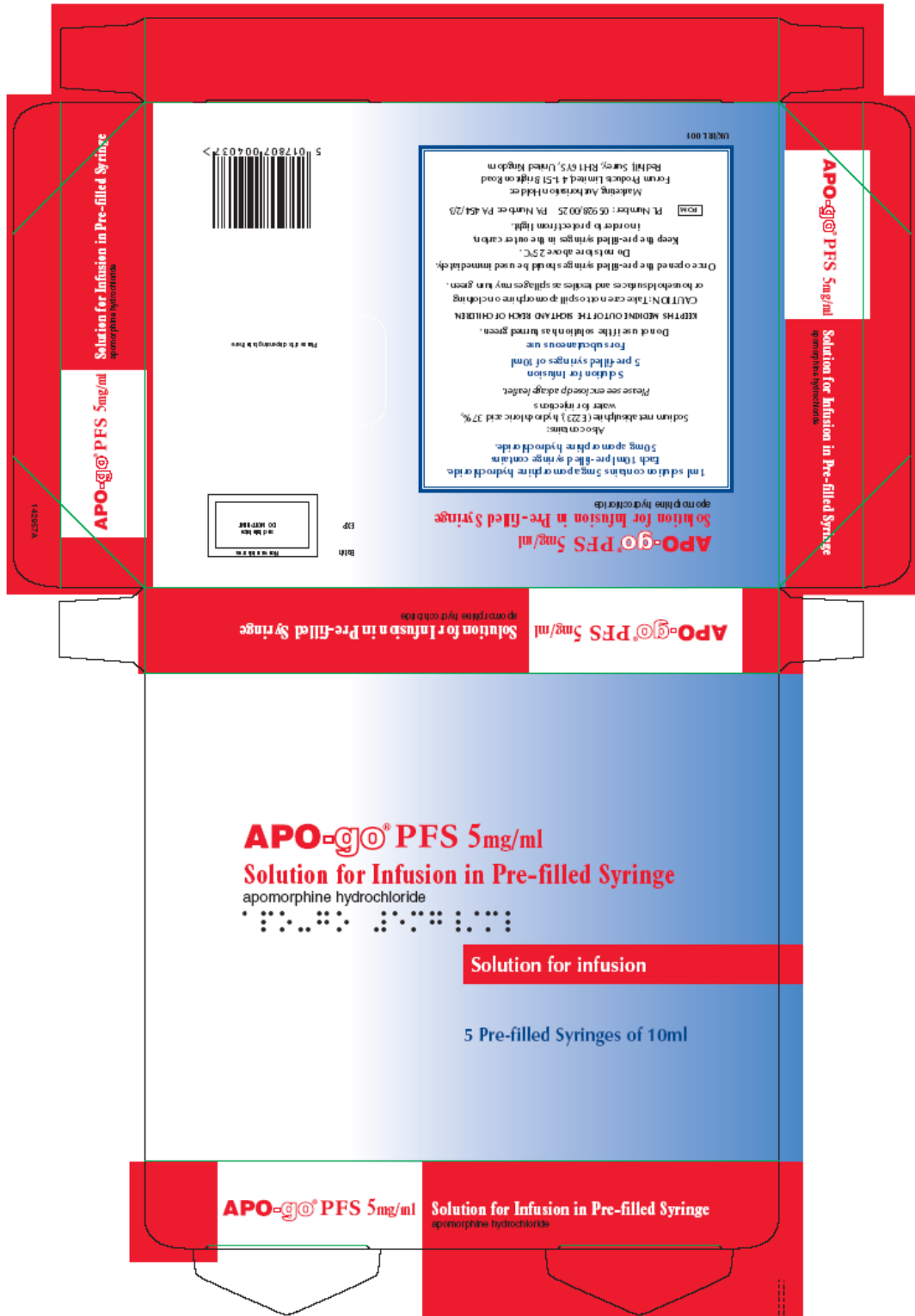
Uncommon side effects (1 to 10 users in 1,000):

- feeling faint or dizzy when standing up.
- increased involuntary movements or increased shakiness during "on" periods.
- anaemia or blood disorders. This is an uncommon side effect that can occur in patients also taking levodopa (another medicine for the treatment of Parkinson's disease). If you are taking levodopa as well as APO-go PFS, your doctor should arrange for you to have blood tests at regular intervals.
- rashes
- shortness of breath

Module 4

Labelling

Outer carton:



Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for APO-go PFS 5mg/ml Solution for infusion in the treatment of the following indications could be approved: disabling motor fluctuations (“on-off” phenomena) in patients with Parkinson’s disease which persist despite individually titrated treatment with levodopa (with a peripheral decarboxylase inhibitor) and/or other dopamine agonists.

A national marketing authorisation was granted on 15th September 2004.

This application was submitted under Article 8.3 of Directive 2001/83 (as amended), for a known active substance. The product is a line extension, with a change or addition of a new pharmaceutical form. The original product is APO-go Ampoules 10 mg/ml Solution for Injection (PL 05928/0020) and APO-go pen 10 mg/ml Solution for Injection (PL 05928/0021) first licensed in 1993.

Apomorphine is a direct stimulant of dopamine receptors and while possessing both D1 and D2 receptor agonist properties 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

No new preclinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	APO-go PFS 5mg/ml Solution for infusion in pre-filled Syringe
Name(s) of the active substance(s) (INN)	Apomorphine Hydrochloride
Pharmacotherapeutic classification (ATC code)	N04 BC07
Pharmaceutical form and strength(s)	Solution for Infusion, 5mg/ml
Reference numbers for the Mutual Recognition Procedure	UK/H/0342/03/MR
Reference Member State	United Kingdom
Member States concerned	Austria, Denmark, Germany, Greece, Spain, Finland, Ireland, Norway, The Netherlands and Sweden
Marketing Authorisation Number(s)	PL 05928/0025
Name and address of the authorisation holder	Forum Products Limited 41-51 Brighton Road, Redhill Surrey, RH1 6YS United Kingdom

III SCIENTIFIC OVERVIEW AND DISCUSSION

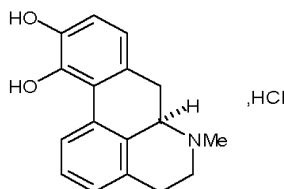
III.1 QUALITY ASPECTS

S. Active substance

INN/Ph.Eur name: Apomorphine Hydrochloride

Chemical name: 6a β - aporphine-10,11-diol hydrochloride hemihydrate
(R)-10,11-dihydroxy-6a β -aporphine hydrochloride hemihydrate
(6aR)-5,6,6a,7-tetrahydro-6-methyl-4H-dibenzo [de,g]
quinolone-10,11-diol hydrochloride hemihydrate
(R)-5,6,6a,7-tetrahydro-6-methyl-4H-dibenzo [de,g] quinolone-
10,11-diol hydrochloride
(6aR)-6,-methyl-5,6,6a,7-tetrahydro-6-methyl-4H-dibenzo
[de,g] quinolone-10,11-diol hydrochloride

Structural formula



Molecular formula: C₁₇H₁₈ClNO₂, ½H₂O

Molecular weight: 312.8

Characteristics: White or greyish crystals or microcrystalline powder.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting material and reagents and these are supported by relevant certificates of analysis.

An appropriate specification based on the European Pharmacopoeia has been provided.

Active apomorphine hydrochloride is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided for three batches and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturers and finished product manufacturer during validation studies.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug. The data demonstrates the stability of the drug substance and supports an appropriate retest period when stored in the proposed packaging.

P. Medicinal Product

Other Ingredients

Other ingredients consist of pharmaceutical excipients namely sodium metabisulphite, hydrochloric acid, nitrogen and water for injection.

All excipients have a respective European Pharmacopoeia monograph. Satisfactory certificates of analysis have been provided for all ingredients showing compliance with their respective monograph/specifications.

None of the excipients used contain material derived from animal or human origin.

Pharmaceutical development

The aim of the development programme was to develop a simple solution for infusion with a concentration of 5 mg/ml apomorphine hydrochloride in water for injections.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated on three pilot scale and three production-scale batches with satisfactory results.

Finished Product Specification

The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container-Closure System

The product is packaged in Clear glass (Type I) pre-filled syringe, 10 ml with a chlorobutyl rubber stopper and tip. Packs contain 5 Pre-filled Syringes in a cardboard tray in an outer cardboard carton.

Satisfactory specifications and certificates of analysis have been provided for all packaging components.

Stability of the product

Stability studies were performed on three pilot-scale and three production scale batches of the finished product in the packaging proposed for marketing, in accordance with current guidelines. All results from stability studies were within specified limits. This data supports a shelf-life of 2 years. Once opened the pre-filled syringe should be used immediately.

SPC, PIL, Labels

The SPC, PIL and Labels are pharmaceutically acceptable.

Conclusion

The grant of marketing authorisations is recommended.

III.2 PRE-CLINICAL ASPECTS**INTRODUCTION**

This is an application for APO-go PFS 5mg/ml Solution for infusion in pre-filled Syringe containing 0.5% apomorphine hydrochloride, as active ingredient together with 0.05% sodium metabisulphite (as preservative). The proposed formulation is intended for subcutaneous injection in the treatment of disabling motor fluctuations in patients with Parkinson's disease which persist despite individually titrated treatment with levodopa and/or other dopamine agonists.

The applicant already holds a licence for a higher strength of this product (10mg apomorphine hydrochloride/ml; PL 05928/0020-21). The rationale for the proposed formulation is that with this lower strength formulation, the amount of sodium metabisulphite can be reduced from 0.1% to 0.05% thus lowering its potential to cause irritation and local cutaneous reactions.

The maximum recommended daily dose is 100mg of apomorphine hydrochloride. This medicine should not be used in children or adolescents under 18 years of age.

OVERVIEW

Apomorphine is a potent dopamine D1 and D2 receptor agonist. The pharmacology and toxicology of apomorphine is well established and will not be re-iterated here.

Acute subcutaneous toxicity of various formulations of apomorphine hydrochloride containing different concentrations of sodium metabisulphite and ascorbic acid were compared in rats. The formulation containing 5mg apomorphine hydrochloride/ml together with 0.5mg ascorbic acid/ml was the least irritant and was used as the basis of the proposed formulation.

The local tolerance of different formulations containing 10mg apomorphine hydrochloride/ml and 1mg sodium metabisulphite/ml together with various concentrations of methyl paraoxybenzoate, benzyl alcohol, sodium edetate and glycerine, after intramuscular injection were studied in rabbits. Apparently the formulation containing no benzyl alcohol and methyl paraoxybenzoate caused the least damage.

The rationale for the proposed formulation is that with this lower strength formulation, the amount of sodium metabisulphite is reduced from 0.1% to 0.05% thus lowering its potential to cause irritation and local cutaneous reactions. Although the preclinical studies discussed in the Expert Report were not performed with formulations identical to that proposed for marketing, the present assessor agrees with the Expert that the proposed formulation is likely to be less irritant than APO-go ampoules 10mg/ml already licensed in the UK.

PHARMACO-TOXICOLOGICAL EXPERT REPORT

A Pharmacotoxicological Expert Report has been written by a person of suitable qualifications and is satisfactory. This consisted of a brief summary of preclinical studies performed with formulations similar to that intended for marketing. These include an acute toxicity study in rats and two local tolerance studies in rabbits.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

Sections 4.3, 4.6, 4.9 and 5.3 of the SmPC are identical to those of APO-go ampoules 10mg/ml already granted and are considered acceptable.

PATIENT INFORMATION LEAFLET

The Patient Information Leaflet is acceptable preclinically.

CONCLUSION

There are no preclinical objections to grant of marketing authorisation for APO-go 5mg/ml solution for infusion.

III.3 CLINICAL ASPECTS**INTRODUCTION & BACKGROUND**

This is a Standard Abridged National Marketing Application for a line extension to Apomorphine Injection 10mg/ml.

Essential similarity is claimed to APO-go Ampoules 10mg/ml Solution for Injection (PL 05928/0020), first authorised in the UK on 10th August 1993 and also to APO-go Pen 10mg/ml Solution for Injection (PL 05928/0021)

The product is half the strength of the existing formulations and originally contained significantly less sodium metabisulphite (apparently a likely cause of tissue irritation / pathology) with the introduction of the excipient ascorbic acid.

During the application process, this has changed because of oxidation problems during stability testing: the ascorbic acid has been removed, the sodium metabisulphite increased to the same as the reference products and sodium chloride has been added.

The legal status is POM. The applicant intends to proceed to MR.

Apomorphine hydrochloride is a morphine derivative with structural similarities to dopamine. It is a potent dopamine agonist and is used in the diagnosis and management of Parkinsonism, especially in the control of the 'on-off' effect. It is only available for treating Parkinson's disease in parenteral formulations.

It is highly emetogenic.

INDICATIONS

The UK approved indication in the SPC is:

The treatment of disabling motor fluctuations ("on-off" phenomena) in patients with Parkinson's disease which persist despite individually titrated treatment with levodopa (with a peripheral decarboxylase inhibitor) and/or other dopamine agonists.

Medical Assessor's Comment: The text is the same as that of the reference product's SPC.

DOSE & DOSE SCHEDULE

The UK approved dosage regimen is:

APO-go PFS 5mg/ml Solution for Infusion in Pre-filled Syringe is a pre-diluted pre-filled syringe intended for use as a continuous subcutaneous infusion by minipump and / or syringe-driver.

Apomorphine must not be used via the intravenous route.

Dosage

Adults

Administration

Selection of Patients Suitable for APO-go:

Patients selected for treatment with APO-go should be able to recognise the onset of their 'off' symptoms and be capable of injecting themselves or else have a responsible carer able to inject for them when required.

It is essential that the patient is established on domperidone, usually 20 mg three times daily for at least two days prior to initiation of therapy.

Apomorphine should be initiated in the controlled environment of a specialist clinic. The patient should be supervised 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 APO-go treatment.

Continuous Infusion

Patients who have shown a good 'on' period response during the initiation stage of apomorphine therapy, 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 driver (see Section 6.6 Instruction for Use/Handling) as follows:-

The threshold dose for continuous infusion should be determined as follows: Continuous infusion is started at a rate of 1 mg apomorphine HCl (0.2 ml) per hour then increased according to the individual response each 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 advised. Tolerance to the therapy does not seem to occur as long as there is an overnight period without treatment of at least 4 hours. In any event, the infusion site should be changed every 12 hours.

Patients may need to supplement their continuous infusion with intermittent bolus boosts, as necessary, and as directed by their physician.

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

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, remains relatively constant for each patient.

Precautions on continuing treatment

The daily dose of APO-go varies widely between patients, typically within the range of 3-30 mg.

It is recommended that the total daily dose of apomorphine HCl should not exceed 100 mg.

In clinical studies it has usually been possible to make some reduction in the dose of levodopa; this effect varies considerably between patients and needs to be carefully managed by an experienced physician.

Once treatment has been established domperidone therapy may be gradually reduced in some patients but successfully eliminated only in a few, without any vomiting or hypotension.

Children and adolescents

APO-go PFS 5mg/ml Solution for Infusion in Pre-filled Syringe is contra-indicated for children and adolescents under 18 years of age (see Section 4.3 Contraindications).

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 APO-go. The management of elderly patients treated with APO-go has not differed from that of younger patients. However extra caution is recommended during initiation of therapy in elderly patients because of 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 Special Warnings and Precautions for Use).

Medical Assessor's Comments: This is in line with the dosage instructions for existing APO-go injectable products.

TOXICOLOGY

A pharmaco-toxicological expert report is included and has been commented upon by the appropriate assessor.

CLINICAL PHARMACOLOGY

No new pharmacological data have been submitted. This product is a solution. There is no need for determining the bioavailability or showing bioequivalence, the subcutaneous route providing 100% bioavailability.

The clinical expert refers back to the clinical expert report submitted in 1999 for APO-go Pen 10mg/ml Solution for Injection (PL 05928/0021).

EFFICACY

No new clinical data have been submitted with this application. The clinical expert again makes reference to the clinical expert report submitted in 1999 for APO-go Pen 10mg/ml Solution for Injection (PL 05928/0021) and also an addendum submitted with the clinical expert report for APO-go Ampoules, 10mg/ml (PL 05928/0020).

SAFETY

The adverse effects of apomorphine are predictable from the pharmacological actions of the drug. Nausea and vomiting, the most frequent may be controlled by domperidone.

The formulation has been changed, twice, from that of the reference product and the argument that the clinical expert provided regarding the likelihood of less tissue irritancy may not still apply. The sodium metabisulphite excipient has been restored to the original formulation's concentration and the ascorbic acid removed.

The current composition is tabulated below:

Active	Function	Quantity	Reference monograph
Apomorphine Hydrochloride	Active	0.5% w/v	Ph Eur
Excipients			
Sodium metabisulphite	Antioxidant	0.05% w/v	Ph Eur
Hydrochloric acid	To adjust pH	QS	Ph Eur
Nitrogen	To prevent oxidation	QS	Ph Eur
Water for Injection	Diluent	To 100% v/v	Ph Eur

EXPERT REPORT

A suitable clinical expert report has been submitted and is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

Clinically satisfactory

PATIENT INFORMATION LEAFLET

Clinically satisfactory

LABELLING

Clinically satisfactory

RECOMMENDATION

A marketing authorisation may be granted.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT QUALITY

The important quality characteristics of APO-go 5mg/ml Solution for Infusion in Pre-Filled Syringe is well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

The preclinical sections are based on a higher strength of this product: APO-go ampoules 10mg/ml already licensed in the UK. The rationale for the proposed formulation is that with this lower strength formulation, the amount of sodium metabisulphite can be reduced from 0.1% to 0.05% thus lowering its potential to cause irritation and local cutaneous reactions. The proposed formulation is likely to be less irritating than the higher strength APO-go ampoules 10mg/ml.

EFFICACY

No new clinical data have been submitted with this application and the Clinical Expert makes reference to the clinical expert report submitted in 1999 for APO-go Pen 10mg/ml Solution for Injection (PL 05928/0021) and also an addendum submitted with the clinical expert report for APO-go Ampoules, 10mg/ml (PL 05928/0020).

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory.

The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with apomorphine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome
28 th September 2008	Type IB variation	To introduce two new pack sizes i.e. 'bundle packs' of 25 and 50 to the product licence. The bundle pack will contain 5 packs of 5 pre-filled syringes or 10 packs of 5 pre-filled syringes. The new bundle packs are introduced in Austria and Germany only. Section 6.5 of the SPC and leaflet are updated as a result.	Granted on 12th November 2008