Summary of Product Characteristics

1. Name of the Medicinal Product

APO-go AMPOULES 10 mg/ml Solution for Injection or Infusion
**** Abbreviated to* APO-go *in the text***

2. Qualitative and Quantitative Composition

1 ml contains 10 mg apomorphine hydrochloride
2 ml contains 20 mg apomorphine hydrochloride
5 ml contains 50 mg apomorphine hydrochloride

Excipient(s) with known effect:
Sodium metabisulphite (E223) 1mg per ml

For the full list of excipients, see Section 6.1.

3. Pharmaceutical Form

Solution for Injection or Infusion.
Clear, colourless or almost colourless, practically free from visible particles.

pH 3.0-4.0.

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 injections:

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.

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).

Refer to the domperidone prescribing information for recommended domperidone dosage information.

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.

Posology

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:

Continuous infusion is started at a rate of 1 mg apomorphine HCl (0.1 ml) per hour, then increased according to the individual response. Increases in the infusion rate should not exceed 0.5 mg per hour at intervals of not less than 4 hours. Hourly infusion rates may range between 1 mg and 4 mg (0.1 ml and 0.4 ml), equivalent to 0.015 - 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.

Determination of the threshold dose

The appropriate dose for each patient is established by incremental dosing schedules. The following schedule is suggested:

1 mg of apomorphine HCl (0.1 ml), that is approximately 15-20 micrograms/kg, may be injected subcutaneously during a hypokinetic or 'off' period and the patient is observed over 30 minutes for a motor response.

If no response, or an inadequate response, is obtained, a second dose of 2 mg of apomorphine HCl (0.2 ml) is injected subcutaneously and the patient observed for an adequate response for a further 30 minutes.

The dosage may be increased by incremental injections with at least a forty-minute interval between succeeding injections, until a satisfactory motor response is obtained.

Establishment of treatment

Once the appropriate dose is determined, a single subcutaneous injection may be given into the lower abdomen or outer thigh at the first signs of an 'off' episode. It cannot be excluded that absorption may differ with different injection sites within a single individual. Accordingly**,** the patient should then be observed for the next hour to assess the quality of their response to 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, given as 1-10 injections and sometimes as many as 12 separate injections per day.

It is recommended that the total daily dose of apomorphine HCl should not exceed 100 mg and that individual bolus injections should not exceed 10 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.

Paediatric population

APO-go Ampoules 10 mg/ml Solution for Injection or Infusion is contraindicated 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).

Method of administration

APO-go Ampoules 10 mg/ml Solution for Injection or Infusion is for subcutaneous use by intermittent bolus injection. APO-go Ampoules 10 mg/ml Solution for Injection or Infusion may also be administered as a continuous subcutaneous infusion by minipump and/or syringe-driver (see Section 6.5).

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.

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.

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1. APO-go should not be administered to patients who have a known hypersensitivity to apomorphine or any excipients of the medicinal product.

The concomitant use of apomorphine with ondansetron is contraindicated (see Section 4.5).

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

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.

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

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.

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 episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution whilst driving or operating machines during treatment with apomorphine. Patients who have experienced somnolence and/or an episode of sudden sleep onset 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, 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.

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.

APO-go Ampoules 10 mg/ml Solution for Injection or Infusion 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., is 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 medications for their Parkinson's disease. In the initial

stages of apomorphine HCl therapy, the patient should be monitored for unusual side-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).

Concomitant use of apomorphine with ondansetron may lead to severe hypotension and loss of consciousness and is therefore contraindicated (see section 4.3). Such effects might also occur with other 5-HT3 antagonists.

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 Drugs

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. Pregnancy and lactation

Pregnancy

There is no experience of apomorphine usage in pregnant women.

Animal reproduction studies do not indicate any teratogenic effects, but doses given to rats which are toxic to the mother can lead to failure to breathe in the newborn. The potential risk for humans is unknown. See Section 5.3.

APO-go should not be used during pregnancy unless clearly necessary.

Breastfeeding

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 APO-go should be made taking into account the benefit of breastfeeding to the child and the benefit of APO-go to the woman.

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 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:

Haemolytic anaemia and thrombocytopenia have been reported in patients treated with 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

Very common:

Hallucinations

Common:

Neuropsychiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine HCl therapy.

Not known:

Impulse control disorders: Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including apomorphine (see Section 4.4).

Aggression, agitation.

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.

Dizziness/light-headedness have also been reported.

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.

Apomorphine has been associated with sudden sleep onset episodes (see also Section 4.4).

Unknown:
Syncope
Headache

Vascular disorders
Uncommon:
Postural hypotension is seen infrequently and is usually transient (see Section 4.4).

Respiratory, thoracic and mediastinal disorders
Common:
Yawning has been reported during apomorphine therapy.

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
Uncommon:
Local and generalised rashes have been reported.

General disorders and administration site conditions
Very common:
Most patients experience injection site reactions, particularly with continuous use. These may include subcutaneous nodules, induration, erythema, tenderness and panniculitis. Various other local reactions (such as irritation, itching, bruising and pain) may also occur.

Uncommon:
Injection site necrosis and ulceration have been reported.

Not known:
Peripheral oedema has been reported.

Investigations
Uncommon:
Positive Coombs' tests have been reported for patients receiving 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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

https://sideeffects.health.gov.il.

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

Pharmacotherapeutic group: Dopamine agonists
ATC Classification: N04B C07

Apomorphine is a direct stimulant of dopamine receptors and, while possessing both D_1 and D_2 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

Distribution and elimination

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.

Absorption

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.

The effect of apomorphine on reproduction has been investigated in rats. Apomorphine was not teratogenic in this species, but it was noted that doses which are toxic to the mother can cause loss of maternal care and failure to breathe in the newborn.

No carcinogenicity studies have been performed.

6. Pharmaceutical Particulars

6.1. List of excipients

Sodium metabisulphite (E223)
Hydrochloric acid, concentrated (for pH adjustment)

Sodium hydroxide (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. Special precautions for storage

Do not store above 25ºC.

Store in the original package in order to protect from light.

Once opened, use immediately. Discard any unused contents.

6.4. Nature and contents of container

Type I glass ampoules containing 2ml Solution for Injection or Infusion, in packs of 5 ampoules.
Type I glass ampoules containing 5ml Solution for Injection or Infusion, in packs of 5 ampoules.

The ampoules are contained in a plastic tray within a cardboard carton.

6.5. Special precautions for disposal

Do not use if the solution has turned green.

The solution should be inspected visually prior to use. Only clear and colourless solutions should be used.
For single use only. Any unused solution should be discarded.

Continuous infusion and the use of a minipump and/or syringe-driver

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.

7. Registration Number

128.26.30682.00.

8. Manufacturer

Britannia Pharmaceuticals Limited, UK.

9. Licence Holder

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The leaflet was revised in March 2024 according to MOH guidelines.