

APOMORPHINE In Parkinson's Disease

INTRODUCTION

Summary:

Apomorphine is a potent, rapid-acting dopamine agonist that is licensed for the treatment of motor fluctuations ('on-off' phenomena) in patients with Parkinson's disease (PD) which are not sufficiently controlled by oral anti-Parkinson medication.^{1,2,3}

Apomorphine can be administered as subcutaneous bolus injection or as continuous infusion via a portable syringe driver depending on the number of off periods per day. The patient must be established on domperidone for three days prior to initiation of therapy to prevent the significant emetic effect.

NICE CG 35⁴ and SIGN 113⁵ recommend apomorphine as an option in later PD to reduce 'off' time in patients with severe motor complications whereby the initiation should be restricted to expert units with facilities for appropriate monitoring.

MTRAC⁶ in 2002 state that there are no contraindications to GPs routinely monitoring PD patients and prescribing apomorphine for them if the drug is used within its licensed indications, with guidance of a shared care protocol and necessary support from hospital specialists.

Intermittent subcutaneous apomorphine provides prompt and consistent rescue from 'off' episodes. The duration of effect is relatively short (up to 100 minutes).

A number of small, non-randomised, mainly retrospective studies indicates that continuous apomorphine infusions may reduce dyskinesias and increase 'on' time in patients with severe motor fluctuations.⁵

BACKGROUND^{7,8,9}

Parkinson's disease (PD) is a progressive neurological disorder that results from the loss of dopaminergic neurones in the substantia nigra. PD is characterised by motor and non-motor symptoms. The main motor features are rigidity, tremor, bradykinesia and hypokinesia. Non-motor symptoms include: neuropsychiatric conditions (e.g. dementia, depression and hallucinations), autonomic disturbances (e.g. constipation, postural hypotension), sleep disorders and sensory symptoms (such as pain).

In the UK there are approximately 60,000–108,000 people affected by PD (based on a prevalence of 100–180 per 100,000). The annual incidence in the UK is between four and 20 per 100,000 people. The average age of onset is 65 years. Young-onset PD, defined as appearance of the condition under the age of 40 years, accounts for about 5–10% of all cases.

Management of PD focuses on relieving the motor and non-motor symptoms of the condition thereby improving patient's quality of life. Most treatments for the motor symptoms work by increasing dopamine in the central nervous system. First choice options for initial pharmacotherapy are levodopa in combination with a dopa-decarboxylase inhibitor, dopamine agonists (preferably non-ergot-derived) and monoamine-oxidase-B (MAO-B) inhibitors.

Over time response to initial treatments will decline; patients experience 'off time', which manifests as akinesia and rigidity. In addition, motor complications, such as dyskinesia and dystonia, occur at peak serum levels. Patients can fluctuate rapidly or erratically between these two states ('on-off' phenomenon). Wearing off can be countered by amending dosing regimens. If these measures fail, combinations of drugs will be necessary. Adjuvant drugs to take alongside

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levodopa in later PD are dopamine agonists, MAO-B inhibitors and Catechol-O-methyltransferase (COMT) inhibitors.

Despite optimal management some patients' disease progresses such that dyskinesia and 'off' periods become unmanageable and conventional treatment is ineffective. For such patients, management options are subcutaneous apomorphine or non-pharmacological options.

THERAPEUTIC CLASS AND MODE OF ACTION^{1,8}

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. It is administered subcutaneously to avoid extensive first-pass metabolism. Apomorphine has a rapid onset of action (5-15 minutes) and a short duration of action (up to 100 minutes).

LICENSED INDICATION^{1,2,3}

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

GUIDANCE

NICE CG 35⁴ 'Parkinson's disease Diagnosis and management in primary and secondary care' recommends apomorphine as an option for adjuvant pharmacotherapy in later PD. Intermittent apomorphine injections may be used to reduce 'off' time in people with PD with severe motor complications.

Continuous subcutaneous infusions of apomorphine may be used to reduce 'off' time and dyskinesia in people with PD with severe motor complications. Its initiation should be restricted to expert units with facilities for appropriate monitoring.

MTRAC⁶ in 2002 states the following: GPs routinely manage the treatment of patients with PD. Apomorphine is currently only licensed for hospital initiation. If used within its licensed indications, with guidance of a shared care protocol and necessary support from hospital specialists, there are no contraindications to GPs routinely monitoring these patients and prescribing this preparation for them.

EFFICACY^{5,9}

The evidence base for the use of both intermittent injections and continuous infusions of apomorphine is relatively poor, but both techniques are licensed for use in England and Wales. The NICE guideline development group considered these to be useful treatments for people with severe 'off' periods that are not responsive to changes in oral medication. However, as with other dopaminergic medication, there is a risk of triggering serious adverse effects such as confusion and hallucinations. In addition, the risk of injection-site reactions is considerable.

A systematic review of RCTs indicated that intermittent subcutaneous apomorphine (dose range 2 to 6 mg), provides rapid and consistent rescue from 'off' episodes. The duration of effect is relatively short (up to 100 minutes).

No RCTs of continuous subcutaneous infusions were identified but a number of small, non-randomised, mainly retrospective studies indicated that continuous apomorphine infusions may reduce dyskinesias and increase 'on' time in patients with severe motor fluctuations. Infusion therapy is associated with a risk of serious adverse events and requires adequate back-up resources.

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DOSE AND ADMINISTRATION^{1,2,3}

It is essential that the patient is established on domperidone, 10(-20) mg three times daily, for three days prior to initiation of therapy. Once treatment has been established, domperidone may be gradually reduced in some patients. Initial supply of domperidone is organised through WVT.

In 2014 the MHRA¹⁰ issued updated drug safety advice on the use of domperidone due to a small increased risk of serious cardiac side effects. Updated contraindications include conditions with impaired cardiac induction, underlying cardiac disease, patients receiving other medication known to prolong QT interval or potent CPY3A4 inhibitors and severe hepatic impairment. All patients will have an ECG performed by the PD specialist team prior to treatment with domperidone/apomorphine.

Apomorphine should be initiated in the controlled environment of a specialist clinic under the supervision of a physician experienced in the treatment of PD. The patient's treatment with levodopa, with or without dopamine agonists, should be optimised before starting APO-go® treatment.

Apomorphine must not be given via the intravenous route. The solution should be inspected visually prior to use and must be discarded if it has turned green. Only clear, colourless and particle free solution should be used.

Apomorphine injections

Refer to the Summary of Product Characteristics (see References for links) when considering patient clinical suitability to receive and manage apomorphine treatment.

Selection of patients suitable for APO-go® injections

Patients 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, 20mg three times daily for three 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.

Determination of the threshold dose (Response Test)

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

1mg of apomorphine (approx. 15-20mcg/kg) may be injected subcutaneously during a hypokinetic or 'off' period and the patient is observed over 30min for a motor response. If no or inadequate response a second dose of 3mg of apomorphine is injected and the patient observed for an adequate response for a further 30min. A further dose of 5mg can be given or the dosage may be increased by incremental injections with at least a 40min interval between succeeding injections, until a satisfactory motor response is obtained.

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Establishment of treatment

Once the appropriate dose is determined, a single subcutaneous injection may be given into the lower abdomen, outer thigh or upper arm (off-label) 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 varies between individuals but, once established, remains relatively constant for each patient.

Continuous apomorphine infusion

Patients who have shown a good 'on' period response during the initiation stage, but whose overall control remains unsatisfactory using intermittent injections, or who require many and frequent injections (>10/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 1mg/h then increased according to the individual response. For patients on intermittent therapy the continuous infusion may be initiated based on the bolus doses previously required. Increases in the infusion rate should not exceed 0.5mg/h at intervals of not less than 4 hours. 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.

Precautions on continuing treatment

The daily dose of APO-go® varies widely between patients, typically within the range of 3-30mg, given as continuous infusion or as 1-10 injections and sometimes as many as 12 separate injections per day. It is recommended that the total daily dose of apomorphine should not exceed 100mg and that individual bolus injections should not exceed 10mg.

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.

Elderly

The elderly are well represented in the population of PD patients and constitute a high proportion of those studied in clinical trials of APO-go®. Their management has not differed from that of younger patients. However, extra caution is recommended during initiation of therapy because of the risk of postural hypotension.

PRESENTATION

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. The pre-filled syringes are for single use only and any unused solution should be discarded.¹

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APO-go® PEN 10mg/ml Solution for Injection is for subcutaneous use by intermittent bolus injection. It is supplied as a disposable multiple dose pen injector system. Each pen contains 3ml of solution for injection. Discard each APO-go Pen no later than 48 hours after first use.²

APO-go® AMPOULES contain a **10mg/ml solution for injection or infusion** in 5ml glass ampoules.³ The product is suitable for subcutaneous use by intermittent bolus injection as well as a continuous subcutaneous infusion by minipump and/or syringe-driver.

The apomorphine solution in APO-go® products is clear, practically colourless, odourless, practically free from visible particles and has a pH 3.0-4.0. Apomorphine should be stored at room temperature (at or below 25°C) and protected from light^{1,2,3}

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.^{1,2,3}

ADVERSE EFFECTS^{1,2,3}

Very common (≥1/10): Injection site reactions, particularly with continuous use.

Common (≥1/100 to <1/10): Neuropsychiatric disturbances (incl. transient mild confusion and visual hallucinations), transient sedation with each dose at the start of therapy (usually resolving over first few weeks), somnolence, dizziness, yawning, nausea and vomiting (particularly on treatment initiation).

Uncommon (≥1/1,000 to <1/100): Postural hypotension (usually transient), sudden sleep onset episodes, breathing difficulties.

Refer to the Summary of Product Characteristics (see References for links) for a full list of adverse effects.

CAUTIONS^{1,2,3}

Driving: Patients on apomorphine presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death until such recurrent episodes and somnolence have resolved.

Overdose: Symptoms may be treated empirically: e.g. excessive emesis with domperidone, respiratory depression with naloxone, bradycardia with atropine, appropriate measures for hypotension.

Drug interactions:

Neuroleptics 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 neuroleptics have to be used in patients treated by dopamine agonists, a gradual reduction in apomorphine dose may be considered when administration is by minipump and/or syringe-driver.

Drugs that act on the cardiovascular system including antihypertensives: Even when co-administered with domperidone, apomorphine may potentiate the antihypertensive effects of these medicinal products.

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

For additional information on drug interactions refer to the Summary of Product Characteristics (Refer to References for links).

CONTRAINDICATIONS^{1,2,3}

Respiratory depression, dementia, psychotic diseases or hepatic insufficiency; 'on' response to levodopa which is marred by severe dyskinesia or dystonia; hypersensitivity to active ingredient/excipients; children and adolescents under 18 years.

MONITORING STANDARDS FOR WYE VALLEY NHS TRUST		
Pre-treatment Monitoring	Coombs' test, full blood count, blood pressure, ECG	
Subsequent Monitoring	Full blood count	4-6 monthly intervals
	Blood pressure	4-6 monthly intervals, during initiation and any dose titration
	Coombs' test	6-12 months
Dosage	All adjustments to dosage to be made under the advice of the PD specialist team	

ACTION AND ADVICE FOR GP'S IN RESPONSE TO BLOOD MONITORING/SIDE-EFFECTS

Blood Test Results	Action
Full blood count/Coomb's test: abnormal/positive	Refer to specialist team
Blood pressure: abnormal readings	Refer to specialist team
Symptoms	Action
Parkinson's disease symptom control not adequately controlled e.g. motor performance, patient/carer unable to administer drug	Refer to specialist team
Adverse effects such as hallucinations, confusion, psychosis etc.	Refer to specialist team
Signs/symptoms of depression	Refer to specialist team
Skin problems at injection site	Refer to specialist team

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SHARED CARE RESPONSIBILITIES

Consultant and/or Specialist Nurse

1. Initiate treatment and supply the first month of treatment or until the patient is stabilised (this includes supply of domperidone)
2. Send a letter to the GP requesting shared care for this patient.
3. Routine clinic follow-up on a regular basis.
4. Send a letter to the GP after each clinic attendance ensuring current dose, most recent blood results and frequency of monitoring are stated.
5. Evaluate any reported adverse effects by GP or patient.
6. Advise GP on review, duration or discontinuation of treatment where necessary.
7. Inform GP of patients who do not attend clinic appointments.
8. Ensure that backup advice is available at all times.

General Practitioner

1. Monitor patient's overall health and well being.
2. Prescribe the drug treatment as described.
3. Monitor blood results (where appropriate) in line with recommendations from hospital specialist.
4. Report any adverse events to the hospital specialist, where appropriate.
5. Help in monitoring the progression of disease.
6. GP may adjust the dose of domperidone if necessary

Ancillary products/apparatus^{11,12}

- a. APO-go® Pens can be prescribed on FP10 in multiples of 5 (original packs). An initial supply may have been issued by the hospital. This is a disposable multiple dose injector system incorporating a clear glass cartridge and supplies of Novofine® Needles for use with the Pen will be made free of charge with the Pens.
- b. APO-go® pre-filled syringe for use with the APO-go® syringe driver for continuous subcutaneous infusion. It is a pre-diluted syringe that will need to be prescribed on FP10 along with Neria infusion sets (line plus needle plus dressing). Details of the Neria line/Neria SC infusion sets (packs of 10) required will be specified by the PD specialist team.

CONTACT NUMBERS FOR ADVICE AND SUPPORT

Wye Valley NHS Trust	
Dr Emma Wales, Consultant	emma.wales@wvt.nhs.uk 01432 355444
Caroline Evans, Parkinson's Disease Clinical Nurse Specialist	caroline.evanspd@nhs.net 01432 378935
Medicines Information, Wye Valley NHS Trust	ruth.bader@wvt.nhs.uk joanne.howe@wvt.nhs.uk 01432 364017
Apo-go Helpline	0844 8801327

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REFERENCES

- 1 APO-go PFS 5mg/ml Solution for Infusion in Pre-filled Syringe. Britannia Pharmaceuticals Limited. Summary of Product Characteristics. Updated 14/02/13.
<http://www.medicines.org.uk/emc/medicine/15992>
- 2 APO-go Pen 10mg/ml Solution for Injection. Britannia Pharmaceuticals Limited. Summary of Product Characteristics. Updated 04/12/14.
<http://www.medicines.org.uk/emc/medicine/12941>
- 3 APO-go Pen AMPOULES 10mg/ml Solution for Injection or Infusion. Britannia Pharmaceuticals Limited. Summary of Product Characteristics. Updated 04/12/14.
<http://www.medicines.org.uk/emc/medicine/12942>
- 4 NICE CG 35. Parkinson's disease. Diagnosis and management in primary and secondary care. June 2006. Accessed via
<http://www.nice.org.uk/nicemedia/live/10984/30088/30088.pdf> 10/09/1.
- 5 Scottish Intercollegiate Guidelines Network. SIGN 113: Diagnosis and pharmacological management of Parkinson's disease. A national clinical guideline (January 2010). Accessed via <http://www.sign.ac.uk/pdf/SIGN113.pdf> 10/09/14.
- 6 Midlands Therapeutics Review & Advisory Committee. Verdict and Summary Sheet for Apomorphine (APO-go®) for the treatment of Parkinson's Disease. November 2002. Accessed via
<http://centreforoptimisation.co.uk/download/59cdc588145409532cd9cab6e6042083/Apomorphine-for-Parkinsons-Verdict-Nov-02.pdf> 10/09/2014.
- 7 Blochberger A, Jones S. Parkinson's disease - clinical features and diagnosis. Clin Pharmacist 2011; 3: 361-366.
- 8 Kearney D, Dunsmure L. Parkinson's disease – management. Clin Pharmacist 2011; 3: 368-373
- 9 National Collaborating Centre for Chronic Conditions. Parkinson's disease: national clinical guideline for diagnosis and management in primary and secondary care. London: Royal College of Physicians, 2006. Accessed via
<http://www.nice.org.uk/nicemedia/live/10984/30087/30087.pdf> 10/09/2014
- 10 Drug Safety Update volume 7 issue 10, May 2014: A1
<http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON418518> [Accessed on 10/09/14]
- 11 Joint Formulary Committee. *British National Formulary* (online) London: BMJ Group and Pharmaceutical Press <<http://www.medicinescomplete.com>> [Accessed on 10/09/14]
- 12 <http://www.apo-go.co.uk>. Accessed 10/09/2014

This document should be read in conjunction with the BNF:
<http://evidence.nhs.uk/formulary/bnf/current>, the Summary of Product Characteristics:
<https://www.medicines.org.uk/emc/> and relevant NICE guidance <http://www.nice.org.uk/>