Apomorphine

Traffic light classification- Amber 1
Information sheet for Primary Care Prescribers

CLINICAL INFORMATION

Key points

- Patients should be pre-treated with domperidone (10mg tds) for at least 2 days before starting on apomorphine **(see MHRA advice below)**.
- Patients using apomorphine by intermittent injection usually need to continue their other medications as before, whereas those on continuous subcutaneous infusions can commonly reduce their other treatments considerably.
- Adjustments to the dosage and route of injection of apomorphine will be made in secondary care. Patients on apomorphine all have telephone access to relevant Parkinsons Disease Nurse Specialists.

Licensed Indications
Apomorphine is licensed for use in refractory motor fluctuations in Parkinson's disease ('off' episodes) inadequately controlled by levodopa with dopa-decarboxylase inhibitor or other dopaminergics (for capable and motivated patients under specialist supervision).

Therapeutic Summary
As per the licensed indication.

NICE recommendations for the use of apomorphine in Parkinson's disease conclude that:

- Intermittent apomorphine injections may be used to reduce off time in people with PD with severe motor complications. (Evidence level B)
- Continuous subcutaneous infusions of apomorphine may be used to reduce off time and dyskinesias in people with PD with severe motor complications. Its initiation should be restricted to expert units with facilities for appropriate monitoring. (Evidence level D)

Medicines Initiation
Consultant neurologist / specialist experienced in the management of PD.

- The patient's treatment with levodopa, with or without dopamine agonists, should be optimised before starting apomorphine.
- Establish patient on Domperidone. In line with the MHRA 2014 recommendations this should be under the following conditions:
  1. The dose is 10mg tds maximum and should be started at least 2 days before starting treatment with Apomorphine
  2. The duration of treatment should not typically exceed 7 days in total
  3. That if patients are receiving medications known to prolong the QT interval (See Appendix 3 and http://www.sads.org.uk/drugs-to-avoid/), or if the patient has a history of cardiac rhythm disturbance or underlying cardiac disease, such as congestive cardiac failure that an ECG is performed prior to starting therapy

4. That concurrent treatment with potent CYP3A4 enzyme inhibiting drugs should be avoided with Domperidone (see Appendix 3)
5. That Domperidone is not given to patients identified in category 3 who have an abnormal ECG, including prolongation of the corrected QT interval.
6. That any patient receiving domperidone is given advice to seek prompt medical attention if symptoms such as syncope or palpitations develop during treatment
7. If symptomatic nausea occurs after 7 days, patients will have an ECG performed to confirm that the QT is not prolonged before a domperidone prescription is re-issued.

- The first dose of apomorphine should be given in the controlled environment of a specialist clinic to establish efficacy, tolerability and appropriate dosage for an adequate patient response. The threshold dose will be determined by the specialist using incremental dosing schedules. Typically, this will performed in our day case unit at the Queens Medical Centre.
- For patients requiring continuous subcutaneous infusions, a specialist nurse will assist in the initiation and titration of the patient's dose, and train the patient and / or carer / district nurse on how to setup the infusion.

Dose Regimen and route of administration
Apomorphine can be administered by either continuous subcutaneous infusion or by intermittent subcutaneous injection.

Maximum daily dose by either route is 100 mg.
If administered by intermittent injection the range is typically 1-10 injections. Each bolus dose should not be more than 10 mg. Continuous subcutaneous infusion would usually be considered if the patient experiences so many 'off' periods that repeated bolus injections are inappropriate (> 10 per day).
Hourly infusion rates are typically 1 – 4 mg per hour (but may be higher, dependent upon individual response) and should normally run for waking hours only. Once the optimal dose for an individual patient has been determined and the patient is stable, the dose is likely to remain relatively constant

Products available
Brand prescribing of apomorphine products is encouraged to prevent confusion and to ensure correct formulation is prescribed. Products available for use are listed in the table below:

Product	Pack size	Cost*	Reconstitution required	Expiry once in use
APO-go® PFS 5mg/ml solution for infusion in pre-filled syringe • Available as 50mg/10ml pre-filled syringe	5	£73.11	No	Single use only. Unused solution should be discarded within 24 hours
Dacepton® 5mg/ml solution for infusion • Available as 100mg/20ml vial	5	£145.00	No	7 days
APO-go® pen 10mg/ml solution for injection	5	£123.91	No	48 hours

• Available as 30mg/3ml pre-filled pen				
Dacepton® 10mg/ml solution for injection cartridges • Available as 30mg/3ml cartridge to be used with D-Mine Pen	5	£123.00	No	15 days
APO-go® ampoules 10mg/ml solution for injection or infusion • Available as 50mg/5ml ampoule • rarely used within Nottinghamshire due to additional risks of dilution	5	£73.11	It is recommended to dilute 50:50 with 0.9% normal saline or water for injection resulting in 5mg/ml strength, to reduce skin complications (i.e. subcutaneous nodules which can develop.	Single use only. Unused or diluted solution should be discarded within 24 hours

***cost correct from NHSBSA Drug Tariff April-20**

Duration of treatment
Apomorphine therapy is a treatment for a chronic disease and therefore course length can be many years. It is used in late-stage Parkinson's disease and some patients have received apomorphine for >5 years.

Contraindications
- Respiratory depression
- Dementia
- Psychotic diseases
- Hepatic insufficiency
- Patients who have an 'on' response to levodopa, which is marred by severe dyskinesia or dystonia.
- Children and adolescents under 18 years of age.
- Known hypersensitivity to apomorphine or any of the excipients of the medicinal product.
- Pregnancy and lactation (See section 4.6 of the Apomorphine Summary of Product Characteristics).

Precautions
- Renal, pulmonary, cardiovascular disease
- Patients prone to nausea & vomiting
- Pre-existing neuropsychiatric conditions
- Pre-existing postural hypotension

Monitoring
Haematological testing (full blood count, reticulocyte count and Coombs test) will be carried out in secondary care prior to and following initiation of apomorphine as appropriate.

Adverse Effects

Side Effects	**Action**
Localised discomfort at needle site	Rotate injection site daily

Nodule formation at needle or infusion site	Usually asymptomatic. Rotate injection site. May persist in pts on high doses. See appendix one. Severe nodule formation may lead to worsening of symptoms due to erratic absorption of Apomorphine. Discuss with neurologist/PD nurse specialist (PDNS) in this instance.
Local infection/abscess/ulceration/scarring	Discuss with neurologist/PDNS
Nausea & vomiting	Usually transient
Sedation	Usually transient. Advise patients not to drive / operate machinery if affected. If persists discuss with neurologist/ PDNS
Orthostatic hypotension	Usually transient
Light-headedness	Discuss with neurologist/ PDNS
Dyskinesias during 'On' periods	Discuss with neurologist/ PDNS
Coomb's positive Haemolytic anaemia	Discuss with neurologist/ PDNS
Eosinophilia	Discuss with neurologist/ PDNS
Neuropsychiatric complications – hallucinations, euphoria, increased libido, confusion, personality changes, agitation, restlessness, psychosis, sleep disturbance	Discuss with neurologist/ PDNS
Allergic reactions including bronchospasm and anaphylaxis (due to sodium bisulphite)	Withhold and discuss with neurologist/ PDNS

Patients, carers and hospital and community nurses should be made aware that apomorphine when spilt on clothes and most surfaces will leave a permanent olive green stain which is almost impossible to remove. The immediate use of lemon juice can be of some use to avoid permanent stains.

Clinically relevant medicine interactions and their management
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 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.
- **Antihypertensive and Cardiac Active Medicinal Drugs**
  Even when co-administered with domperidone, apomorphine may potentiate the antihypertensive effects of these drugs. Caution should be used in patients taking vasoactive medicinal products such as antihypertensives, especially in patients with pre-existing postural hypotension.
- The possible effects of apomorphine on the plasma concentrations of other drugs have not been studied. Therefore caution is advised when combining apomorphine with other drugs, especially those with a narrow therapeutic range.

Information given to patient
Audio visual and written literature for patients, showing practical advice on using apomorphine and frequently asked questions, will be provided by secondary care as per responsibilities.

NEEDLES, TUBING and PUMPS

Although the manufacturers loan infusion pumps to patients on apomorphine, the tubing and needles for infusion must be prescribed separately. The Neria® lines made by Unomedical are recommended and have been stability tested with APO-go® and Dacepton®. These lines have an attached needle with an adhesive patch which makes it easy for patients to insert the needle at the correct angle.

Batteries for Apo-go pumps should be changed approximately every 6 months and a spare will be supplied by Britannia when the pump is issued. In the event of any malfunction or concerns with the Apo-go pump, Britannia should be contacted via their 24 hour helpline (0844 8801327).

Two rechargeable batteries with a charging docking station is supplied by Ever Pharma UK Ltd for the D-Mine pump. The battery life is 6 days, however it is recommended that the battery is changed every day, so full charge is available. An 80% battery charge is required to fill the reservoir. In the event of any malfunction on concerns with D-Mine pump, Ever Pharma should be contacted via their 24 hours support line (0800 2540175).

Storage

Do not store above 25°C. Store in the original package. 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.

An estimate of the number of patients affected

Apomorphine is typically indicated in 1% of the total PD population. This would equate to approximately 18 patients locally.

An estimate of the potential medicine costs (and any additional costs) to primary care

See appendix two

REFERENCES

British National Formulary, April 2020
NHSBSA Drug Tariff, April 2020
Apo-go® Summary of Product Characteristics, last updated July 18
Dacepton® Summary of Product Characteristics, last updated November 18
NICE NG71 Parkinson's Disease in Adults, July 2017
Medicines and Healthcare products Regulatory Agency. Domperidone: risks of cardiac side effects. Drug Safety Update. 2014; 7(10).

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Appendix One

At the moment there are no proven effective strategies to reduce or prevent nodules from occurring (Hagell & Odin 2001). However, the following may be of benefit:

Practical advice on how to reduce nodule formation:

- Ensure a clean aseptic technique.
- Good insertion technique is essential. The needle should be inserted at a 45 degree angle to the horizontal plane when sited in the abdomen, and at a 45 degree angle to the vertical plane when sited in the thigh.
- If possible minimise the number of people involved in setting up the infusion. The more people who are involved, the more likely it is that quality of the insertion technique will vary.
- It is crucial that the needle site is rotated daily.
- Gentle massage of the injection site on a daily basis by hand or with a hand-held massage device may be helpful in reducing nodule formation.
- There have been some anecdotal reports that local application of ultrasound (McGee 2002) may help. Some patients have received ultrasound treatment for many years and continue to maintain good skin quality and reduction in nodules. However ultrasound therapy has not been subject to any formal trials. There is no clinical evidence to support their use or conversely to suggest that it may be harmful.

Appendix Two

An estimate of the potential medicine costs (and any additional costs)

NUH and SFHT will use Britannia Pharmaceuticalfor support with APO-go® products and Ever Pharma UK Ltd for support with Dacepton® products. The cost paid in secondary care includes the services of a specialist nurse who performs the Apomorphine response test on each new patient and provides training to nursing staff. This also includes;

- APO-go Infusion pump plus syringes
- APO-go pen needles

Average annual NHS costs per patient;

- APO-go penject system: £3,500
- APO-go Pre-filled syringe/ampoules (infusion): £5,500
- Neria® tubing (£48.16 per pack of 10) : £1,758

The addition of Dacepton® products to the formulary, offers similar drug acquisition cost to existing APO-go® preparations (as above), but potentially lower cost to the NHS as the products have longer shelf-life stability, therefore allowing for a reduction in wastage. Since pumps could be refilled less frequently rather than daily as for APO-go®, Dacepton® also has the benefit of reduced District Nurse time as the number of visits could potentially be reduced.

The optimal daily dosage of apomorphine varies considerably between patients, and not all patients stay on one presentation for a full 12 months, which leads to a slight difference in suggested average costs from company data to the range below. The drug costs are therefore most meaningfully expressed as a range rather than an average.

Intermittent subcutaneous apomorphine using APO-go® Pen 10mg/ml solution for injection or Dacepton® 10mg/ml cartridges for injection (delivered via D-Mine Pen)

Daily use	Daily Dose		
		Weekly	Annually
1/2 x 3ml Pen	Up to 15mg	£86.73	£4509.96
1 x 3ml Pen	Up to 30mg	£173.46	£9019.92

Costing based on 48 hour expiry of APO-go pen verses the 15 day expiry of Dacepton® pen means that doses between 6mg-12mg could offer annual savings of £2,714 - £929 respectively. Average: £1,821

Continuous subcutaneous apomorphine using APO-go® 5mg/ml solution for infusion in Pre-filled Syringe or Dacepton 5mg/ml solution for infusion vials

Daily use	Daily Dose		
		Weekly cost	Annual cost
1 x Pre-filled Syringe	Up to 50mg	£102.34	£5321.68
2 x Pre-filled Syringe	Up to 100mg	£204.68	£10643.36

The 24 hour expiry of Apo-go® Pre-filled syringe verses 7-day expiry of Dacepton® solution infusion means that doses between 64-80mg can offer annual savings of approximately £3,888-£2,229 respectively. Average savings: £3,058

Continuous subcutaneous apomorphine using APO-go ampoules

Daily use	Daily Dose	Weekly	Annual
1 x 5ml ampoule	Up to 50mg	£102.34	£5321.68
2 x 5ml ampoule	Up to 100mg	£204.68	£10643.36

Source: Prices quoted are exclusive of VAT. Drug Tariff (accessed online April 2020).

An estimate of the potential medicine costs (and any additional costs) to secondary care
Apomorphine in secondary care equivalent to NHS price (as above) plus VAT.

Appendix Three

Domperidone cardiac effects and use of concomitant medicines.

Commonly prescribed drugs which can prolong the QT interval include:

SSRIs (including citalopram, sertraline, venlafaxine)
Quinolones (including Ciprofloxacin, levofloxacin)
Ondansetron
Midodrine
Antipsychotics (including risperidone, quetiapine)

However, practitioners are advised to consult: http://www.sads.org.uk/drugs-to-avoid/ for up-to-date guidance.

Potent CYP3A4 enzyme inhibitors (that may increase domperidone levels) include:

Clarithromycin
Telithromycin
Itraconazole
Ketoconazole
HIV protease inhibitors (eg atazanavir, darunavir, ritonavir).

Full guidance on domperidone restrictions can be found in the SmPC at www.medicines.org.uk, or at https://www.gov.uk/drug-safety-update/domperidone-risks-of-cardiac-side-effects.