Apomorphine
Traffic light classification- Amber 2
Information sheet for Primary Care Prescribers

CLINICAL INFORMATION

Key points

- Patients should be pre-treated with domperidone (20mg tds) for several days before starting on apomorphine (see MHRA advice below). The majority are able to stop the domperidone after a few weeks.
- 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 – usually 20mg tds – for at least 2 days prior to starting treatment with Apomorphine. MHRA advice is to use the lowest effective dose of domperidone. Prescribers should exercise caution for patients who have: existing prolongation of cardiac conduction intervals (particularly QTc); significant electrolyte disturbances; or underlying cardiac diseases such as congestive heart failure, and patients who are known to be taking prescribed medicines for these conditions, particularly for patients older than 60 years and patients who receive daily oral doses of more than 30 mg. Domperidone should be avoided in patients who are taking concomitant medication known to cause QT prolongation (eg, ketoconazole or
erythromycin). Patients should be advised to seek prompt medical attention if symptoms such as syncope or tachyarrhythmias appear during treatment.

- 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.
- 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.

Reconstitution

1. **APO-go PFS 5mg/ml Solution for Infusion in Pre-Filled Syringe**
   There is no need to dilute APO-go PFS 5mg/ml Solution for Infusion in Pre-filled Syringe prior to use. APO-go PFS 5mg/ml Solution for Infusion in Pre-filled Syringe is for single use only. Any unused solution should be discarded.

2. **APO-go PEN 10mg/ml Solution for Injection**
   As the APO-go PEN is a Penject system there is no need to dilute prior to use. Discard each pen no later than 48 hours from first use.

3. **10mg/ml Solution for Injection**
   For continuous infusion it is recommended to dilute Apomorphine 10mg/ml injection 50:50 with 0.9% normal saline or Water for Injections resulting in 5mg/ml strength. This is in order to minimise skin complications (i.e. subcutaneous nodules which can develop). Once diluted the solution is stable for up to 24 hours. For intermittent injection pens are used. For single use only. Any unused solution should be discarded.

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

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localised discomfort at needle site</td>
<td>Rotate injection site daily</td>
</tr>
<tr>
<td>Nodule formation at needle or infusion site</td>
<td>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.</td>
</tr>
<tr>
<td>Local infection/abscess/ulceration/scarring</td>
<td>Discuss with neurologist/PDNS</td>
</tr>
<tr>
<td>Nausea &amp; vomiting</td>
<td>Usually transient</td>
</tr>
<tr>
<td>Sedation</td>
<td>Usually transient. Advise patients not to drive / operate machinery if affected. If persists discuss with neurologist/ PDNS</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>Usually transient</td>
</tr>
<tr>
<td>Light-headedness</td>
<td>Discuss with neurologist/ PDNS</td>
</tr>
<tr>
<td>Dyskinesias during ‘On’ periods</td>
<td>Discuss with neurologist/ PDNS</td>
</tr>
<tr>
<td>Coomb’s positive Haemolytic anaemia</td>
<td>Discuss with neurologist/ PDNS</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>Discuss with neurologist/ PDNS</td>
</tr>
<tr>
<td>Neuropsychiatric complications – hallucinations, euphoria, increased libido, confusion, personality changes, agitation, restlessness, psychosis, sleep disturbance</td>
<td>Discuss with neurologist/ PDNS</td>
</tr>
<tr>
<td>Allergic reactions including bronchospasm and anaphylaxis (due to sodium bisulphite)</td>
<td>Withhold and discuss with neurologist/ PDNS</td>
</tr>
</tbody>
</table>

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.

Products available

It is recommended that these products are prescribed as the APO-go® brand.

1. **5mg/ml Solution for Infusion in Pre-Filled Syringe 10ml syringe (APO-go® PFS)**
2. **10mg/ml Solution for Injection 3ml Pen (APO-go® Pen)**
3. **10mg/ml Solution for Injection 5ml Ampoules**

NEEDLES AND TUBING

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. These lines have an attached needle with an adhesive patch which makes it easy for patients to insert the needle at the correct angle. Further information is available through the Apo-go helpline (0844 8801327).

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 March 2012
Summary of Product Characteristics July 2012
NICE CG35 Parkinson’s Disease June 2006
MHRA Drug Safety Update May 2012: Domperidone: small risk of serious ventricular arrhythmia
and sudden cardiac death available here

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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 currently use Genus Pharmaceuticals’ APO-go® 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 (£45.80 per pack of 10) : £1672

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 Pens

<table>
<thead>
<tr>
<th>Daily use</th>
<th>Daily Dose</th>
<th>Weekly*</th>
<th>Annually*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2 x 3ml Pen</td>
<td>Up to 15mg</td>
<td>£86.73</td>
<td>£4509.96</td>
</tr>
<tr>
<td>1 x 3ml Pen</td>
<td>Up to 30mg</td>
<td>£173.46</td>
<td>£9019.92</td>
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</table>

Continuous subcutaneous apomorphine using APO-go Pre-filled Syringe

<table>
<thead>
<tr>
<th>Daily use</th>
<th>Daily Dose</th>
<th>Weekly cost***</th>
<th>Annual cost***</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 x Pre-filled Syringe</td>
<td>Up to 50mg</td>
<td>£102.34</td>
<td>£5321.68</td>
</tr>
<tr>
<td>2 x Pre-filled Syringe</td>
<td>Up to 100mg</td>
<td>£204.68</td>
<td>£10643.36</td>
</tr>
</tbody>
</table>

Continuous subcutaneous apomorphine using APO-go ampoules

<table>
<thead>
<tr>
<th>Daily use</th>
<th>Daily Dose</th>
<th>Weekly</th>
<th>Annual</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 x 5ml ampoule</td>
<td>Up to 50mg</td>
<td>£102.34</td>
<td>£5321.68</td>
</tr>
<tr>
<td>2 x 5ml ampoule</td>
<td>Up to 100mg</td>
<td>£204.68</td>
<td>£10643.36</td>
</tr>
</tbody>
</table>

* The costs relate to APO-go Pens having an expiry of 48 hours after being started.
*** The costs relate to APO-go Pre-filled Syringes having an expiry of 24 hours after being started.

Source: Prices quoted are exclusive of VAT. MIMS (accessed online Sept 2012)

It is recommended to dilute APO-go Ampoules 50:50 with 0.9% normal saline resulting in 5mg/ml strength, in order to minimise skin complications. Saline is therefore a small additional cost.

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.