SHARED CARE GUIDELINE
Apopomorphine injection or infusion for Parkinson’s disease.

Implementation Date: January 2019
Review Date: January 2022

This guidance has been prepared and approved for use within Sunderland in consultation within the CCG, and Secondary Care Trusts.
The guideline sets out the details of the transfer of prescribing and respective responsibilities of GPs and specialist services within shared care prescribing arrangements. It is intended to provide sufficient information to allow GPs to prescribe this treatment within a shared care setting.

Approved by:

<table>
<thead>
<tr>
<th>Committee</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Joint Formulary Committee</td>
<td>September 2018</td>
</tr>
<tr>
<td>The Medicines Optimisation and Guidelines Group</td>
<td>October 2018</td>
</tr>
<tr>
<td>The Transfer of Care Group</td>
<td>January 2019</td>
</tr>
</tbody>
</table>

Instructions for completion:
- Consultant to counsel patient on medication and ensure patient has been provided with information leaflet
- Consultant to ensure all clinical details completed on this document
- Consultant to ensure patient understands proposed monitoring and prescribing arrangements if a shared care agreement is entered into
- GP to complete final section of form and return to specialist prescriber within 28 days
- GP to retain copy of document on patient record within surgery

Clinicla details:

<table>
<thead>
<tr>
<th>Non-proprietary name (1)</th>
<th>APOMORPHINE</th>
<th>Brand name</th>
<th>Licensed Y/N?</th>
<th>BNF Code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>APO-go® PFS</td>
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<td>4.9.1</td>
</tr>
</tbody>
</table>

Dopaminergic drugs used in Parkinson’s Disease

Indication (1, 2)
Refractory motor fluctuations in Parkinson’s disease (‘off’ episodes) inadequately controlled by co-beneldopa or co-careldopa or other oral dopaminergics for capable and motivated patients under specialist supervision.
Symptom relief/control of complex Parkinson’s disease as per Parkinson’s disease in adults NICE guidelines 2017 (NG71) 1.8.1

Dosage and Administration (1, 3, 4)
Apopomorphine has an onset of action of between 5-15 minutes, lasting usually for about one hour.
The form (i.e. injection or infusion) and dosage are determined on an individual basis and can range from a few milligrams daily by intermittent subcutaneous
injections, up to 100mg daily - usually by continuous infusion. Once the optimal dose has been established it remains relatively constant for each patient.

**Subcutaneous injection (pen)**
- **Usual dose:** 3-30mg daily in divided doses
- Maximum single dose 10mg
- Maximum daily dose 100mg (10 x 10mg single doses)

**Continuous subcutaneous infusion (pump)**
Usually for patients requiring more than 10 daily doses of subcutaneous pen or if an infusion is clinically indicated when undertaking the Apomorphine response test.
- **Usual dose:** 1-4mg per hour; for 10-12 hours daily during waking hours.
  Dose is titrated over several weeks, usually in doses of 0.5mg by the Apomorphine specialist nurse as oral anti-parkinsonian drugs are reduced.
  Maximum daily dose 100mg.
- 24-hour infusions are not recommended unless severe night-time symptoms in which case the pump will be set up with a variable flow rate.
- Tolerance may follow if there is not a treatment free period of 4 hours.
- Infusion site/line to be changed 12 hourly, or as directed by Apomorphine specialist nurse.
- Patients still usually require intermittent bolus doses to supplement the infusion.

**Administration**
- To be conducted, in all most all cases by patient (with carer support).
- If district nursing support is required; prior to commencement of Apomorphine, the PD team will ensure appropriate education of Apomorphine administration is provided to district nurses.

**Eligibility criteria for shared care**
- GP has agreed to shared care of the patient and returned the shared care agreement after the Apomorphine response test and within 28 days of the shared care request. The GP has received a request to prescribe the product that the patient requires i.e. prefilled pen for subcutaneous injection or prefilled syringe for subcutaneous infusion and the patient’s established dose.
- The patient has received one month’s initial supply of Apomorphine from the hospital.
- The patient and carer have received training on the use of Apomorphine and can self-manage OR community nursing support has been arranged for the patient by the specialist team.
- The patient understands and consents to shared care.
- The patient’s dose is stable
- The prescription has been requested one week in advance of the supply being required (to allow time for ordering through community pharmacy).
- When shared care is declined, the PD team at City Hospitals Sunderland will continue to provide ongoing prescriptions of Apomorphine.

**Excluded patients**
See contraindications and cautions section below.

**Initiation**
- Before starting treatment, patients have an Apomorphine response test at Sunderland Royal Hospital.
- If the patient responds they will be issued with a 28 day supply of Apomorphine prefilled pens for injection or prefilled syringes for infusion from the hospital,
determined by the specialist team.

- The initial treatment dose will often be established on completion of the test, but in some cases it may require further titration by the specialist team.
- The patient will be discharged with an individual management plan detailing the patient’s dose, any further titration that may be required and how this will be carried out.
- The Apomorphine specialist nurse will continue to review the patient and titrate dose on confirmed instruction from consultant, until optimum dose is established.
- Initial dose should be stable before a request for shared care is sent to the patient’s GP.

| Specialist Responsibilities | 1. Patient selection and assessment of suitability of treatment with Apomorphine.  
2. Inform GP that the patient may benefit from Apomorphine, explain the process for initiation and request shared care, providing the rationale for the request prior to initiation.  
3. Discuss the aims, benefits and side effects of treatment with the patient/carer and obtain consent.  
4. Provide and complete the, ‘Patient acknowledgement form for impulsive compulsive behaviours’ provided by PDUK below. Signed copy to be given to patient, GP and filed in the medical notes.  
5. PDUK information sheet provided to patient on, ‘Impulsive and compulsive behaviours in Parkinson’s’ as per requirement of Patient Acknowledgement form.  
6. Explain to the patient the treatment plan including the dosing schedule.  
7. Perform and review all baseline monitoring prior to Apomorphine response test, including: Lying and Standing blood pressures, U&Es, LFTs, FBC, ECG, direct Coombs test, reticulocyte count.  
- Consider whether the benefits of concomitant Apomorphine and Domperidone treatment outweigh the small increased risk of cardiac side effects.  
  The risk of QT-prolongation may be increased in people on concomitant Apomorphine and Domperidone who have certain risk factors, including:  
  - Pre-existing QT-interval prolongation  
  - Serious underlying cardiac disorders such as heart failure  
  - Severe hepatic dysfunction  
  - Significant electrolyte disturbances  
  - Concomitant drug therapy that may increase Domperidone levels (e.g. cytochrome P450 3A4 inhibitors)  
- Discuss the benefits and risks of Apomorphine with patients and carers and advise them to contact their doctor immediately if they develop palpitations or syncopal symptoms during treatment.  
- Check the QT-interval before starting Domperidone, during the Apomorphine initiation phase and if clinically indicated thereafter (e.g if a QT-prolonging or interacting drug is started or if symptoms of cardiac side effects are
• Regularly review Domperidone treatment to ensure patients take the lowest effective dose for the shortest duration.

• Advise patients to inform their doctor of any changes that could increase their risk of arrhythmia, such as:
  o Symptoms of cardiac or hepatic disorders
  o Conditions that could cause electrolyte disturbances (e.g., gastroenteritis or starting a diuretic)
  o Starting any other medicines


  Domperidone is contraindicated in people:
  o With conditions where cardiac conduction is, or could be, impaired
  o With underlying cardiac diseases such as congestive heart failure
  o Receiving other medications known to prolong QT interval or potent CYP3A4 inhibitors
  o With severe hepatic impairment

• The specialist is responsible for providing the full course of Domperidone required and instructing the patient on its use.

   Note: this requires pre-treatment with Domperidone 10mg tds for two days prior to the response test and continued for a short period of time if the patient continues on Apomorphine. It can then be gradually reduced and then discontinued. BP monitoring to be perform during test.

10. **Initiate treatment** with Apomorphine:
    • Either intermittent injection or continuous infusion – and optimise anti-Parkinson’s drug therapy.
    • Prescribe 28 days’ supply of Apomorphine.
    • Ensure sufficient supply of Domperidone.
    • Titrate the dose of Apomorphine.
    • ECG to be conduct during initiation phase with concurrent use of Apomorphine and Domperidone.
    • Provide the patient with a large sharps bin (to be returned to the hospital when full). A telephone number will be located on the side of the sharps box for the patient/carer to contact when full and City Hospitals Sunderland will arrange collection.
    • Provide the patient and carer with full training on the use of Apomorphine injections/infusion. If the patient with carer support cannot manage then community district nursing support will be organised. The specialist team is responsible for providing training to the community nursing service to support this.

11. **Follow up**
    **Intermittent injection therapy:**
    After the patient is discharged from the hospital and established on the medication they will be followed up by the Apomorphine nurse within the first 4 weeks either by phone, at home or in clinic according to patient need.
    **Continuous infusion therapy:**
    Once the patient begins infusion with a titration range in place they will be followed up in the community, by phone or in clinic by the Apomorphine specialist nurse for oral medication optimisation.
12. Monitor and evaluate response to Apomorphine treatment including titration of the dose, adverse drug reactions, and continue/discontinue treatment in line with agreed treatment plan.

13. Annual FBC, reticulocyte count and Coombe’s test if clinically indicated.

14. Ensure prompt communication with the GP of any changes in treatment or dose requirements, results of monitoring undertaken and assessment of adverse effects.

15. Provide telephone contacts for patients, carers and health professionals.

16. Provide the GP with relevant contact information with clear arrangements for back-up advice and support should further assistance be required.

**GP Responsibilities** [1, 3, 4, 7, 8]

1. Agree to or decline the request for shared care within 28 days of receipt of request and return documentation to the specialist. Sufficient time should be allowed for prescription to be issued by GP or City Hospitals Sunderland.

2. After a positive response test, on receipt of the patient’s treatment plan and the request to prescribe; prescribe Apomorphine as requested by the specialist:

   - **For intermittent subcutaneous injection**
     Apomorphine hydrochloride 10 mg/ml, 3-ml pen injector (APO-go® Pen)
     - Usual dose: 3-30mg daily in divided doses
     - Maximum single dose: 10mg
     - Maximum daily dose: 100mg (10 x 10mg single doses)
     - Novofine needles are required and should be prescribed with the pen on a when required basis (the patient may not need a supply at every prescription as they are supplied in boxes of 100)

   - **For subcutaneous infusion**
     Apomorphine hydrochloride 5 mg/ml, 10-ml prefilled syringe (APO-go® PFS)
     - Usual dose: 1-4mg per hour
     - Usually given for 10-12 hours daily during waking hours
     - Maximum daily dose 100mg
     Prescription Neria subcutaneous infusion lines x 30-40 per month.
     Infusion site/line to be changed 12 hourly.
     The infusion is given via Crono APO-go ambulatory infusion pump which is loaned to the patient from the Britannia. PDSN’s will arrange this.
     If required, record the concomitant Domperidone supplied by the hospital, on the patient’s record in EMISweb.
     The hospital will supply the first 28 day’s supply of treatment.
     As Apomorphine is not a widely used medicine, note that it may take a number of days for the community pharmacy to obtain stock.
     Prescribe a large sharps bin when requested by the patient.

3. There is no requirement for any monitoring of disease or the drug, as all monitoring will be undertaken by the hospital. However, be aware of the precautions and adverse effects described in the shared care guideline and contact the specialist for advice if the patient presents with any of these, or if there is deterioration in their Parkinson’s disease symptoms.

4. If clinically indicated and requested by the specialist continue prescribing Domperidone, in line with MHRA guidance:
### Community Nursing Services responsibilities

Community nursing input may be required if patients cannot self-manage. If community nurses are required to assist patients in setting up the Apomorphine infusion, the specialist nurse team will liaise with the appropriate community nursing team to facilitate training. Roles include:

- Daily setting up and administration of the infusion
- Daily discontinuation of the infusion including removal of line
- Monitoring of surrounding skin integrity and nodule formation
- Monthly lying and standing BP (this may be more often if the patient is symptomatic i.e. complaining of dizziness)
- Regular liaison with Parkinson's disease nurse specialist

### Contra-indications:

- Respiratory depression, dementia, psychotic disease, hepatic impairment.
- Patients with an “on” response to levodopa which is marred by severe dyskinesia or dystonia.
- Hypersensitivity to Apomorphine or any of the excipients.
- Children and adolescents under the age of 18 years.

### Cautions:

- Use with caution in renal, pulmonary or cardiovascular disease and people prone to nausea and vomiting.
- Dosing in renal impairment – renal drug database recommends to start at the same dose in any degree of renal dysfunction/type of dialysis and monitor for side effects.
- History of postural hypotension.
- Susceptibility to QTc interval prolongation.
- Neuropsychiatric conditions.
- Pregnancy – use to be avoided unless clearly necessary.
- Breast feeding – No information available. May suppress lactation.

### Adverse effects:

- **Hypotensive reactions** can occur in some patients taking dopamine-receptor agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery. Use with caution in patients with pre-existing cardiac disease, pre-existing postural hypotension or those taking anti-hypertensives.

- **QT prolongation** – Apomorphine can cause QT prolongation, therefore use with caution in patients at risk of torsades de pointes. Note patients will be at increased risk of this during treatment initiation, whilst also taking Domperidone. Other risk factors for QT prolongation include: underlying heart conditions, severe hepatic impairment and significant electrolyte disturbance. Specialist to conduct ECG prior to treatment with Domperidone, during treatment initiation and as clinically indicated thereafter.

**GP to be aware of possible cardiac symptoms, including palpitations and syncope. In addition, the risk factors for hypokalaemia such as gastroenteritis or initiation of diuretic therapy. Discuss with specialist if these occur.**

(Please consult the Summary of Product Characteristics at [www.medicines.org.uk](http://www.medicines.org.uk) for full details)
<table>
<thead>
<tr>
<th>Adverse reaction (frequency of side effect)</th>
<th>Action required</th>
</tr>
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<tbody>
<tr>
<td><strong>Nodule formation at needle or infusion site (very common)</strong></td>
<td>Patient/carer to rotate injection site and injection site to be massaged.</td>
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<tr>
<td><strong>Allergic reactions including bronchospasm and anaphylaxis (rare)</strong></td>
<td>GP to immediately contact PD team, or Neuro registrar out of hours and stop Apomorphine.</td>
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<tr>
<td><strong>Significant dyskinesia during ‘on’ periods (less common)</strong></td>
<td>GP to contact PD team.</td>
</tr>
<tr>
<td><strong>Confusion and hallucinations (very common)</strong></td>
<td>Contact PD team.</td>
</tr>
<tr>
<td><strong>Somnolence and episodes of sudden sleep onset (common).</strong></td>
<td>Contact PD team immediately.</td>
</tr>
<tr>
<td>Patients will 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. A reduction of dosage may be considered.</td>
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<td><strong>Impulse control disorders (rare)</strong></td>
<td>Contact PD team immediately.</td>
</tr>
<tr>
<td>Treatment with dopamine-receptor agonists and levodopa is associated with impulse control disorders, including: pathological gambling, excessive shopping, dopamine dysregulation syndrome, binge eating, and hyper sexuality. Patients and their carers are informed about the risk of impulse control disorders by the specialist team. If the patient develops an impulse control disorder, the specialist may withdraw or reduce dose.</td>
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<tr>
<td><strong>Dopamine dysregulation syndrome</strong> (DDS) is an addictive disorder resulting in excessive use of dopaminergic medicines. Before initiation of treatment, patients and caregivers are warned of the potential risk of developing DDS.</td>
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<td><strong>Dopamine agonist withdrawal syndrome (DAWS) (Unknown)</strong></td>
<td>Contact PD team immediately.</td>
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<tr>
<td>On dose reduction of Apomorphine all health care professionals are to be alert for DAWS. Evidence is limited, however most common signs and symptoms of DAWS include: depression, fatigue, anxiety and insomnia. Further symptoms include: generalised pain, restless legs, nausea and vomiting, postural hypotension, flushing, diaphoresis, irritability, confusion, agitation, dysphoria panic attacks, suicidal ideation and social phobia.</td>
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</table>
Symptom onset is variable upon dose reduction of DAs and may be confused with non-motor symptoms of Parkinson’s disease.

The following medicines are ineffective for the symptoms of DAWS: antidepressants, benzodiazepines, opiates, gabapentin, cognitive behaviour therapy, levodopa.

Half of Parkinson’s disease patients with DAWS have a full recovery within days to weeks.

**Nausea and vomiting** (common)
Apomorphine is highly emetogenic. This is transient (6 to 8 weeks) in most patients.

Specialist will manage this on initiation of Apomorphine. If nausea returns on stopping Domperidone and if appropriate, Domperidone can be reinstated.

(See specialist responsibility section for full details).

**Other adverse reactions:**

**Common:**
- Yawning
- Dizziness

**Less common side effects:**
- Postural hypotension
- Dyspnoea
- Dyskinesia during ‘on’ periods (may require discontinuation)
- Haemolytic anaemia and thrombocytopenia with levodopa
- Rash

**Rare side effects:**
- Eosinophilia
- Peripheral oedema
- Compulsive behaviour and dizziness also reported

**Unknown:**
- Syncope
- Headache

**Drug interactions causing Multiple adverse effects with concurrent use**

- **Ondansetron (and other 5HT3 receptor antagonists)** - Manufacturer contraindicates concurrent use, due to extrapyramidal adverse effects, profound hypotension and loss of consciousness.

**Medications antagonising dopaminergic action:**

- Antipsychotics and anti-emetics (e.g. metoclopramide, prochlorperazine, levomepromazine)
  - Note clozapine and quetiapine are recommended for neuropsychiatric presentations in PD; initiated by specialist only.
- Methyldopa possibly antagonises antiparkinsonian effect of dopaminergics.
Medications enhancing dopaminergic action:
- Dopaminergics listed in section 4.9.1 of the BNF.
- Memantine possibly enhances effects of Apomorphine

Medicines which elicit hypotensive effects

Please refer to BNF, Appendix 1 Interactions table for medicines which can cause hypotension. Caution is advised.

Patients should be advised to lie down and raise their legs if symptoms such as nausea, dizziness, pallor and/or sweating occur.

QT interval prolongation

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

Concurrent use may lead to potentially fatal torsade de pointes arrhythmia. If concurrent use is essential, ECG monitoring is required.

Increasing age, female sex, cardiac disease, and metabolic disturbances (notably hypokalaemia) predispose to QT prolongation; in their presence use with greater caution.

Medicines which may prolong the QTc interval are listed below, according to currently known risk. This list is not exhaustive. Please see individual drug monographs.

Medicines with high risk
- Antiarrhythmics, class Ia (ajmaline, cibenzoline, disopyramide, hydroquinidine, procainamide, quinidine), Antiarrhythmics, class III (amiodarone, cibenzoline, dofetilide, dronedarone, ibutilide, sotalol, vernakalant), Artemisinin derivatives (artemisinin, artemether/lumefantrine, artenimol), Halofantrine, Haloperidol, Ketanserin, Panobinostat, Pimozide, Ribociclib, Sertindole, Thioridazine, Vandetanib.

Medicines with some risk

Medicines where risk is not categorised
- Amifampridine, Androgen antagonists (abiraterone, bicalutamide, enzalutamide, flutamide, nilutamide), Anthracyclines, Apomorphine, Atomoxetine, Azithromycin, Beceprevir, Chloroquine, Ciprofloxacin, Clarithromycin, Clozapine, Erythromycin, Foscarinet, Gonadorelin analogues (buserelin, goserelin, histrelin, leuprorelin, triptorelin, degarelix) Gonadorelin antagonists, Levofloxacin, Lithium, Olanzapine, Oxaliplatin, Oxycodone, Quetiapine Rilpivirine Risperidone, Solifenacin, Spiramycin, Sulpiride, Tacrolimus, Telavancin, Telithromycin, Terlipressin, Tizanidine, Trazodone, Venlafaxine, Zuclopenthixol
Communication/Contact Details

Please contact the PD team at Sunderland Royal Hospital for advice or alternatively the APO-go helpline.

Neurology Department
Dr U. Nath, Consultant Neurologist 0191 5656256 extension 41240 (secretary)
Dr A Cassidy Consultant Neurologist 0191 5656256 extension 42778 (secretary)
Parkinson’s Disease Nurse Specialists - 01915656256 Lisa Renton bleep 52387 / Victoria Rumis bleep 52003 / 0191 5656256 extension 49854, or PDSN secretary 0191 5656256 extension 47162

Care of the Elderly Department
Dr R Telford, COTE physician 0191 5656256 extension 42192 (secretary)

PD Specialist Pharmacist
Sharlene Hindmarsh 0191 5656256 bleep 52337

Apo-go telephone helpline 24/7 0844 880 1327
Apo-go website https://www.apo-go.com

This information is not inclusive of all prescribing information and potential adverse effects. Please refer to full prescribing data in the SPC or the BNF.

References:

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Shared Care Request/Confirmation

Patient information:
To be completed by specialist prescriber:

<table>
<thead>
<tr>
<th>Consultant</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Department</td>
<td>Address</td>
</tr>
<tr>
<td>Hospital</td>
<td></td>
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<tr>
<td>Postcode</td>
<td>Sex</td>
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</tbody>
</table>

Treatment Requested for Prescribing in Accordance with Shared Care Arrangement:
To be completed by specialist prescriber:

<table>
<thead>
<tr>
<th>Drug name and formulation</th>
<th>The above patient has been started on:</th>
</tr>
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<tbody>
<tr>
<td>Apomorphine hydrochloride 10mg/ml pens</td>
<td>☐</td>
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<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>Apomorphine hydrochloride 5mg/ml prefilled syringes</td>
<td>☐</td>
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<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>BOTH</td>
<td>☐</td>
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</tbody>
</table>

Dose
Frequency
Indication
Other information

Name (print)……………………… Signature (of specialist prescriber)…………………….. Date……...

Acceptance/rejection of treatment under Shared Care Agreement:
To be completed by GP:

Please tick one box

I ACCEPT the proposed shared care arrangement for this patient ☐

or

I ACCEPT the proposed shared care arrangement with the caveats below ☐

or

I DO NOT ACCEPT the proposed shared care arrangement for this patient ☐

My caveats / reason(s) for not accepting include: ...................................................................................................................

Name (print)……………………… Signature (of GP)…………………….. Date……...

N.B. Participation in this shared care arrangement implies that prescribing responsibility is shared between the specialist prescriber and the patient’s GP

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APOMORPHINE FOR PARKINSON’S DISEASE