SHARED CARE GUIDELINE

Drug: Apomorphine
Indication Parkinson's Disease

Introduction	**Indication:** Treatment of Parkinson's Disease with Apomorphine **Background:** Patients with Parkinson's disease with disabling motor fluctuations (''on-off" phenomena) which persist despite individually titrated treatment with other Parkinson's medications. Apomorphine is a directly acting dopaminergic agonist, licensed for use in patients with Parkinson's disease who have troublesome motor fluctuations and dyskinesia not controlled by levodopa or other dopaminergic medication. Apomorphine is a dopamine agonist, which acts directly on D1 and D2 receptors, stimulating areas of the brain where dopamine works. It produces a similar effect to levodopa, that is, the ability to prevent and reverse disabling "off" periods. Despite its name **it has no opiate or addictive properties**. Apomorphine cannot be used orally because it undergoes extensive first pass metabolism (in the liver) to an inactive metabolite; for this reason it is administered subcutaneously.
Dose & Administration	• Apomorphine may be administered as a "rescue therapy" with intermittent subcutaneous bolus injections given via a prefilled Apomorphine Pen: **10mg/ml Solution for Injection 3ml Pen (Apomorphine Pen)** Patients selected for treatment with Apomorphine 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. • For those patients who experience more complex motor fluctuations, including dyskinesia, a continuous subcutaneous infusion using an ambulatory Apomorphine pump may be used with the Apomorphine PFS: **5mg/ml Solution for Infusion in Pre-Filled Syringe 10ml syringe (Apomorphine PFS)** • Apomorphine is occasionally used for patients with swallowing difficulties and at the palliative stage **It is essential that the patient is established on domperidone 10mg oral TDS daily, 48 hours prior to initiation of apomorphine.** This dose can be increased to 20mg if necessary and weaned off if no nausea. If nausea persists or returns on reducing the dose, domperidone can be reinstated. **Please see the MHRA drug safety alert for apomorphine and domperidone:** https://www.gov.uk/drug-safety-update/apomorphine-with-domperidone-minimising-risk-of-cardiac-side-effects

	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. 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 (eg if a QT-prolonging or interacting drug is started or if symptoms of cardiac side effects are reported) 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: symptoms of cardiac or hepatic disorders conditions that could cause electrolyte disturbances (eg, gastroenteritis or starting a diuretic) starting any other medicines **Please see the MHRA drug safety alert for domperidone:** https://www.gov.uk/drug-safety-update/domperidone-risks-of-cardiac-side-effects There is a risk of serious ventricular arrhythmia and sudden cardiac death. Patients should not be given Domperidone whilst on medications known to prolong the QT interval or strongly inhibit CYP3A4 (e.g., ketoconazole or erythromycin). Domperidone should not be prescribed in patients with specific contraindications, including known QTc prolongation (e.g. on baseline ECG). If the patient cannot take Domperidone, the PDNS will initiate the Apomorphine at 0.5mg/hr rather than 2mg/hr and will monitor for nausea and increase slowly as tolerated (over a few weeks). • The optimal dosage of Apomorphine has to be determined on an individual patient basis and the threshold dose is determined by the specialist using incremental dosing schedules. Once the optimal dose for an individual patient has been determined and the patient is stable, the dose is likely to remain relatively constant • The daily dose of Apomorphine varies widely between patients, • **Intermittent injection** – typically 1-10 injections per day, each dose no more than 10mg • **Continuous infusion** - typically 1–6 mg per hour (but may be higher, dependent upon individual response), mostly during waking hours but may be necessary for overnight infusion according to patient's needs. Considered if the patient experiences so many "off" periods that repeated bolus injections are inappropriate. • Maximum licensed daily dose by either route is 100 mg. Any doses prescribed over 100mg are with documented Consultant consent and the GP will be informed. **Conditions which might require dose reduction depending on clinical judgment:** • Hypotension which is symptomatic to patient. • Cognitive impairment • Hallucinations • Obsessive compulsive disorder • Impulse control disorder
Secondary Care	• Patient suitability/selection

Responsibilities	• Provision of information to patient & primary care team regarding Apomorphine therapy. • Provision of information to patient, carer (video, DVD and written material) • Baseline tests – as outlined below • Baseline ECG monitoring prior to commencing domperidone and repeat ECG after two weeks of treatment if the patient is receiving >30mg daily of domperidone maintenance therapy* – as outlined below. • Assessment at month one of therapy to be completed by the PDNS • To arrange prescription for /prescribe domperidone 10mg oral TDS daily, 48 hours prior to initiation/challenge of apomorphine. • Arrange Apomorphine challenge/initiation within outpatient clinic, community setting or hospital inpatient clinic • Provide patient/carer education and training • Arrange infusion pump training for District Nurses • Advise District Nurse as required on dose and titration • Arrange monitoring test with GP as required (FBC, reticulocyte 6 monthly) • Titration. Optimisation and evaluation of medication • Monitor and evaluate potential adverse drug reactions • Provision of information and support to patient, carers and primary care team as appropriate • Provide point of contact for community team and patients • Monitor blood results • Provide clear, documented advice about changes if necessary *please refer to latest recommendations for Domperidone Prescribing responsibility will only be transferred when: • Treatment has been initiated and the patient has been stabilised by the secondary care specialist. • The patient's initial reaction to and progress on the drug is satisfactory. • The GP has agreed that shared care is appropriate. • The patient's general physical, mental and social circumstances are such that he/she would benefit from shared care arrangements
Primary Care Responsibilities	**GPs:** Reply to request for shared care within 14 days Prescribe ongoing Apomorphine and any concomitant therapy e.g. domperidone (only if prescribed in line with MHRA recommendations). 6 monthly FBCs & reticulocyte or more frequently if recommended Provision of dressings, lines and sharps bins Report side effects or issues relating to Apomorphine treatment to PDNS/treating Consultant **District Nurses** Supervision and support as required Inform PDNS/GP/treating Consultant of any problems Report side effects or issues relating to Apomorphine treatment to PDNS/treating Consultant and GP Maintain appropriate level of knowledge and skills. **Patient** • Patients should be advised to seek prompt medical attention if symptoms such as syncope or palpitations occur. • Collects prescription as per practices repeat prescription procedure for dispensing at community pharmacy

	• Attend Outpatient and GP appointments • Attend appointments for blood tests • Report concerns to GPs / PDNS / Specialist **NB: Ongoing prescribing will depend on attendance at clinics as requested by the clinicians** **Apomorphine must not be stopped without advice – please see contact section if advice is required.**
Monitoring	Baseline assessment: All baseline investigations; ECG, FBC, Coombs, Reticulocytes count to be done by the hospital in all circumstances. At 1 month: Lying and standing blood pressure, Haemoglobin, Reticulocyte count Coombs test ECG to check the QTc interval, prior to the use of domperidone, will be carried out by secondary care. If the QTc is greater than 450 milliseconds in a male or more than 470 milliseconds in a female then domperidone should not be prescribed and a cardiology opinion obtained. If a second QT prolonging drug or a strong CYP3A4 inhibitor is added then the ECG should be repeated (e.g. Ketoconazole or Erythromycin). The ECG should be repeated once at 2 weeks if the prescribed dose is maintained at more than 30mg daily. The second ECG is to be conducted by secondary care if required. Haemoglobin and reticulocyte count at 6 monthly intervals but there is no requirement to keep doing Coombs tests. These will be carried out by the GP. PDNS Will monitor when tests are due and send out forms.

Adverse Effects

Specialist to detail below the action to be taken upon occurrence of a particular adverse event as appropriate. Most serious toxicity is seen with long-term use and may therefore present first to GPs.

Adverse Event	Action to be taken	By whom
Localised discomfort at needle site	Consider Hirudoid cream	
Nodules formation at needle or infusion site. Usually asymptomatic but may persist in patients on high doses. Severe nodule formation may lead to worsening of symptoms due to erratic absorption of Apomorphine	Rotate injection site. Massage to injection sites is recognised to reduce nodule formation. Ultrasound therapy has been anecdotally said to alleviate severe nodule formation Anecdotally Hirudoid cream can be used on nodules	Patient / carer
Nausea & vomiting. Usually transient and resolved within 6-8 weeks	It is essential that the patient is established on domperidone 10mg oral TDS daily, 48 hours prior to initiation of apomorphine. This dose can be increased to 20mg if necessary and weaned off if no nausea. If nausea persists or returns on reducing the dose, domperidone can be reinstated. **See 'Dose and Administration' section above for full details.**	GP as advised by Consultant / PDNS
Allergic reactions including bronchospasm and anaphylaxis (due to sodium bisulphate)	Withhold and discuss with PDNS or Neuro Registrar if out of hours.	GP
Light-headedness	Discuss with Consultant /PDNS	GP
Postural hypotension is seen infrequently and is usually transient	Care should be exercised in patients with pre-existing cardiac disease or in patients taking vasoactive medicinal products such as antihypertensives, and in patients with pre-existing postural hypotension.	GP
Dyskinesia's during "On" periods	Discuss with Consultant /PDNS	GP
Coombs positive Haemolytic anaemia	Coombs test is carried out depending on Consultant/ PDNS clinical judgement. 6 monthly FBCs, reticulocyte as necessary	GP

	Eosinophilia in up to 10% of patients	Discuss with Consultant /PDNS	
	Dopamine dysregulation syndrome / Neuropsychiatric complications – hallucinations, euphoria, increased libido, confusion, personality changes, agitation, restlessness, psychosis, sleep disturbances, pathological gambling and over eating	Discuss with Consultant /PDNS	GP
	Sedation. Usually transient	Advise patients not to drive / operate machinery if affected. If persists discuss with Consultant / PDNS	GP

Always consult the latest version of the Summary of Product Characteristics (SPC) at www.medicines.org.uk for full details

Common Drug Interactions

The following drugs must not be prescribed *without consultation with the specialist*:

Clozapine
NB This is a RED Drug; liaison may be required with mental health services.

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.

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 medicinal products, especially those with a narrow therapeutic range.
It is recommended to avoid the administration of Apomorphine with other drugs known to prolong the QT interval.
Examples being: Amiodarone, Chlorpromazine, Cisapride, Citalopram, Clarithromycin, Clomipramine, Disopyramide, Erythromycin, Flecainide, Haloperidol, Mesoridazine, Moxifloxacin, Pentamidine, Procainamide, Sotalol, Vandetanib

See BNF for full details

Contraindications

Contra-indications

- Children and adolescents (up to 18 years of age)
- Known sensitivity to Apomorphine or any other ingredients of the product.
- Respiratory depression
- Dementia
- Psychotic disease
- Hepatic insufficiency
- Intermittent Apomorphine HCl treatment is not suitable for patients who have an 'on' response to levodopa which is marred by severe dyskinesia or dystonia

	Cautions • Pulmonary, renal or cardiovascular disease • Persons prone to nausea and vomiting • Elderly and/ or debilitated patients • pre-existing cardiac disease or in patients taking vasoactive medicinal products such as antihypertensives, and especially in patients with pre-existing postural hypotension
This guidance does not replace the SPC, which should be read in conjunction with this guidance.	

RELEVANT CONTACT LIST

Nicola Mason PD Nurse Specialist
Nicola.MASON@lthtr.nhs.uk 017720523575 or 07788415933
Britannia Pharmaceuticals 24/7 helpline
for problems with apomorphine PFS/Pump or Pen 08448801327

References

NICE	Guideline	National Institute for Health and Clinical Excellence (2017) Parkinson's disease in adults NICE clinical guideline 71. Manchester, NICE. https://www.nice.org.uk/guidance/ng71/resources/parkinsons-disease-in-adults-pdf-1837629189061
eMC	SPC	Britannia Pharmaceuticals Limited (2020) SPC: APO-go Pen 10mg/ml Solution for Injection. [Online] Available from: https://www.medicines.org.uk/emc/product/2232/smpc
eMC	SPC	Britannia Pharmaceuticals Limited (2018) SPC: APO-go PFS 5mg/ml Solution for Infusion in Pre-filled Syringe. [Online] Available from: https://www.medicines.org.uk/emc/product/3908/smpc
MHRA	Drug Safety Alert	Medicines and Healthcare Products Regulatory Agency (2014) Domperidone: risks of cardiac side effects - indication restricted to nausea and vomiting, new contraindications, and reduced dose and duration of use. Drug Safety Update, 7 (10): A1. [Online] Available from: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON418518 Medicines and Healthcare Products Regulatory Agency (2016) Apomorphine with domperidone: minimising risk of cardiac side effects [Online] Available from: https://www.gov.uk/drug-safety-update/apomorphine-with-domperidone-minimising-risk-of-cardiac-side-effects

Shared Care Agreement

Request by specialist for GP to enter into shared care agreement for prescription of Apomorphine

Part 1 – to be completed by specialist

Date _____

Name of Patient _____

Address _____

Patient NHS No: _____-_____

Patient hospital unit No _____

If using addressograph label please attach one to each copy

Dear Dr _____

I request that you prescribe Apomorphine for the above patient in accordance with the enclosed shared care protocol. Details of dosage will follow.

Specialist _____ Date _____

Part 2 – to be completed by GP

I agree/do not* agree to prescribe Apomorphine for the above patient in accordance with the enclosed shared care protocol.

GP _____ Date _____

Practice Address _____ _____

GP: Please sign and return by POST to:

Nicola Mason PD Nurse Specialists
Royal Preston Hospital
Sharoe Green Lane
Fulwood
Preston
PR2 9HT

Shared Care Agreement Form

Specialist request

***IMPORTANT: ACTION NEEDED**

Dear Dr *[insert Doctors name here]*

Patient name: *[insert Patients name here]*
Date of birth: *[insert date of birth]*
Diagnosis: *[insert diagnosis here]*

This patient is suitable for treatment with Apomorphine (APO-go) for the treatment of Parkinson's

This drug has been accepted for Shared Care according to the enclosed protocol (as agreed by Trust). I am therefore requesting your agreement to share the care of this patient.

Treatment was started on *[insert date started]* *[insert dose].*

The patient was discharged with *[insert number of days of medication]* supply of Apomorphine

If you are in agreement, please undertake monitoring and treatment from *[insert date]*

Baseline tests: *[insert information]*

Next review with this department: *[insert date]*
You will be sent a written summary within 14 days. The medical staff of the department are available at all times to give you advice. The patient will not be discharged from out-patient follow-up while taking *[insert text here]*.

The Consultant or PDNS is responsible for any dose adjustment

Please complete the reply slip overleaf and Post it as soon as possible to:
Nicola Mason PD Nurse Specialists. Royal Preston Hospital. Sharoe Green Lane. Fulwood. Preston. PR2 9HT

Thank you.

Yours

[insert Specialist name]

Patient Information Letter

Dear [insert patient's name],

As you are aware Dr [insert Dr's name] wants you to come in for treatment with Apomorphine.

To prevent the Apomorphine from producing sickness, we would like you to take the anti-sickness tablet Domperidone, 10mg three times daily, starting three days before your admission date and on the morning of your visit.

Please attend [insert date, time and location]. Please take just enough oral Parkinson's medication (as agreed with your specialist) to get you up and to the venue for your response test.

We have written to your GP accordingly, so that you can collect a prescription.

If you have any queries please contact [insert contact name and details],

Kind regards

Yours sincerely

[insert PDNS' signature] [insert Consultant's signature]

[insert PDNS' name] **Dr** [insert Dr's name]
Parkinson's Disease Specialist Nurse **Consultant** [insert Dr's role]

Outcome / Prescribing Information

Copy to be given to the patient

Dear Dr *[insert Doctors name here]*

Patient name: *[insert Patients name here]*
Date of birth: *[insert date of birth]*
Diagnosis: *[insert diagnosis here]*

This patient is suitable for treatment with Apomorphine (APO-go) for the treatment of Parkinson's

This drug has been accepted for Shared Care

Treatment was started on *[insert date started]*

- Dose is set at: *[insert dose mg.hr].*
- Flow rate: *[insert flow rate].*
- Syringe setting: *[insert 10ml or 20ml].*
- Bolus setting: *[insert bolus setting].*
- Time:
    - From: [insert time].
    - To: [insert time].

Please undertake prescribing and haemoglobin and reticulocyte count at 6 monthly intervals from *[insert date]*

You will be sent a written summary within 14 days.

Ongoing prescribing will depend on attendance at clinics as requested by the clinicians.

The Consultant or PDNS is responsible for any dose adjustment

Thank you.

Yours sincerely

[insert Specialist signature]
[insert Specialist name and role]