Milton Keynes Clinical Commissioning Group

NHS Central and North West London NHS Foundation Trust

NHS Milton Keynes University Hospital NHS Foundation Trust

Working in partnership

SHARED CARE PRESCRIBING GUIDELINE

Apomorphine in Parkinson's disease

NOTES to the GP

The expectation is that these guidelines should provide sufficient information to enable GPs to be confident to take clinical and legal responsibility for prescribing this drug.

The questions below will help you confirm this:

- Is the patient's condition predictable or stable?
- Do you have the relevant knowledge, skills and access to equipment to allow you to monitor treatment as indicated in this shared care prescribing guideline?
- Have you been provided with relevant clinical details including monitoring data?

If you can answer YES to all these questions (after reading this shared care guideline), then it is appropriate for you to accept prescribing responsibility.
If the answer is NO to any of these questions, you should not accept prescribing responsibility. You should write to the consultant within 14 days, outlining your reasons for NOT prescribing. If you do not have the confidence to prescribe, we suggest you discuss this with the appropriate Milton Keynes Hospital specialist service, who will be willing to provide training and support.
It would not normally be expected that a GP would decline to share prescribing on the basis of cost.

The patient's best interests are always paramount

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Approval group:	Milton Keynes Prescribing Advisory Group (MKPAG) June 2016	

Introduction and reason for shared care

Introduction

Apomorphine is a potent dopamine-receptor agonist that is sometimes helpful in advanced disease for patients experiencing unpredictable 'off' periods with levodopa treatment. Apomorphine cannot be given orally because it undergoes extensive first pass metabolism to an inactive metabolite. It is usually given by intermittent subcutaneous (SC) injection or continuous SC infusion.

Shared Care

A shared care guideline (SCG) is used to facilitate the sharing of care and transfer of prescribing. As with all SCGs, this guideline highlights relevant prescribing issues with Apomorphine and should be used in conjunction with relevant NICE guidance (NG71), the BNF, the Summary of Product Characteristics (SPC) and does not replace them. The sharing of care would usually take place once the patient's condition is stable; the patient is demonstrably benefiting from the treatment and is free from any significant side effects. In such an event, the total clinical responsibility for the patient with the diagnosed condition remains with the specialist. In practice, we anticipate there will only be a handful of patients across the whole MKCCG area that can be successfully treated with Apomorphine.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

Apomorphine in the patients with Parkinson's disease

1. CIRCUMSTANCES WHEN SHARED CARE IS APPROPRIATE

- Prescribing responsibility will only be transferred when the consultant and the GP are in agreement that the patient's condition is stable or predictable.
- Patients will only be referred to the GP once the GP has agreed in each individual case and the hospital will continue to provide prescriptions until successful transfer of responsibilities as outlined below

2. AREAS OF RESPONSIBILITY

Consultant

1. Assessment of suitability of patients for treatment, including assessment of parkinsonian signs and symptoms, fluctuations and dyskinesias and determining the best mode of administration (intermittent injection or continuous infusion).
2. Provision of information regarding apomorphine treatment, including discussing the aims, benefits and risks associated with apomorphine therapy with the patient and spouse/carers.
3. Explain to the patient their treatment plan including the dosing schedule.
4. Coombs positive haemolytic anaemia is a rare side effect of apomorphine which can also occur in patients treated with levodopa. Full blood count and reticulocyte count and Coombs test will be carried out by the hospital prior to initiation and at 6-12 monthly intervals thereafter.
5. **Apomorphine response test**: Start domperidone 10mg** three times daily prior to apomorphine therapy and arrange apomorphine response test. ***Domperidone should NOT BE USED in patients with serious underlying heart conditions. Domperidone should be avoided in patients who are taking concomitant medication known to cause QT prolongation (such as ketoconazole and erythromycin).* Once apomorphine treatment is established, the domperidone dose can be gradually reduced and then discontinued.
6. Ensure sitting and standing BP monitoring during initiation.
7. Initiation of apomorphine, including initial supply of the necessary equipment. Ensure hospital prescribing and supply for a minimum of 3 months, titrating dose accordingly over this initial treatment period. During that time optimise anti-parkinsonian drug treatment
8. Organisation of training for patient and carers to administer apomorphine if appropriate, including safe storage and disposal of sharps.
9. Monitoring and evaluation of response to therapy, including adverse drug reactions, with the patient and continue/discontinue treatment in line with agreed treatment plan.
10. Prior to initiation and during dose titration period, discuss the possibility of shared care with the GP practice and then with the patient, and ensure they understand the plan for their treatment.
11. Liaison with GP to participate in the shared care management of the patient, prior to and during the titration period and after shared care is established.
12. Communication of any changes in treatment or dose requirements, results of monitoring undertaken and assessment of adverse events to the GP.
13. Advise GP when treatment is considered to be no longer efficacious or if side effects outweigh benefit and treatment is to be discontinued.
14. Inform GP if patient does not attend planned follow-up appointment.
15. Provide telephone contact point with Parkinson's Disease Nurse Specialist (PDNS) for patients, carers and primary care team.

GP

1. Subsequent prescribing of apomorphine at the dose recommended, when patient is stabilised.
2. Inform the hospital team of any changes in the patient's condition which may be related to treatment with apomorphine and if the patient experiences any adverse effects of treatment or complications of apomorphine administration.
3. Conduct a full blood count, urea, creatinine and liver function tests, blood pressure and heart rate measurement every 6-12 months and report results outside normal range to the hospital team.
4. Consult promptly with the hospital consultant or the PDNS if the patient deteriorates, has problems administering apomorphine or when test results are abnormal or patient defaults from blood test appointments; adjust the dose or stop or change treatment as advised by the hospital consultant.
5. Inform the hospital consultant if declining shared care for apomorphine

Patient

1. Discuss potential benefits and side effects of treatment with the PDNS and GP, to identify whether they have a clear picture of these from the PDNS and to raise any outstanding queries.
2. Report to the hospital consultant or GP if he or she does not have a clear understanding of the treatment.
3. Share any concerns in relation to the treatment with the medicine.
4. Inform the hospital consultant or GP of any other medications being taken, including over-the-counter products.
5. Report any adverse effects to the hospital consultant or GP.
6. Participate in the monitoring of therapy and the assessment of outcomes, to assist health professionals to provide safe and appropriate treatment.
7. If wishing to self-administer, will agree to appropriate training and to protocols for the safe disposal of sharps.

Contact Information

Hospital contact:	The referral letter will indicate named consultant	
Hospital name (MKUH)	Milton Keynes University Hospital NHS Foundation Trust, Standing Way, Eaglestone, Milton Keynes, MK6 5LD	01908 660033
Out-of-hours	Contact Hospital A&E	01908 660033
Consultant Neurologist, MKUH	Dr John Jacob	01908 997070
Parkinson's Disease Nurse Specialist (PDNS)	Tess Adams	01908 724554
APO-go® order line	E-mail: customerservices@britannia-pharm.com	0844 8801326
Pharmacy Medicines Information	Based in MKUH	01908 995738

3. COMMUNICATION AND SUPPORT

Specialist support/resources available to GP including patient information:

APO-go® Helpline (365 days a year, 24 hours a day)	http://www.apo-go.co.uk/	0844 8801327

4. CLINICAL INFORMATION

Indication(s):	**Indication for Therapy** Treatment of motor fluctuations ("on-off" phenomena) in patients with Parkinson's disease which are not sufficiently controlled by oral anti-Parkinson medication.
Place in Therapy:	In patients not sufficiently controlled by oral anti-Parkinson medication.
Therapeutic summary:	Apomorphine is a potent dopamine-receptor agonist that is sometimes helpful in advanced disease for patients experiencing unpredictable 'off' periods with levodopa treatment
Dose & route of administration:	**Recommended Dosage and Administration** Apomorphine is available as either an intermittent subcutaneous injection, via a prefilled pen, or by continuous subcutaneous infusion, using an infusion pump or syringe driver. The apomorphine dose will be determined on an individual patient basis by the specialist team. It is essential that the patient is established on the lowest effective dose of domperidone for at least 3 days prior to the initiation of therapy. Note recent MHRA warnings on the use of domperidone: Drug Safety Update April 2016 Drug Safety Update May 2014 To suit patient needs, there are two modes via which Apomorphine can be administered into subcutaneous tissue: **1. By intermittent subcutaneous injection**, to determine threshold dose, initially 1mg of apomorphine HCl (0.1ml), that is approximately 15-20 micrograms/kg, may be injected subcutaneously during a hypokinetic, or 'off' period and the patient is observed over 30 minutes for a motor response. If no response, or an inadequate response, is obtained a second dose of 2 mg of apomorphine HCl (0.2ml) is injected subcutaneously and the patient observed for an adequate response for a further 30 minutes. The dosage may be increased by incremental injections with at least a forty minute interval between succeeding injections, until a satisfactory motor response is obtained; usual range 3 to 30mg daily in divided doses; maximum single dose 10mg **2. By continuous subcutaneous infusion** Subcutaneous infusion may be preferable in those requiring division of injections into more than 10 doses daily; patients who have shown a good 'on' period response during the initiation stage of apomorphine therapy, but whose overall control remains unsatisfactory using intermittent injections, or who require many and frequent injections (more than 10 per 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 1 mg apomorphine HCl (0.2 ml) per hour then increased according to the individual response each day. Increases in the infusion rate should not exceed 0.5 mg at intervals of not less than 4 hours. Hourly infusion rates may range between 1mg and 4mg (0.2ml and 0.8ml), equivalent to 0.014 – 0.06 mg/kg/hour. 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 ***Note***: Total daily dose by either route (or combined routes) maximum 100mg **Administration site** Intermittent subcutaneous injections should be administered into the lower abdominal wall (below the umbilicus), the upper outer aspects of the thighs or outer aspects of the top of the arms. The injection site should be rotated for each injection. The best sites for needle placement for continuous subcutaneous infusion are the anterior abdominal wall below the umbilicus and the upper outer aspects of the thighs. Less commonly, the shoulder is used (the fatty tissue over the trapezius muscle). **The injection site should be rotated daily to minimise possible localised skin irritation.**
Duration of treatment:	When treatment is considered to be no longer efficacious or if side effects outweigh benefit - treatment is to be discontinued.

Preparations available (Manufacturer)

Preparation available	Administration	Pack size	*Cost (excl VAT)
APO-go® ampoules (Apomorphine hydrochloride 10mg/mL) Injection	By intermittent bolus injection or continuous SC infusion	2mL ampoule	£7.59
		5mL ampoule	£14.62
APO-go® Pen (Apomorphine hydrochloride 10mg/mL)	By intermittent bolus injection	3mL pre-filled pen injector	£24.78
APO-go® PFS (Apomorphine hydrochloride 5mg/mL)	By continuous SC infusion. It is intended for use without dilution	10mL pre-filled syringe	£14.62

**eBNF prices (Feb 2019); There is no VAT on FP10s, but VAT applies when hospital purchase and supply*

Frequency of adverse effect	Clinical condition
Very Common	Injection site reactions
Common	Nausea, vomiting, neuropyschiatric disturbances, sedation, somnolence, dizziness, yawning
Uncommon	Haemolytic anaemia, thrombocytopenia, dyskinesias during 'on' periods, sudden sleep onset, postural hypotension, breathing difficulties, local and generalized rashes, injection site necrosis and ulceration

Positive Coombs' tests have been reported for patients receiving apomorphine.
This list is not exhaustive. Please refer to the relevant SPC (at www.medicines.org.uk) for full information

Monitoring Requirements by specialist:	See Consultant responsibility for full details
Monitoring Requirements by GP:	Conduct a full blood count, urea, creatinine and liver function tests, blood pressure and heart rate measurement every 6-12 months and report results outside normal range to the hospital team.
Clinically relevant drug interactions:	In the initial stages of apomorphine therapy, the patient should be monitored for unusual side effects or signs of potentiation of effect. Particular caution should be given in patients with pre-existing cardiac disease or in patients taking vasoactive medicinal products such as antihypertensives. **Neuroleptic medicinal products** may have an antagonistic effect if used with apomorphine. There is a potential interaction between clozapine and apomorphine, however where necessary, clozapine may also be used to reduce the symptoms of neuropsychiatric complications. [*Clozapine is only available*

	where the prescriber and the dispensary pharmacy are each registered with, and comply with the requirements of, the clozapine monitoring service, to manage the risk of agranulocytosis]; Effects of apomorphine possibly enhanced by **entacapone;** Possible increased hypotensive effect when apomorphine given with **ondansetron** (avoid concomitant use); Effects of dopaminergics possibly enhanced by **memantine;** Antiparkinsonian effect of dopaminergics antagonised by **methyldopa** The possible effects of apomorphine on the plasma concentrations of other medicinal products have not been studied. Therefore caution is advised when combining apomorphine with other medications, 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.
Clinically relevant Precautions and Contraindications:	It must not be administered to patients who have an 'on' response to levodopa which is marred by severe dyskinesia or dystonia.
Precautions and Contra-Indications Apomorphine should be **used with caution** in patients: 1. with renal diseases 2. with pulmonary diseases 3. with cardiovascular diseases 4. prone to nausea and vomiting 5. with pre-existing postural hypotension 6. susceptible to QT-interval prolongation	Apomorphine is **contra-indicated** in patients: 1. with any respiratory depression 2. with dementia 3. with psychotic diseases 4. with hepatic insufficiency 5. with known hypersensitivity to apomorphine or any of the excipients 6. under 18 years of age
Pregnancy and Lactation	There is no experience of apomorphine usage in pregnant women. The potential risk for humans is unknown. Apomorphine hydrochloride is not recommended during pregnancy and in women of childbearing potential not using contraception. It is not known whether apomorphine is excreted in breast milk. A risk to the new-borns/infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from apomorphine therapy taking into account the benefit of breastfeeding to the child and the benefit of therapy for the woman.
Practical issues / Pharmaceutical precautions	Do not store above 25°C and protect away from light. Once the ampoules are opened, it should be used immediately. The solution should be inspected visually prior to use. Only clear and colourless solutions should be used. Do not use if the solution has turned green. APO-go® pens should be used within 48 hours after opening.
Supply arrangements	**Manufacturer:** Britannia Pharmaceuticals Ltd, 200 Longwater Avenue, Green Park, Reading, Berkshire, RG2 6GP Website: http://www.britannia-pharm.co.uk **In hospital** The apomorphine (APO-go®) syringes are supplied by the company free of charge for the challenge tests. It is good practice to record the batch no of the syringes used together with the expiry dates against the patient name preferably on the prescription chart. Pharmacy will also have a note of receipt and will store the syringes until needed. The APO-go® pump Britannia pharmaceuticals will loan the pump free of charge to the hospital consultant for use by the patient. Full training is provided from the manufacturer via the APO-go® Package of Care

	In the community Apomorphine is prescribable on FP10 but is not available from local wholesalers, only direct from the manufacturer
Key references:	1. Summary of Product Characteristics: Apomorphine APO-go® ampoules 10mg/mL solution for injection. Last updated on the eMC: 03/07/2018. 2. Summary of Product Characteristics: Apomorphine APO-go® ampoules 10mg/mL solution for injection or infusion. Last updated on the eMC: 03/07/2018. 3. Summary of Product Characteristics: APO-go® PFS 5mg/mL solution for infusion in pre-filled syringe. Last updated on the eMC: 03/07/2018. 4. British National Formulary (BNF); Accessed Feb 2019 Via https://bnf.nice.org.uk/drug/apomorphine-hydrochloride.html 5. University College London Hospitals NHS Foundation Trust – Treatment of Parkinson's Disease with Apomorphine Shared Care Guidelines 5th Edition 2005; Last accessed July 2014 6. NHS Fife Shared Care Protocol Jan 2014 – Apomorphine for patients with Parkinson's disease. Last accessed Nov 2014 7. Surrey and Sussex Healthcare NHS Trust – Shared Care Prescribing Guideline: Apomorphine hydrochloride for the treatment of motor fluctuations ('on-off' phenomena) in patients with Parkinson's Disease which are not sufficiently controlled by oral anti-Parkinson medication. This SCG was adapted from Royal Cornwall Hospitals Trust Shared Care Guidelines for Treatment of Parkinson's Disease with Apomorphine (Nov 2012) and Bedfordshire Protocol for Apomorphine Shared Care in Parkinson's Disease (2009). Last accessed: Nov 2014 8. Drug Safety Update. Domperidone: risks of cardiac side effects. Accessed via https://www.gov.uk/drug-safety-update/domperidone-risks-of-cardiac-side-effects (Feb 2019) 9. Northamptonshire CCG, KGH/NGH Shared Care Protocol August 2014 – Apomorphine in Parkinson's Disease; Last accessed Nov 2014

Apomorphine in Parkinson's Disease

Shared Care Guideline: Prescribing Agreement

(Note: Sections A and B MUST be forwarded to GP and returned by GP back to the hospital together)

Section A: To be completed by the hospital consultant initiating the treatment

GP Practice Details:	**Patient Details:**
Name: ……	Name: ……
Address: ……	Address: ……
Tel no: ……	DOB: ……/……/……
Fax no: ……	Hospital number: ……
NHS.net e-mail: ……	NHS number (10 digits): ……

Consultant name: ……
Clinic name: ……
Contact details:
Address: .....
Tel no: …… Fax no: ……
NHS.net e-mail: ……

Diagnosis:	**Drug name & dose to be prescribed by GP:**
……	……

Next hospital appointment: ……/……/……..

Dear Dr. ……..,
Your patient was seen on …../…../……and I have started ……(insert drug name and dose) for the above diagnosis. I am requesting your agreement to sharing the care of this patient from …../…../…….. in accordance with the (attached) Shared Care Prescribing Guideline (approval date: …./…./……..). Please take particular note of Section 2 where the areas of responsibilities for the consultant, GP and patient for this shared care arrangement are detailed.

Patient information has been given outlining potential aims and side effects of this treatment and ……* supplied *(* insert any support materials issued such as patient held monitoring book etc where applicable).* The patient has given me consent to treatment possibly under a shared care prescribing agreement (with your agreement) and has agreed to comply with instructions and follow up requirements.

The following investigations have been performed on ……/……/…… and are acceptable for shared care. Please monitor…….....every ……..

Test	**Result**	**Test**	**Result**

Other relevant information: ……..
……..

Consultant Signature: ……Date: …/…/…..

Section B: To be completed by the GP and returned to the hospital consultant as detailed in Section A above

Please sign and return your agreement to shared care within 14 days of receiving this request
Tick which applies:
□ I accept sharing care as per shared care prescribing guideline and above instructions
□ I would like further information. Please contact me on:……..
□ I am not willing to undertake shared care for this patient for the following reason:
……

GP name: ……

GP signature: ……Date: …/…/…..

(Note: Sections A and B MUST be forwarded to GP and returned by GP back to the hospital together)