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Royal Cornwall Hospitals NHS Trust

Apomorphine for treatment of Parkinson's Disease Shared Care Guideline

V3.0

May 2019

1. Aim/Purpose of this Guideline

1.1. This guideline applies to medical, nursing and pharmacy staff in the safe and appropriate prescription and administration of apomorphine when used in Parkinson's Disease.

1.2 This shared care guideline sets out details for the sharing of care of adult patients prescribed apomorphine. These guidelines provide additional limited information necessary to aid in the treatment these patients. As with all shared care guidelines they highlight relevant prescribing issues but should be used in conjunction with relevant NICE guidance, the BNF, ABPI summary of product characteristics and do not replace them.

1.3. **Data Protection Act 2018 (General Data Protection Regulation – GDPR) Legislation**

The Trust has a duty under the DPA18 to ensure that there is a valid legal basis to process personal and sensitive data. The legal basis for processing must be identified and documented before the processing begins. In many cases we may need consent; this must be explicit, informed and documented. We can't rely on Opt out, it must be Opt in.

DPA18 is applicable to all staff; this includes those working as contractors and providers of services.

For more information about your obligations under the DPA18 please see the 'information use framework policy', or contact the Information Governance Team rch-tr.infogov@nhs.net

2. The Guidance

2.1 Parkinson's disease (PD) is a common neurodegenerative disorder with a prevalence of about 145,000 in the UK; typical age of onset is between 50-65 years. This is roughly one person in every 350 people.

Motor symptoms (bradykinesia, rigidity and tremor) dominate the clinical picture. The aetiology of PD is unknown but motor symptoms are believed to be caused by a dopamine deficit in the striatum due to progressive loss of dopaminergic neurons that project to the striatum from the substantia nigra.

Drug therapy with levodopa (a precursor to dopamine) and oral dopamine agonists usually provide good symptomatic relief without significant side effects in early disease. However, after some years of treatment many patients develop motor complications which include fluctuations in motor control and dyskinesias. As the disease progresses, the motor fluctuations often cause increasing disability.

Disabling motor fluctuations include unpleasant "off" periods. "Off" periods can be associated with dystonia, depression, pain, sleep dysfunction, bladder dysfunction and swallowing difficulties. With disease progression 'off' periods can occur suddenly rendering someone immobile in a matter of minutes. 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. However optimizing treatment can be difficult and complex for many patients.

2.2 Apomorphine (as APO-go®) is licensed for use in patients with disabling motor fluctuations who are inadequately controlled with levodopa or dopamine agonists. The license covers both subcutaneous intermittent injections and continuous subcutaneous infusions. Despite its name it has no opiate or addictive properties.

Apomorphine cannot be used orally because it undergoes extensive first pass metabolism to an inactive metabolite; for this reason it is administered subcutaneously.

2.3 Preparations and Dosage

2.3.1. This shared care guideline describes the use of the APO-go brand of apomorphine, though other non-proprietary makes are available.

2.3.2. Apomorphine may be administered as a “rescue therapy” with intermittent subcutaneous bolus injections given via a prefilled APO-go® Pen to give a ‘boost’ in dopaminergic stimulation when needed. Apomorphine Pens can provide a means of rescue within 10 minutes of administration, thereby regaining mobility and independence. The effect usually lasts for about an hour. Injections are given subcutaneously either into the lower abdominal wall, below the umbilicus or in the upper outer aspects of the thighs. The injection site is rotated for each injection to avoid irritation of the skin. This injectable route of administration via a Pen is usually undertaken first.

2.3.3. For those patients who experience more complex motor fluctuations, including dyskinesias, a continuous subcutaneous infusion using an ambulatory APO-go® pump may be used with the APO-go® prefilled syringe.

The infusion site should be changed daily and apomorphine given during waking hours only unless there are severe night-time symptoms. Intermittent bolus boosts are also sometimes needed.

2.3.4. The dose of apomorphine is carefully titrated on an individual basis, and can range from a few milligrams daily by intermittent subcutaneous injections, up to 100 milligrams daily by continuous infusion. In rare cases it may be necessary to give higher doses

2.3.5. Products available are:

APO-go® Pen 10mg/ml 3ml pen injector

Usual range following initiation: 3-30mg daily in divided doses. Subcutaneous infusion may be preferable in those requiring division of injections into more than 10 doses daily.

2.3.6. APO-go® PFS 5mg/ml 10ml prefilled syringe

Usual range following initiation: 1-4mg/hour or a range of 14-60 micrograms/kg/hour

2.3.7. Maximum daily dose by either (or combined routes) is 100mg.

2.3.8. Apomorphine is prescribable on FP10 but is not available from local wholesalers, only direct from the manufacturer:

Britannia Pharmaceuticals, 200 Longwater Avenue, Green Park, Reading, Berkshire,

RG2 6GP

Orderline: 0844 8801326

e-mail: customerservices@britannia-pharm.com

2.4 Contraindications and Precautions

Contraindications in patients with respiratory depression, dementia, psychotic diseases or hepatic insufficiency. Apomorphine HCl treatment must not be administered to patients who have an 'on' response to levodopa which is marred by severe dyskinesia or dystonia. Hypersensitivity to the active substance or to any of the excipients. APO-go should not be administered to patients who have a hypersensitivity to apomorphine or any excipients of the medicinal product.

APO-go is contra-indicated for children and adolescents under 18 years of age.

2.4.1. Apomorphine should be used with caution as follows:

Pulmonary or cardiovascular disease, history of postural hypotension (special care on initiation), neuropsychiatric reactions or dementia; hepatic, haemopoietic, renal, and cardiovascular monitoring *on administration with levodopa;* test every six months for haemolytic anaemia (development calls for specialist haemotological care with dose reduction and possible discontinuation). Positive Coombs' tests have been reported for patients receiving apomorphine and levodopa, renal impairment, pregnancy.

Since apomorphine, especially at high dose, may have the potential for QT prolongation, caution should be exercised when treating patients at risk for torsades de pointes arrhythmia.

2.4.2. Patients receiving apomorphine and domperidone require an assessment of cardiac risk factors and ECG monitoring to reduce the risk of serious arrhythmia related QT-prolongation.

2.5 Monitoring - SPECIALIST TEAM

Undertake any baseline assessments including ECG. If this is not possible to undertake, an ECG and routine bloods will be requested for general practice, with the ECG returned to Specialist Team for review.

Monitoring therapy and evaluation of adverse drug reactions.

BP monitoring (eg standing and sitting) during initiation and any dose titration phase

2.6 Monitoring - GENERAL PRACTICE

Perform a full blood count at 4-6 monthly intervals

BP monitoring at 4-6 monthly intervals

If patient remains on domperidone therapy long term, undertake ECG monitoring if clinically indicated (ie if a QT-prolonging or interacting drug is started or if symptoms of cardiac side effects are reported)

2.7 Side Effects

Nausea, vomiting, drowsiness (including sudden onset of sleep), confusion, hallucinations, injection-site reactions (including nodule formation) and ulceration) – change injection sites in rotation; *less commonly* postural hypotension, breathing difficulties, dyskinesias during 'on' periods (may require discontinuation), haemolytic anaemia with levodopa (see Cautions), and rash; *rarely* eosinophilia, pathological gambling, increased libido, and hypersexuality also reported.

2.8 Significant Drug Interactions

Patients should be monitored for potential interactions during initial stages of apomorphine therapy. Particular caution should be given in patients with pre-existing cardiac disease or in patients taking vasoactive medicinal products such as antihypertensives, and especially in patients with pre-existing postural hypotension.

- Effects of apomorphine antagonized by antipsychotics
- Effects of apomorphine possibly enhanced by entacapone
- Effects of dopaminergics possibly enhanced by memantine
- Antiparkinsonian effect of dopaminergics antagonized by methyldopa

2.9 Notes

2.9.1. Prefilled syringes of apomorphine should be stored at room temperature (at or below 25ºC) and protected from light. Once opened, they should be used immediately. No antimicrobial preservative is included in the formulation so prepared syringes should be used within 24 hours. The solution must not be used if it is green or discoloured.

2.9.2. APO-go Pens should be stored in a cool dry place, but not in a fridge and discarded 48hrs after opening.

2.9.3. APO-go stains green on contact so care should be taken to avoid spillages. Lemon juice may prevent green colouring from developing if used immediately. Bleach may help reduce stains on kitchen surfaces.

2.10. Areas of Responsibility for the Sharing of Care

2.10.1. These are suggested ways in which the responsibilities for the management of adult patients with who are prescribed **apomorphine** can be shared between the specialist and the general practitioners. The expectation is that these guidelines should provide sufficient information to enable GPs to be confident to take clinical and legal responsibility for prescribing these drugs. If a specialist asks the GP to prescribe this drug the GP should reply to this request as soon as practical. Sharing of care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient and be accepted by them.

2.10.2. In the NHS E guidelines on responsibility for prescribing (January 2018) between hospitals and GPs, it is advised that legal responsibility for prescribing lies with the doctor who signs the prescription.

2.10.3. **Specialist:**

- Patient selection and conduct any necessary baseline assessments to determine suitability.
- Agreement to initiate treatment reached between patient, GP and Specialist Team (under Shared Care Guideline) using the shared care agreement letter.
- Liaison (including provision of information) with patient, spouse, carers and Primary Care Teams.
- Start domperidone 10 mg** three times daily three days prior to apomorphine challenge (See Appendix 3 for Challenge instructions) and arrange day case admission for apomorphine challenge.** Domperidone is contraindicated in people with underlying cardiac conditions and other risk factors, including those who take concomitant medication known to cause QT prolongation or potent CYP3A4 inhibitors (such as ketoconazole and erythromycin); and in people with severe hepatic impairment. Once apomorphine treatment is established, the domperidone dose should be gradually reduced to the lowest effective dose and discontinued as soon as possible
- Specialist team to initiate either intermittent apomorphine injection or continuous infusion driver and optimise anti-parkinsonian drug therapy.
- Monitoring and evaluation of adverse drug reactions.
- Telephone contact for patients, carers and health professionals, providing the GP with relevant contact information with clear arrangements for back-up advice and support should further assistance be required relating to this drug.
- The Consultant / Specialist Team will be responsible for disease and drug response monitoring; this will be undertaken in the out-patient setting, and where necessary, the patient's home.
- Discontinue treatment when considered to be no longer efficacious or if side-effects outweigh benefit.
- Specify review dates at clinically relevant time intervals for both the GP and the consultant.
- Prompt communication with GP of any changes in treatment or dose requirements, results of monitoring undertaken and assessment of adverse events.
- The Specialist Team will inform the relevant community pharmacy / dispensing surgery of supply arrangements for apomorphine and consumables.

2.10.4. **General Practitioner:**

- If the GP disagrees to undertake shared care he/she will notify the consultant in writing without undue delay by completing the shared care agreement letter.

- To inform the specialist team of any significant developments, or deterioration, such as the occurrence of side effects or an inability to administer apomorphine.
- Be aware that domperidone may be associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death, and hence is contraindicated in those with underlying cardiac conditions and other risk factors.
- Perform a full blood count at 4-6 monthly intervals.
- BP monitoring at 4-6 monthly intervals.
- For patients remaining on domperidone therapy long term, ECG monitoring if clinically indicated.
- Following initiation to prescribe on-going drug therapy as recommended by the specialist team including a 7 litre sharps box (unless Homecare Service is initiated).
- To facilitate the co-ordination of on-going patient care within the community and home environment, liaising with the Specialist Team when necessary.

2.10.5. **Patient / parent / guardian / carer:**

- Sign the shared care agreement letter.
- Report any adverse effects to their GP and/or specialist regarding their treatment. Patients should specifically report if they experience a racing heartbeat, palpitations, dizziness, fainting, or black outs.
- Ensure that they have a clear understanding of their treatment and they attend for monitoring requirements as per shared care guideline.
- Take prescriptions to the pharmacy / dispensing surgery as soon as possible so they have adequate time to obtain supplies of the medicine.

2.10.6. BACK-UP ADVICE AND SUPPORT IS AVAILABLE FROM THE PARKINSON'S TEAM AND RELEVANT APO-GO SUPPORT ROUTES

3. Monitoring compliance and effectiveness

Element to be monitored	Compliance with prescribing and administration in accordance with this guideline (or other safe practice)
Lead	Head of Prescribing Support Unit
Tool	No specific tool
Frequency	As required according to clinical incident reports
Reporting arrangements	Via Cornwall Area Prescribing Committee / Medication Practice Committee
Acting on recommendations and Lead(s)	Relevant Clinical Staff
Change in practice and lessons to be shared	Lessons and changes in practice will be communicated through various channels to relevant staff

4. Equality and Diversity

4.1. This document complies with the Royal Cornwall Hospitals NHS Trust service Equality and Diversity statement which can be found in the 'Equality, Inclusion & Human Rights Policy' or the Equality and Diversity website.

4.2. Equality Impact Assessment

The Initial Equality Impact Assessment Screening Form is at Appendix 2.

Appendix 1. Governance Information

Document Title	Apomorphine for treatment of Parkinson's Disease Shared Care Guideline V3.0		
Date Issued/Approved:	March 2019		
Date Valid From:	May 2019		
Date Valid To:	May 2022		
Directorate / Department responsible (author/owner):	Parkinson's Disease Team / Pharmacy - Head of Prescribing Support Unit		
Contact details:	01872 253548		
Brief summary of contents	Some clinical issues and details of prescribing responsibilities for GP and specialists		
Suggested Keywords:	Apomorphine		
Target Audience	RCHT	CFT	KCCG
	✓		✓
Executive Director responsible for Policy:	Medical Director		
Date revised:	March 2019		
This document replaces (exact title of previous version):	Shared care guideline for treatment of Parkinson's Disease with apomorphine		
Approval route (names of committees)/consultation:	Cornwall Area Prescribing Committee		
Care Group Manager confirming approval processes	Robin Jones		
Name and Post Title of additional signatories	Not required		
Name and Signature of Divisional/Directorate Governance Lead confirming approval by specialty and divisional management meetings	{Original Copy Signed}		
	Name: Kevin Wright		
Signature of Executive Director giving approval	{Original Copy Signed}		

Publication Location (refer to Policy on Policies – Approvals and Ratification):	Internet & Intranet	✓	Intranet Only	
Document Library Folder/Sub Folder	Pharmacy			
Links to key external standards	None			
Related Documents:	Summaries of Product Characteristics APO-go information for both patients and healthcare professionals https://www.apo-go.com/ 24/7 Helpline manned by APO-go advisers: 0844 8801327			
Training Need Identified?	No			

Version Control Table

Date	Version No	Summary of Changes	Changes Made by *(Name and Job Title)*
21 Nov' 2012	V1.0		M Wilcock, Head of Prescribing Support Unit
Sept 2014	V2.0	Update warning for domperidone	M Wilcock, Head of Prescribing Support Unit
May 2016	V2.1	ECG monitoring advice included	M Wilcock, Head of Prescribing Support Unit
Mar 2019	V3.0	New format and minor changes 2.3 and 2.10.3	M Wilcock, Head of Prescribing Support Unit

All or part of this document can be released under the Freedom of Information Act 2000

This document is to be retained for 10 years from the date of expiry.
This document is only valid on the day of printing

Controlled Document

This document has been created following the Royal Cornwall Hospitals NHS Trust Policy for the Development and Management of Knowledge, Procedural and Web Documents (The Policy on Policies). It should not be altered in any way without the express permission of the author or their Line Manager.

Appendix 2. Initial Equality Impact Assessment Form

This assessment will need to be completed in stages to allow for adequate consultation with the relevant groups.

<table>
<tr><td colspan="7">Apomorphine for treatment of Parkinson’s Disease Shared Care Guideline V3.0</td></tr>
<tr><td colspan="3">Directorate and service area: Pharmacy</td><td colspan="4">Is this a new or existing Policy?
Existing</td></tr>
<tr><td colspan="3">Name of individual completing assessment:
Dan Thomas, Pharmaceutical Services Contracting Team, NHS Kernow</td><td colspan="4">Telephone:
01726 627953</td></tr>
<tr><td>1. Policy Aim*

Who is the strategy / policy / proposal / service function aimed at?</td><td colspan="6">To provide information on prescribing of apomorphine to enable General Practitioners to take over prescribing responsibility from secondary care.</td></tr>
<tr><td>2. Policy Objectives*</td><td colspan="6">To promote a consistent level of shared care between primary and secondary care (in relation to RCHT catchment area)</td></tr>
<tr><td>3. Policy – intended Outcomes*</td><td colspan="6">Confident and competent prescribers, enabling medicines to be access in a primary care setting.</td></tr>
<tr><td>4. *How will you measure the outcome?</td><td colspan="6">Six monthly review</td></tr>
<tr><td>5. Who is intended to benefit from the policy?</td><td colspan="6">General practitioners, hospital specialists and community pharmacists – from understanding local guidance around use of these medicines. Patients/carers, from being able to access medicines from their GP.</td></tr>
<tr><td rowspan="3">6a Who did you consult with

b). Please identify the groups who have been consulted about this procedure.</td><td>Workforce</td><td>Patients</td><td>Local groups</td><td>External organisations</td><td colspan="2">Other</td></tr>
<tr><td>X</td><td></td><td></td><td>X</td><td colspan="2"></td></tr>
<tr><td colspan="6">Please record specific names of groups
Cornwall Area Prescribing Committee</td></tr>
<tr><td>What was the outcome of the consultation?</td><td colspan="6">Agreed</td></tr>
</table>

7. The Impact
Please complete the following table. **If you are unsure/don't know if there is a negative impact you need to repeat the consultation step**.

Are there concerns that the policy **could** have differential impact on:

Equality Strands:	Yes	No	Unsure	Rationale for Assessment / Existing Evidence
Age		**X**		
Sex (male, female, trans-gender / gender reassignment)		**X**		
Race / Ethnic communities /groups		**X**		
Disability - Learning disability, physical impairment, sensory impairment, mental health conditions and some long term health conditions.		**X**		
Religion / other beliefs		**X**		
Marriage and Civil partnership		**X**		
Pregnancy and maternity		**X**		
Sexual Orientation, Bisexual, Gay, heterosexual, Lesbian		**X**		

You will need to continue to a full Equality Impact Assessment if the following have been highlighted:

- You have ticked "Yes" in any column above and
- No consultation or evidence of there being consultation- this excludes any *policies* which have been identified as not requiring consultation**. or**
- Major this relates to service redesign or development

8. Please indicate if a full equality analysis is recommended.	**Yes**		**No X**	

9. If you are **not** recommending a Full Impact assessment please explain why.

Not indicated.

Date of completion and submission	Nov 2018.	Members approving screening assessment	Policy Review Group (PRG) **APPROVED**

This EIA will not be uploaded to the Trust website without the approval of the Policy Review Group.

A summary of the results will be published on the Trust's web site.

Appendix 3. Apomoprhine Challenge

Before therapy can be initiated an apomorphine challenge is necessary in order to:
1. Determine whether a patient has a positive response to the medication
2. Establish the optimum dose for the individual patient
3. Observe the patient for side effects such as nausea, vomiting, postural hypotension, hallucinations and sleepiness. Three days prior to and throughout the challenge, domperidone 10mg** orally TDS is commenced (usually at home) to avert the significant emetic effects of apomorphine. Exceptionally a higher dose of domperidone 20mg TDS may be used).The challenge is usually performed as a day case in a safe clinical environment with medical support.

Procedure
1. Obtain a starter pack of 5 APO-go Pens. This is available free of charge from Britannia Pharmaceuticals for the challenge procedure
2. Pre-treat with domperidone 10mg TDS** for 72 hours prior to and ongoing following a positive outcome of the challenge. The dosage may then be titrated downwards as tolerance develops.
3. Patients should obtain a prescription from the specialist team. The patient should not receive any oral anti-Parkinson medication for a minimum of eight hours prior to the challenge, unless necessary in order to provoke an “off” state. The patient’s mobility should be considered if the challenge is to be performed as a day case. If necessary for mobility a dose of medication such as co-beneldopa dispersible 62.5mg may be required.
4. Motor function is assessed at baseline using the Unified Parkinson’s Disease Rating Scale (UPDRS) section III Motor Function, together with a timed a 12 (if practicable) metre walk (the time it takes the patient to rise from a chair with arms folded then walk 6m, turn, return 6m, then sit down). Lying and standing blood pressure is also recorded due to the possible hypotensive effects of dopamine agonists. These assessments are repeated after sequential doses of apomorphine.
5. Administer 1mg apomorphine subcutaneously as a test dose and repeat above motor assessment and blood pressure 20-30 minutes following dose, monitor for side effects and observe for a positive response.
6. If there is no or a poor response, give a subsequent dose of 2-3 mg apomorphine. Continue to assess as above and observe.
7. Increase the dose in incremental steps every 45-60 minutes (eg. 2mg, 3mg, 5mg, 7mg) Stop when a positive response is seen. If at 7 mg there is no response, then the patient is termed a non-responder. If a mild response is noted at 7mg, discuss with the patient’s neurologist as to whether then the maximum dose of 10mg should be administered.

A challenge is positive if either the following are seen, for example:
1. A decrease in UPDRS motor score by at least 20%.
2. A minimum of 20% improvement in timed walking.

<u>Supply arrangements</u>
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.

** Note recent MHRA safety warnings with domperidone. See ‘Specialist Team Responsibilities’ above.