Cambridge University Hospitals NHS
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Clinical Commissioning Group

Shared Care Guideline Cover Sheet

Shared Care Guideline: Apomorphine use in Parkinson's disease
This is a NEW shared care guideline.
Estimated number of patients over a 1 year period: 10
Rationale for shared care guideline
To provide guidance on the prescribing and monitoring of Apomorphine to patients with Parkinson's disease in primary and secondary care. This document provides advice on the initiation, prescribing and monitoring of Apomorphine 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 guideline will align practice across the region, improve transfer of care and patient safety The guideline will also ensure all parties involved in the patient's care are aware of their responsibilities.
Summary of changes made to updated existing shared care guideline
Name: Emma Bines **Role:** Lead Pharmacist – Department of Medicine for the Elderly **Date: 22/06/17**

Shared Care Guideline

Apomorphine use in Parkinson's disease

Executive Summary

- The responsibility of initiating Apomorphine will remain with the Hospital Specialist.
- Guideline produced in accordance with recommendations in NICE guidelines.
- Apomorphine will be prescribed for use in patients with Parkinson's disease for the treatment of frequent and/or severe akinesia ("off periods") not controlled by individually titrated levodopa and/or other dopamine agonists.
- GP specific responsibilities are to prescribe domperidone and apomorphine and additional concomitant medications advised by the specialist team, arrange FBC's, Coombs' test, LFT's and renal function tests at 6-12 month intervals as directed by the Hospital Specialist.
- The responsibilities of the hospital specialist, GP and patient for this Shared Care Guideline can be found within this document in detail here.

Sharing of care depends on communication between the specialist team, GP, community Parkinson's disease (PD) Nurse, Apo Nurse and the patient or their parent/carer. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. The doctor/healthcare professional who prescribes the medication has the clinical responsibility for the drug and the consequences of its use. Further information about the general responsibilities of the hospital specialist and GP can be found here

1. Scope

This document provides advice on the initiation, prescribing and monitoring of Apomorphine 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.

2. Aim

To provide guidance on the prescribing and monitoring of Apomorphine to patients with Parkinson's disease in primary and secondary care.

3. Introduction

Apomorphine is a potent injectable dopamine agonist with a high affinity for D1, D2 and D3 receptors and has no narcotic properties.
It is licensed for the treatment of frequent and/or severe akinesia ("off periods") not controlled by individually titrated levodopa and/or other dopamine agonists. Treatment is by intermittent subcutaneous injection at the onset of an "off" period or by continuous subcutaneous infusion by a pump.

The decision to initiate Apomorphine is primarily undertaken by a Parkinson's disease specialist. The Specialist Team at Addenbrooke's Hospital includes; Consultant Neurologists, Consultant Geriatricians, Parkinson's Disease Specialist Nurse (PDSN) Prescribers and Apo Nurse.

Sharing of care assumes communication between the specialist team who recommends the initiation of therapy, the Community PDNS, the Apo Nurse, the GP, the patient and any carer or relative nominated by the patient, and other members of the care team including the patient's Community Pharmacist.

The intention to share care between the specialist team and the GP will be explained to the patient by a member of the specialist team. It is important that patients are consulted about treatment and are in agreement with it.
The specialist will contact the patient's GP to request a shared care arrangement.
If the specialist team asks the GP to share care, the GP should reply to this request as soon as practical (usually within 3 weeks).

If the GP has any concerns regarding undertaking this role their concerns should be raised as soon as possible.
Once agreement to share care has been received, the patient will be referred for an Apomorphine challenge trial. The challenge must not be undertaken until a response from the GP is received.

If the GP is not confident to undertake the roles outlined below, they are under no obligation to do so.
In such an event the responsibility for Apomorphine treatment, if it were to go ahead, remains with the specialist team.

Training, education and professional support will be provided for all those involved by the PDNS.

4. Abbreviations

SC – subcutaneous
BP – blood pressure
ECG – electro-cardiogram

5. Dose and Administration

Challenge Procedure

- The challenge may take place in an outpatient clinic/day case, in community by an appropriate specialist or as an inpatient.
- Patients may need to be pre-treated with domperidone 10mg three times a day THREE days prior to apomorphine challenge and arrange day case admission for apomorphine challenge.
- Avoid domperidone in patients taking concomitant medication known to cause QT prolongation.
- Routine ECG is reviewed to exclude cardiac conduction problems or significant cardiac disease. If these are present the challenge will not take place and the patient will be referred to a cardiologist.
- Routine blood test results are reviewed (FBC, U&Es and CPK)
- Written patient consent is obtained
- The patient must be in an "off" state prior to starting the challenge so their morning PD medication is usually omitted however the patient's mobility needs to be considered if the challenge is to be performed as a day case. The hospital team will provide specific instructions for each patient.

- The challenge is normally carried out first thing in the morning to avoid unnecessary patient discomfort.
- A baseline motor function examination using a clinical assessment tool is often performed to provide an assessment of the patient's response to consecutive doses of apomorphine.
- Single injections of increasing doses of apomorphine are administered (e.g. 1mg, 3mg, 5mg, 6mg and 7mg) at 45 minute to 1 hour intervals with subsequent recordings using the clinical assessment tool until a response is seen (the patient switches "on").
- If 7mg is administered without any positive effect the patient is usually considered to be a non-responder. However in rare cases the specialist team may consider administering a slightly higher dose (max 10mg).
- The patient is closely observed and monitored throughout for any side effects.
- Lying and standing BP is monitored.
- The challenge will be stopped if the patient experiences any side effects.

Dosage and Administration	
Intermittent Doses	**APO-go Pen 10mg/ml Solution for Injection** APO-go Pen 10mg/ml Solution for Injection is for subcutaneous use by intermittent bolus injection. The dosage is determined on an individual patient basis, typically within the range 3-30mg daily, usually given as 1-10 injections per day. The pen must be discarded every 48 hours and the needles changed after every injection. **Individual bolus injections should not exceed 10mg.** **The total daily dose should not exceed 100mg.** Apomorphine has an onset of action of between 5-15 minutes, lasting usually for about one hour. The optimal dosage of apomorphine hydrochloride varies between individuals but, once established, remains relatively constant for each patient.
Continuous Infusion	**APO-go PFS 5mg/ml Solution for Infusion in Pre-filled Syringe** APO-go PFS 5mg/ml Solution for Infusion in Pre-filled Syringe is a pre-diluted pre-filled syringe intended for use without dilution as a continuous subcutaneous infusion by mini-pump and / or syringe-driver. It is not intended to be used for intermittent injection. A continuous subcutaneous infusion maybe preferable in those requiring more than 10 separate injections per day. A challenge procedure is not necessarily required) a. Commence pump at a rate of apomorphine 1mg/hour then increased according to individual's response. Increases in the infusion rate should not exceed 0.5mg/hour at intervals of not less than 4 hours. b. 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. c. The infusion site should be changed every 24 hours.

Further information can be found in the Summary of Product Characteristics
https://www.medicines.org.uk/emc/medicine/21983

6. Adverse Effects

Very common (≥ 1 in 10)
Hallucinations and delusions
Confusion
Injection site reactions; irritation, itching, bruising and pain.

Common (≥ 1 in 100 and < 1 in 10)
Yawning
Nausea and vomiting, particularly when first initiated
Transient sedation
Somnolence
Dizziness / light-headedness

If affected avoid driving or operating machinery.

Uncommon (≥ 1 in 1000 and < 1 in 100)
Local and generalised rashes
Haemolytic anaemia and thrombocytopenia
Postural hypotension - usually transient

Rare (≥ 1 in 10000 and < 1 in 1000)
Eosinophilia

Unknown
Impulse control disorders - Pathological gambling, increased libido, hypersexuality; compulsive spending or buying, binge eating and compulsive eating

Further information can be found in the Summary of Product Characteristics
https://www.medicines.org.uk/emc/medicine/21983

7. Cautions

- Patients with renal, pulmonary or cardiovascular disease
- Elderly and/or debilitated patients
- Patients with neuropsychiatric disturbances - may be exacerbated by apomorphine
- Patients at risk for torsades de pointes arrhythmia; due to potential for QT prolongation
- Patients with postural hypotension or those taking antihypertensives

Further information can be found in the Summary of Product Characteristics
https://www.medicines.org.uk/emc/medicine/21983

8. Contraindications

- Hypersensitivity to the active substance or to any of the excipients (sodium metabisulphite, hydrochloric acid, sodium hydroxide.
- Patients with respiratory depression, dementia, psychotic diseases or hepatic insufficiency.
- Intermittent apomorphine treatment is not suitable for patients who have an 'on' response to levodopa that is marred by severe dyskinesia or dystonia.
- Children and adolescents under 18 years of age

Further information can be found in the Summary of Product Characteristics
https://www.medicines.org.uk/emc/medicine/21983

9. Interactions

- Avoid administration of apomorphine with other drugs known to prolong the QT interval.
- Patients taking concomitant medications for their Parkinson's disease should be monitored for unusual side-effects or signs of potentiation of effect.
- Neuroleptic medicinal products may have an antagonistic effect if used with apomorphine.

Further information can be found in the Summary of Product Characteristics
https://www.medicines.org.uk/emc/medicine/21983.

10. Monitoring Standards & Actions to take in the event of abnormal test results/symptoms

The Hospital Specialist team will:	• ECG and BP performed at baseline • Inform patients to report nodule formation and/or ulceration, somnolence, or persistent side-effects to the GP without delay
Community PDNS/Apo Nurse will:	• Arrange monitoring BP and response to apomorphine and side-effects during the first month after initiation of therapy • Conduct regular patient review
The GP will continue treatment, but seek advice immediately	• Monitor FBCs regularly: ○ if WBC < 3.5 x 10^9/L *or* neutrophils < 2.0 x 10^9/L *or* platelets < 150 x10^9/L x 2 separate tests ○ Low Hb Request Coomb's test and refer • if creatinine > 150 µmol/L (used with caution in renal impairment • if potassium > 5.5 mmol/L (Cardiac side effects) • if ALT is raised above normal limits (extensively metabolised by the liver).
The GP will STOP treatment	• seek advice in the event of a hypersensitivity reaction

11. Shared Care Responsibilities

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

Specialist Responsibilities

1. Confirm diagnosis.
2. Perform baseline tests*:
    a. FBC,
    b. LFTs,
    c. Renal function tests,
    d. ESR,
    e. BP,
    f. Cardiovascular function.

   (Send a copy of the baseline test results to the GP for information (a paper copy may not be required if the GP can access results electronically.)
3. Advise GP on the frequency of routine bloods
4. Discuss benefits and side effects of treatment with the patient.
5. Check for any contra-indications to apomorphine or domperidone when considering apomorphine therapy.
6. Prescribe domperidone if required for test dose.
7. Check for possible drug interactions when considering apomorphine therapy.
8. Obtain patient's agreement to proposed shared care arrangement. Provide information to the patient/carer.
9. Arrange apomorphine challenge trial if appropriate
10. Advise the GP by standard letter of the diagnosis and proposed treatment, and invite the GP to share care. If SystmOne is used by GP practice, this will be tasked by the community PD nurse/Apo nurse. If EMIS or alternative systems are used, sharing of care will be assumed as per other shared care guidance.
11. Opportunity for discussion with GP regarding Parkinson's management.
12. Recommend any concomitant medication that maybe required e.g. domperidone, (please note dosage and duration is off-label use – see appendix 2 and 3 for details of MHRA safety update and advice on dosing regimen and ECG monitoring advice from the Association of British Neurologists on the use of domperidone in general and with specific reference to use with apomorphine.)
13. Recommend route of administration and dose to GP. Advise GP of the monitoring tests needed, test intervals and date of review appointment.
14. Ensure compliance with NICE CG71. https://www.nice.org.uk/guidance/cg71
15. Provide backup advice and support to community PDNS / GP if required.
16. A mechanism in place to receive rapid referral of a patient in the event of deteriorating clinical condition

Apomorphine Challenge Test:

1. Assess suitability of patient by conducting an apomorphine challenge test in day assessment unit in secondary care or within the community setting with the Apo Nurse
2. Provide training/information to patient and carer. Training may also be provided by nursing staff from the drug company who manufacture apomorphine (Britannia Pharmaceuticals).

3. Communicate promptly with the GP in writing, providing details of:
    - the dose
    - method of administration
    - the frequency of routine blood monitoring
    - type of infusion line/ needles associated with apomorphine use (PIP codes)
    - and details regarding the dosage / monitoring requirements for domperidone (if applicable)

Community PDNS Responsibilities and Apo Nurse Responsibilities

1. Inform the GP and Specialist team promptly (within 48 hours) of changes in treatment or dose. Apo Nurse will be working within written titration guidance of Hospital Specialist team.
2. Periodically review patient's condition and need for medication at agreed intervals (minimum 3 monthly)
3. Ensure 6 monthly/annual blood test (as directed by the Hospital Specialist) requested and results actioned by GP.
4. Have a mechanism in place to deal with mechanical failure of an apomorphine pump. (Britannia 24hour hotline: 0844 880 1327)
5. Ensure that clear backup arrangements exist for GPs to obtain advice and support.
6. Report significant adverse events to the MHRA and GP.
7. Carry out on-going monitoring of PD symptoms, drug response and blood pressure and refer if required.

General Practitioner Responsibilities

1. Document confirmation of agreement to shared care via response to task in SystmOne (created by Apo nurse/community PD nurse) OR if practice uses EMIS (or alternative) then agreement will be assumed (as per other shared care agreements).
2. **As part of this shared care, the GP agrees to take over the prescribing and monitoring of Apomorphine including blood tests at the frequency specified by the specialist team.**
3. Prescribe apomorphine at the dose and for the route of administration recommended by the specialist team and prescribe the relevant needles / infusion lines / sharps device (bin) as specified by the Hospital Specialist team/Apo Nurse.
4. Prescribe any concomitant medication as directed by the specialist team.
5. Check compatibility with other or new concomitant medication (e.g. computer-generated warnings).
6. **Arrange and monitor blood test results at 6-12 month intervals as directed by the specialist (FBC, LFTs and Renal Function tests)***
7. Monitor the patient's overall health and well-being when patient presents and at intervals agreed with specialist team.
8. Consult promptly with the Specialist team if the patient deteriorates, has problems administering apomorphine, or when test results are abnormal, or if patient defaults from blood test appointments.

9. When urgent advice is required and the community PDNS / Apo Nurse or Hospital Specialist team are not available, GPs are advised to contact the Britannia hotline (0844 880 1327).
10. Adjust the dose or stop or change treatment as advised by the specialist team.
11. Always consult with the Hospital Specialist team before changing the dose or frequency of apomorphine.
12. Periodically remind patient of which warning symptoms to report.
13. Report significant adverse events to the specialist team and MHRA (if not already reported by the community PDSN/Apo Nurse).

Patient/Carer Responsibilities

1. Ask the Specialist team for clarification of anything that is not clearly understood regarding the treatment.
2. Share any concerns about treatment with Apomorphine with a doctor or nurse involved in shared care.
3. Inform nurses and doctors involved in shared care of any other medication being taken, including over-the-counter products or herbal remedies.
4. Attend appointments for reviews and blood tests.
5. Ensure copies of blood test kept with prescribing information.
6. Report any adverse effects or warning symptoms to a nurse or doctor involved with shared care.
7. Report any suspected pregnancy of the patient ***or partner*** to a nurse or doctor involved with shared care.
8. Dispose of waste products in sharps bin as instructed by the PDNS/Apo Nurse
9. Report to the Hospital Specialist or GP if they do not have a clear understanding of their treatment.
10. Patients must not exceed the recommended dose.
11. Patients must attend their scheduled clinic and blood test appointments (where relevant).
12. Must inform other clinical staff that they are receiving treatment.
13. Report any adverse effects to the hospital specialist or GP.

GP/Hospital Communication Network

In case of any concern regarding monitoring blood tests or any other aspect of a patient's care, please contact the Hospital specialist by phone (see contact details in section 12) giving patient's name, a contact number for the patient and GP along with details of the problem. The specialist will respond as soon as possible.

Patients are given an out of hours contact for Britannia Pharmaceuticals in case of mechanical breakdown of pumps. Community PDNS also hold a spare pump.

Apo Nurse letters will be communicated with 48 hours of patient review.
Primarily this will be via letter.

***Coombes Test only required if 2 x abnormal FBC results or low Hb.**

12. Contact numbers for advice and support

Cambridge University Hospitals NHS Foundation Trust		
Specialist	**Post**	**Telephone/ Email**
Dr Duncan Forsyth	Consultant Geriatrician	01223 217785
Dr Alistair Mackett	Consultant Geriatrician	01223 217785
Dr Paul Worth	Consultant Neurologist	01223 216760
Dr Philip Buttery	Consultant Neurologist	01223 331160
Dr Wendy Phillips	Consultant Neurologist	07932630376
Nicola McQueen	Parkinson's Specialist Nurse	01223 349814
Marilyn Turner	Apo go Nurse	07827965208
Medicines Information	Pharmacy	01223 217502/217478

North West Anglia Foundation Trust		
Specialist	**Post**	**Telephone/ Email**
Dr SH Guptha	Consultant Physician	01733 673885
Dr John Thorpe	Consultant Neurologist	01733 673549
Liz Carter	Apo go Nurse	07503230128

Community Parkinson's Nurse Specialist (CPFT)		
Specialist	**Post**	**Telephone/ Email**
Hazel White	Parkinson's Specialist Nurse	01223 723018
Amanda Eady	Parkinson's Specialist Nurse	01223 723018
Carolyn Noble	Parkinson's Specialist Nurse	01733 776145
Danielle Duffill	Parkinson's Specialist Nurse	01733 776145
Karen Aird	Parkinson's Specialist Nurse	01733 776145

13. Equality and Diversity Statement

This document complies with the Cambridge University Hospitals NHS Foundation Trust and Peterborough and Stamford NHS Foundation Trust service Equality and Diversity statement.

14. Disclaimer

It is your responsibility to check that this printed out copy is the most recent issue of this document.

15. Document Management

Document ratification and history	
Approved by:	CUH JDTC - TBC
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Authors:	Emma Bines (Lead Pharmacist – DME, CUHFT) Charlotte Murray (Lead Pharmacist – Medicine, NWAFT) Jacqueline Young (PDNS – CUHFT) Karen MacGinley (PDNS – CUHFT)
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The information contained in this guideline is issued on the understanding that it is accurate based on the resources at the time of issue. For further information please refer to the most recent Summary of Product Characteristics https://www.medicines.org.uk/emc/medicine/21983.

Appendix 1

FLOWCHART DEMONSTRATING THE USE OF APOMORPHINE IN PARKINSON'S DISEASE: SHARED CARE PROTOCOL

Britannia Pharmaceuticals
Provide 24 hour helpline for any problems with the pump or pen
0844 880 1327

Review in Parkinson's Clinic
Patient identified as appropriate for Apomorphine
- ECG performed
- Baseline bloods
- Prescribe domperidone if required for challenge

Request for Shared Care sent to GP via Clinic letter

Patient booked for Apo Challenge

Hospital PDSN/Apo Nurse to perform challenge
- Day case
- Hospital admission
- Community setting

If challenge successful
- Patient issued with free supply of pen from Britannia (3 pens)
- Follow-up appointment booked in clinic

Specialist Responsibilities

1. Confirm diagnosis.
2. Perform baseline tests*:
3. Advise GP on the frequency of routine bloods
4. Discuss benefits and side effects of treatment with the patient.
5. Check for any contra-indications to apomorphine or domperidone when considering apomorphine therapy.
6. Prescribe domperidone if required for test dose.
7. Check for possible drug interactions when considering apomorphine therapy.
8. Obtain patient's agreement to proposed shared care arrangement. Provide information to the patient/carer.
9. Arrange apomorphine challenge trial if appropriate
10. Advise the GP by standard letter of the diagnosis and proposed treatment, and invite the GP to share care. If SystmOne is used by GP practice, this will be tasked by the community PD nurse/Apo nurse. If EMIS or alternative systems are used, sharing of care will be assumed as per other shared care guidance.
11. Opportunity for discussion with GP regarding Parkinson's management.
12. Recommend route of administration and dose to GP. Advise GP of the monitoring tests needed, test intervals and date of review appointment.
13. Ensure compliance with NICE CG71. https://www.nice.org.uk/guidance/cg71
14. Provide backup advice and support to community PDNS / GP if required.
15. A mechanism in place to receive rapid referral of a patient in the event of deteriorating clinical condition
16. Communicate promptly with the GP in writing, providing details of:

- the dose
- method of administration
- the frequency of routine blood monitoring
- type of infusion line/ needles associated with apomorphine use (PIP codes)
- and details regarding the dosage / monitoring requirements for domperidone (if applicable)

GP Responsibilities

1. Document confirmation of agreement to shared care via response to task in SystmOne (created by Apo nurse/community PD nurse) OR if practice uses EMIS (or alternative) then agreement will be assumed (as per other shared care agreements).
2. **As part of this shared care, the GP agrees to take over the prescribing and monitoring of Apomorphine including blood tests at the frequency specified by the specialist team.**
3. Prescribe apomorphine at the dose and for the route of administration recommended by the specialist team and prescribe the relevant needles / infusion lines / sharps device (bin) as specified by the Hospital Specialist team/Apo Nurse.
4. Prescribe any concomitant medication as directed by the specialist team.
5. Check compatibility with other or new concomitant medication (e.g. computer-generated warnings).
6. **Arrange and monitor blood test results at 6-12 month intervals as directed by the specialist**
7. Monitor the patient's overall health and well-being when patient presents and at intervals agreed with specialist team.
8. Consult promptly with the Specialist team if the patient deteriorates, has problems administering apomorphine, or when test results are abnormal, or if patient defaults from blood test appointments.
9. When urgent advice is required and the community PDNS / Apo Nurse or Hospital Specialist team are not available, GPs are advised to contact the Britannia hotline (0844 880 1327).
10. Adjust the dose or stop or change treatment as advised by the specialist team.
11. Always consult with the Hospital Specialist team before changing the dose or frequency of apomorphine.
12. Periodically remind patient of which warning symptoms to report.
13. Report significant adverse events to the specialist team and MHRA (if not already reported by the community PDSN/Apo Nurse).

Community PDNS/Apo Nurse Responsibilities

1. Inform the GP and Specialist team promptly (within 48 hours) of changes in treatment or dose. Apo Nurse will be working within written titration guidance of Hospital Specialist team.
2. Periodically review patient's condition and need for medication at agreed intervals (minimum 3 monthly)
3. Ensure 6 monthly/annual blood test (as directed by the Hospital Specialist) requested and results actioned by GP.
4. Have a mechanism in place to deal with mechanical failure of an apomorphine pump. (Britannia 24hour hotline: 0844 880 1327)
5. Ensure that clear backup arrangements exist for GPs to obtain advice and support.
6. Report significant adverse events to the MHRA and GP.
7. Carry out on-going monitoring of PD symptoms, drug response and blood pressure and refer if required.

Patient/Carer Responsibilities

1. Ask the Specialist team for clarification of anything that is not clearly understood regarding the treatment.
2. Share any concerns about treatment with Apomorphine with a doctor or nurse involved in shared care.
3. Inform nurses and doctors involved in shared care of any other medication being taken, including over-the-counter products or herbal remedies.
4. Attend appointments for reviews and blood tests.
5. Ensure copies of blood test kept with prescribing information.
6. Report any adverse effects or warning symptoms to a nurse or doctor involved with shared care.
7. Report any suspected pregnancy of the patient ***or partner*** to a nurse or doctor involved with shared care.
8. Dispose of waste products in sharps bin as instructed by the PDNS/Apo Nurse
9. Report to the Hospital Specialist or GP if they do not have a clear understanding of their treatment.
10. Patients must not exceed the recommended dose.
11. Patients must attend their scheduled clinic and blood test appointments (where relevant).
12. Must inform other clinical staff that they are receiving treatment.
13. Report any adverse effects to the hospital specialist or GP.

Appendix 2:
Domperidone: risks of cardiac side effects

From: Medicines and Healthcare Products Regulatory Agency (MHRA) Published: 30 May 2014
Indication restricted to nausea and vomiting, new contraindications, and reduced dose and duration of use.

Domperidone is a dopamine antagonist with antiemetic properties.
A European review assessed the benefits and risks of domperidone following continued reports of cardiac side effects. The review confirmed a small increased risk of serious cardiac side effects. A higher risk was observed particularly in people older than 60 years, people taking daily oral domperidone doses of more than 30 mg, and those taking QT-prolonging medicines or CYP3A4 inhibitors at the same time as domperidone. For indications other than nausea and vomiting, the benefits were not considered to outweigh the cardiac risk. Based on the results of this review, the treatment advice for domperidone has been updated.
The overall safety profile of domperidone, and in particular its cardiac risk and potential interactions with other medications, should be taken into account if there is a clinical need to use it at doses or durations greater than those authorised (eg, to control side effects of Parkinson's disease treatment in some patients).
Domperidone use in children is under further investigation. Domperidone licence-holders are required to conduct studies to provide further data to support domperidone efficacy in children.

Advice for healthcare professionals

Indication

- Domperidone is now restricted to use in the relief of nausea and vomiting
- It should be used at the lowest effective dose for the shortest possible time

Contraindications:
Domperidone is now contraindicated in people:

- with conditions where cardiac conduction is, or could be, impaired
- with underlying cardiac diseases such as congestive heart failure
- receiving other medications known to prolong QT interval or potent CYP3A4 inhibitors
- with severe hepatic impairment
- Patients with these conditions should have their treatment reviewed at their next routine appointment and be switched to an alternative treatment if required

Posology:
Oral formulations

- For adults and adolescents over 12 years of age and weighing 35 kg or more, the recommended maximum dose in 24 hours is 30 milligrams (dose interval: 10 milligrams up to three times a day)
- In children under 12 years of age and weighing less than 35 kg, the recommended maximum dose in 24 hours is 0.75 mg/kg body weight (dose interval: 0.25 mg/kg body weight up to three times a day)

Suppository formulation

- Suppositories should only be used in adults and adolescents weighing 35 kg or more, the recommended maximum daily dose in 24 hours is 60 milligrams (dose interval: 30 milligrams twice a day)

Duration of treatment:

- The maximum treatment duration should not usually exceed one week
- Patients currently receiving long-term treatment with domperidone should be reassessed at a routine appointment to advise on treatment continuation, dose change, or cessation

Administration of liquid formulations:

- Oral liquid formulations of domperidone should only be given via appropriately designed, graduated measuring devices (eg, oral syringes for children and cups for adults and adolescents) to ensure dose accuracy

Additional advice for pharmacists:

Non-prescription availability of domperidone:

- Pharmacists are asked to take the following steps when supplying domperidone without prescription:
- Ask questions to exclude supply for people for whom domperidone is contraindicated (see above)
- Advise people to take domperidone only for nausea and vomiting–it should no longer be taken for bloating and heartburn
- Advise people to take the lowest dose for the shortest possible time up to a maximum daily dose of 3 tablets and for a maximum period of 48 hours

Advice to give to patients:

- Domperidone should only be used for short periods of time to treat nausea and vomiting
- Speak to your doctor or pharmacist at your next routine visit if you are taking domperidone and have any
- problems with your heart or concerns about your treatment
- Seek medical attention immediately if you experience heart-related symptoms such as irregular heartbeat or fainting while taking domperidone

Appendix 3:

Association of British Neulorogists Website extract;
http://www.theabn.org/news/abn-clinical-research-training-fellowship-2015.html

Domperidone
You will have recently received notification from the MRHA regarding a **LOW RISK** of serious cardiac side-effect (prolonged QTc) with domperidone (see refs below). The ABN has asked the MHRA to provide guidance on the use of this drug in people with Parkinson's disease, but they have not been able to do so. Please click here for recommendations from the ABN.

Copy of letter published on the ABN website:
Dear Colleague,

You will have recently received notification from the MRHA regarding a LOW RISK of serious cardiac side-effect (prolonged QTc) with domperidone (see refs below). The ABN have asked the MHRA to provide guidance on the use of this drug in people with Parkinson's disease, but they have not been able to do so. Members will be aware that a significant proportion of people with Parkinson's disease are only able to tolerate initiation, dose increase, or in some cases maintenance of dopaminergic therapy with domperidone co-administration. For these patients the availability of domperidone as an anti-emetic can make a dramatic difference to their mobility and quality of life. There is no alternative to domperidone in this situation so the balance of risk and benefit should be carefully considered. The ABN wishes to make the following recommendations: Domperidone SHOULD NOT be prescribed routinely for patients commencing dopaminergic medication, and particularly for those over the age of 60 years or with serious underlying heart conditions such as congestive cardiac failure, severe hepatic impairment or significant electrolyte disturbance.

For Parkinson's patients who develop nausea:

- **Domperidone is the preferred anti-emetic.**
- **A baseline ECG must be performed before prescribing domperidone and the potential benefits / risks of prescribing domperidone discussed with the patient.**
- **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 (ECG machines often overestimate, and less commonly underestimate). If a second QT prolonging drug or a strong CYP3A4 inhibitor is to be added then the ECG should be repeated (e.g., ketoconazole or erythromycin).**
- **Patients should be advised to seek prompt medical attention if symptoms such as syncope or palpitations occur.**
- **The prescription of domperidone should not routinely exceed 10mg tds for oral therapy, and should be used for as short a period as possible.**
- **It is recommended that the initiation of Apomorphine therapy be covered by domperidone at a dose of 20mg tds commencing 2 days before the first dose. The dose should be reduced to 10mg tds after 2 weeks if the patient is not experiencing nausea. If nausea persists or returns on reducing the dose, domperidone can be continued in the same dose.**
- **The ECG should be repeated once at 2 weeks if the prescribed dose is maintained at more than 30mg daily.**

- **Tolerance usually develops with oral therapy and can develop with Apomorphine, so that a trial of domperidone dose reduction or withdrawal should be regularly considered.**
- Domperidone may also be beneficial in the management of orthostatic hypotension in Parkinson's patients. The same recommendations will apply.
- The initiation of domperidone should be under the recommendation and guidance of the Parkinson's specialist.
- For Parkinson's patients who cannot swallow and need an antiemetic, rectal domperidone 30mg bd may be prescribed.
- There is no need immediately to withdraw domperidone in any Parkinson's patients currently on this drug. The continued necessity for prescribing domperidone should be reviewed at their next, and every subsequent, Parkinson's clinic review.

How low is the cardiovascular risk?

- Four epidemiology studies[1] [2] [3] [4]have reported on the relation between domperidone and either sudden cardiac death alone, or on serious ventricular arrhythmia and sudden cardiac death as a combined endpoint. The findings from the two most recent studies [1,2] are summarised below.
- Van Noord and colleagues[1] looked at 1304 cases of sudden cardiac death and 13 480 matched controls, of which ten cases were currently exposed to domperidone. For current use of domperidone, the adjusted odds ratio (OR) for a risk of sudden cardiac death was 1.92 (95% CI: 0.78–4.73). Analysis by dose suggested a higher risk for patients prescribed domperidone at higher doses (>30 mg/day), although there were only 4 exposed cases in each group and the 95% confidence intervals overlapped: OR 11.4 (1.99–64.9) for patients prescribed >30mg/day, compared with 0.99 (0.23–4.23) for patients receiving 30mg/day.
- The study by Johannes and colleagues [2] was the largest and most robust study in terms of exposed cases and included 1608 cases and 6428 controls (proton pump inhibitor [PPI] users), of which there were 169 cases and 482 controls with current exposure to domperidone. Compared with users of PPIs, the OR for current domperidone exposure was 1.44 (1.12–1.86). Stratified analyses by age and sex suggested a slightly higher risk for patients older than 60 years (OR1.47 [1.14–1.91]) compared with those younger than 60 years (OR 1.23 [0.32–4.76]), although the 95% confidence intervals overlapped.

References:

1) Van Noord C, et al. Drug Saf 2010; 33: 1003-14
2) Johannes C, et al. Pharmcoepidemiol Drug Saf 2010; 19: 881-88
3) Straus SM, et al. Eur Heart Journal 2005; 19: 2007-12
4) De Bruin ML, et al. Clin Pharmacol 2007; 63: 216-23

Yours Sincerely,