BEDFORDSHIRE AND LUTON JOINT PRESCRIBING COMMITTEE

SHARED CARE GUIDELINE FOR THE USE OF APOMORPHINE IN TREATMENT OF PARKINSON'S DISEASE

(Updated June 19 , Review date June 2021)

PATIENT'S NAME: PATIENT'S ADDRESS: HOSPITAL NAME AND NUMBER / PATIENT IDENTIFIER: SPECIALIST'S NAME:

What are key elements of the process to ensure good shared care arrangements are in place?

- It is imperative that the GP is contacted to discuss shared care arrangements **before** treatment is commenced to ensure that they are willing to jointly manage the patient's therapy.
- It is reasonable to expect the hospital clinician to prescribe if the patient will have to regularly attend hospital for specialist monitoring.
- CCG policies on clinical effectiveness should be adhered to.
- The GP should have sufficient information on the drug to either allow them to monitor the patient's response to therapy and adjust dosages as required or know in what circumstances they should refer the patient back to the hospital clinician.
- Where the specialist clinician retains responsibility for monitoring drug therapy or making dosage adjustments, the GP must be informed of any dose changes as soon as possible to avoid an incorrect dose being prescribed/administered. Similarly if the GP changes the patient's medication then the hospital clinician involved in the shared care agreement should be informed of any changes that the GP undertakes.
- GPs should be able to contact the Specialist team directly for advice and support on an ongoing basis.

Bedfordshire CCG
Luton CCG

- **Patients should continue to be reviewed by the Specialist team at scheduled out-patient appointments** (frequency will vary on an individual basis).
- **The shared care arrangements will rely upon** clear communication between the Specialist, the PDNS, the GP and the individual patient and / or their carer and other members of the care team including the patient's Community Pharmacist.
- If a GP is unhappy to participate in a shared care agreement, the CCG should be asked for assistance in facilitating suitable prescribing arrangements for the patient.
- If shared care is not achievable, the responsibility for apomorphine treatment, where it is to go ahead, will remain with the specialist team.

NB: The clinician who prescribes the medication, legally assumes clinical responsibility for the drug and the consequences of its us

GUIDELINE FOR APOMORPHINE SHARED CARE IN PARKINSON'S DISEASE

Considerations prior to commencing apomorphine treatment:-

- The decision to initiate apomorphine will be undertaken by a Specialist (primarily this will be a Consultant Neurologist although other specialists e.g. Care of the Eldery Consultants may initiate therapy. (varies depending on geographical area).
- Apomorphine should **only be** recommended for use when a Parkinson's Disease Nurse Specialist (PDNS) is available to undertake the Apomorphine Challenge Trial **and** monitor treatment in the longer term.
- The intention to share care between the Specialist team (i.e. Specialist & PDNS) and the GP should 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 should contact the patient's GP to discuss shared care arrangements **BEFORE an apomorphine challenge test is carried out** to ensure that they are willing to jointly manage the patient's therapy
- Once agreement to share care has been received, the Specialist will then refer the patient to the Parkinson Disease Nurse Specialist (PDNS) for consideration of an Apomorphine challenge trial.
- Ensure that all training, education and professional support will be provided for all those involved by the PDNS.

What are key elements of the process to ensure good shared care arrangements are in place?

- It is imperative that the GP is contacted to discuss shared care arrangements **before** treatment is commenced to ensure that they are willing to jointly manage the patient's therapy.
- It is reasonable to expect the hospital clinician to prescribe if the patient will have to regularly attend hospital for specialist monitoring.
- CCG policies on clinical effectiveness should be adhered to.
- The GP should have sufficient information on the drug to either allow them to monitor the patient's response to therapy and adjust dosages as required or know in what circumstances they should refer the patient back to the hospital clinician.
- Where the specialist clinician retains responsibility for monitoring drug therapy or making dosage adjustments, the GP must be informed of any dose changes as soon as possible to avoid an incorrect dose being prescribed/administered. Similarly if the GP changes the patient's medication then the

hospital clinician involved in the shared care agreement should be informed of any changes that the GP undertakes.

- GPs should be able to contact the Specialist team directly for advice and support on an ongoing basis.
- **Patients should continue to be reviewed by the Specialist team at scheduled out-patient appointments** (frequency will vary on an individual basis).
- **The shared care arrangements will rely upon** clear communication between the Specialist, the PDNS, the GP and the individual patient and / or their carer and other members of the care team including the patient's Community Pharmacist.
- If a GP is unhappy to participate in a shared care agreement, the CCG should be asked for assistance in facilitating suitable prescribing arrangements for the patient.
- If shared care is not achievable, the responsibility for apomorphine treatment, where it is to go ahead, will remain with the specialist team.

NB: The clinician who <u>prescribes</u> the medication, legally assumes clinical responsibility for the drug and the consequences of its us

Specialist Responsibilities

1. Confirm diagnosis. Perform baseline tests: FBC, Coombs' test, LFT, Renal function tests, ESR, BP and 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.)
2. Discuss benefits and side effects of treatment with the patient.
3. Check for any contra-indications when considering apomorphine therapy.
4. Check for possible drug interactions when considering apomorphine therapy.
5. Obtain patient's agreement to proposed shared care arrangement. Provide information to the patient/carer, including discussing the benefits and risks of concomitant apomorphine and domperidone treatment (if appropriate) and advise patients to inform their doctor (GP or Specialist) /Specialist Nurse of any changes that could increase their risk of arrhythmia (see Appendices 1 and 2)
6. Liaise with PDNS to arrange Apomorphine Challenge trial
7. Advise the GP by standard letter of the diagnosis and proposed treatment, and invite the GP to share care explaining the role of the PDNS. (This should be done **before** an Apomorphine Challenge test is carried out).
8. Recommend any concomitant medication that maybe required e.g. domperidone
9. If domperidone is co-prescribed, please note dosage and duration is an off-label use: – see appendix 1 for details of 2 separate MHRA safety updates (published April 16 and May 14) which include advice on dosing regimen and ECG monitoring requirements and appendix 2 for advice from the Association of British Neurologists on the use of domperidone in general and with specific reference to use with apomorphine.
10. **Check QT-interval before starting domperidone.**
11. Recommend route of administration and dose to GP. Advise GP of the monitoring tests needed, test intervals and date of review appointment.
12. Ensure compliance with NICE guideline [NG71] – Parkinson's disease in adults, Published date: July 2017 www.nice.org.uk/guidance/NG71
13. Provide backup advice and support to PDNS / GP if required.

Parkinson's Disease Nurse Specialist (PDNS) Responsibilities*

(* To participate in this shared care guideline, the PDNS is required to be a registered prescriber)

14. Assess suitability of patient by conducting an Apomorphine Challenge test in day assessment unit in secondary care or within the Community setting.
15. Arrange initiation of treatment with apomorphine plus concomitant domperidone therapy and **prescribe the first** 28 days treatment of apomorphine +/- domperidone for the patient.
16. If domperidone is co-prescribed, please note dosage and duration is an off-label use: – see appendix 1 for details of 2 separate MHRA safety updates (published April 16 and May 14) which include advice on dosing regimen and ECG monitoring requirements and appendix 2 for advice from the Association of British Neurologists on the use of domperidone in general and with specific reference to use with Apomorphine.
17. **Check the QT interval during the apomorphine initiation phase.**
18. **Inform the GP for the need to check QT intervals if clinically indicated.**
19. **Advise patients to inform their doctor (Specialist or GP) / Specialist Nurse of any changes that could increase their risk of arrhythmia).**
20. The required number of needles / infusions lines (whichever is applicable), sharps device (bin) should also be prescribed to cover the first 28 days treatment.
21. Provide training/information to patient and carer. Training may also be provided by nursing staff from the drug company who manufacture apomorphine (Dacepton® Brand – Ever Pharma® ; Apo-Go® brand - Britannia Pharmaceuticals).
22. Prescribe a sharps device (bin) and advise the patient on the local procedure for collection of sharps waste. (This may vary in different geographical areas.)
23. Communicate promptly with the GP in writing, providing details of the dose / method of administration, the **specific brand** of apomorphine to prescribe, the type of infusion line/ needles associated with the specific apomorphine brand being used and details regarding the dosage / monitoring requirements for domperidone (if applicable).
24. Inform the GP promptly of changes in treatment or dose.
25. Periodically review patient's condition and need for medication at agree intervals (minimum 3 monthly)
26. Have a mechanism in place to receive rapid referral of a patient in the event of deteriorating clinical condition.
27. Have a mechanism in place to deal with mechanical failure of an apomorphine pump.
28. Ensure that clear backup arrangements exist for GPs to obtain advice and support.
29. Report significant adverse events to the MHRA and GP.
30. Carry out ongoing monitoring of PD symptoms, drug response and blood pressure and refer if required.

General Practitioner Responsibilities

1. **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.**
2. Reply to the request for shared care as soon as possible.
3. Prescribe the specific apomorphine brand that has been specified by the PDNS.
4. 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 PDNS.
5. Prescribe any concomitant medication as directed by the specialist team. e.g. domperidone ,
6. If domperidone is co-prescribed, please note dosage and duration is an off-label use: – see appendix 1 for details of 2 separate MHRA safety updates (published April 16 and May 14) which include advice on dosing regimen and ECG monitoring requirements and appendix 2 for advice from the Association of British Neurologists on the use of domperidone in general and with specific reference to use with Apomorphine.

7. **If patient is prescribed apomorphine in combination with domperidone, check the QT interval if clinically indicated,** (eg if a QT-prolonging or interacting drug is started or if symptoms of cardiac side effects are reported) **and advise patients to inform their doctor (Specialist or GP) / Specialist Nurse of any changes that could increase their risk of arrhythmia).)**
8. Check compatibility with other or new concomitant medication (e.g. computer-generated warnings).
9. **Arrange and monitor blood test results at 6-12 month intervals (FBC, Coombs' test, LFT and Renal Function tests.**
10. Monitor the patient's overall health and well-being when patient presents and at intervals agreed with specialist team.
11. 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.
12. When urgent advice is required and the PDNS and specialist are not available, GPs are advised to contact the relevant hospital's Neurology department.
13. Adjust the dose or stop or change treatment as advised by the specialist team.
14. Always consult with the specialist team before changing the dose or frequency of apomorphine.
15. Periodically remind patient of which warning symptoms to report.
16. Report significant adverse events to the specialist team and MHRA (if not already reported by the PDSN).

Patient's role

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. Inform the local community pharmacists of the **brand of** apomorphine that is being used to ensure that they have adequate stock in place to dispense the prescription.
5. Attend appointments for reviews and blood tests.
6. Report any adverse effects or warning symptoms to a nurse or doctor involved with shared care.
7. If receiving apomorphine/domperidone combination, patients should advise doctor/specialist nurse of any changes that could increase their risk of arrhythmia such as:- symptoms of cardiac or hepatic disorders; conditions that could cause electrolyte disturbances (e.g. gastroenteritis or starting a diuretic);starting other medicines.
8. Report any suspected pregnancy of the patient **or partner** to a nurse or doctor involved with shared care.
9. Dispose of waste products in sharps bin as instructed by the PDNS.

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 PDNS by phone/SystmOne/email giving patient's name, a contact number for the patient and GP along with details of the problem. The PDNS will respond as soon as possible.

In the event of an emergency / urgent query during normal working hours, the GP should contact the relevant PDNS or relevant Specialist / Neurology Department via the hospital switchboard: **Bedford Hospital 01234 355122 / Luton & Dunstable Hospital 01582 491166**. Patients are given an out of hours contact for Britannia Pharmaceuticals in case of mechanical breakdown of pumps. PDNS also hold a spare pump.

Bedford Hospital Specialists	**Tel**	**BHT Contacts Email Address**	
Dr Danute Kucinkiene	01234 355122 ext: 2886		
Luton & Dunstable Hospital Specialists	**Tel**	**Contacts Email Address**	
Dr A Gale	01582 497429	andrew.gale@ldh.nhs.uk	
Dr Watts	01582 497998	paul.watts@ldh.nhs.uk	
Dr A Schrag	01582 718295	Anette.Schrag@ldh.nhs.uk Or A.Schrag@ucl.ac.uk	
Dr A Cohen	01582 4972429	Anna.Cohen@ldh.nhs.uk	
Dr Amit Batla	01582 491166 ext 2023		
Parkinson's Disease Nurse Specialist (PDNS) (Bedfordshire CCG Patients)			
Debbie Blake (ELFT Community Services, Bedfordshire CCG)	01234 310118 M: 07870 576103	Debbie.blake@nhs.net	
Hazel White(ELFT Community Services, Bedfordshire CCG)	01234 310118	hazel.white7@nhs.net	
Parkinson's Disease Nurse Specialist (PDNS) (Luton CCG Patients)			
Ruth Shaw (PDNS , Cambridge Community Services ELFT)	0333 405 3000	ruthshaw@nhs.net.	
Sinead Hardiman PDNS		sinead.hardiman1@nhs.net	
Pharmacy Department: Principal Medicines Information Pharmacist			
Bedford Hospital Medicine Information Pharmacist	01234 355122 ext: 2475	Pharmacy.MI@bedfordhospital .nhs.uk	
Luton & Dunstable Hospital Medicine Information Pharmacist	01582 497114	drug.info@ldh.nhs.uk	

Apomorphine - Drug Information Summary

The following information is not an exhaustive list – clincians should refer to the individual SmPCs for full drug information details. www.medicines.org.uk/emc/

Available products:	**APO-go®** • Apo-go Pen 10mg/ml solution **for injection**, available as a 3ml PEN (each 3ml pen contains 30mg apomorphine hydrochloride as a clear, practically colourless solution) • APO-go PFS 5mg/ml Solution **for infusion** in a Pre-filled syringe (each 10ml pre-filled syringe contains 50mg apomorphine hydrochloride as a clear, practically colourless solution) **Dacepton®** • Dacepton 10 mg/ml solution **for injection** in cartridge. Each 3 ml cartridge contains 30 mg apomorphine hydrochloride hemihydrate. • Dacepton 5 mg/ml solution **for infusion**. Each 20 ml contain 100 mg apomorphine hydrochloride hemihydrate See individual SmPC's for full list of excipients. www.medicines.org.uk/emc/
Licensed Indications	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.
Prescribing Information	**See individual SmPCs for full drug information, including information on side effects / contraindications/ cautions etc.** www.medicines.org.uk/emc/
Dosage and administration	**APOMORPHINE MUST NOT BE USED VIA THE INTRAVENOUS ROUTE.** **Intermittent subcutaneous injections** • The dosage is determined on an individual patient basis, typically within the range 3-30mg daily, usually given as 1-10 injections per day.and sometimes as many as 12 separate injections per day. **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

Dosage and administration (continued)	• Once the appropriate dose is determined a single subcutaneous injection may be given into the lower abdomen or outer thigh at the first signs of an 'off' episode. It cannot be excluded that absorption may differ with different injection sites within a single individual. Accordingly, the patient should then be observed for the next hour to assess the quality of their response to treatment. Alterations in dosage may be made according to the patient's response. **If using dacepton® brand:** • The D-*mine* Pen that is required for the application of Dacepton solution for injection in cartridge is **not suitable for patients needing doses above 6 mg/bolus**. For these patients, other products have to be used • Dacepton solution for injection in cartridge is intended for **use** using, **only the dedicated D-mine-Pen.** • Patients and caregivers must receive detailed instructions in the preparation and injection of doses, with particular attention paid to the correct use of the required dosing pen (see instructions for use included with the dosing pen). • There are differences in the dosing pen of this product and other apomorphine products on the market. Therefore when a patient has received a particular pen and is trained on it, a switch to a different product should be accompanied by re-training under the supervision of a health care professional. • Any remaining air in the cartridge should be removed before use (see Instructions for Use of the dosing pen). **Continuous Subcutaneous infusion** • A continuous subcutaneous infusion maybe preferable in those requiring more than 10 separate injections per day. • See individual SmPCs / electronic BNF for dosing information **Continuous infusion and the use of a minipump and or syringe-driver** The choice of which minipump and or syringe-driver to use, and the dosage settings required, will be determined by the physician in accordance with the particular needs of the patient. A**PO-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 minipump and / or syringe-driver. It is not intended to be used for intermittent injection. **Dacepton 5 mg/ml solution for infusion** • Dacepton 5 mg/ml solution for infusion is a pre-diluted vial intended for use without dilution for subcutaneous use and to be administered as a continuous subcutaneous infusion by minipump and/or syringe-driver. It is not intended to be used for intermittent injection.

Equipment required and availability	**The following Items need to be prescribed on an FP10:** **<u>If prescribing APO-go® product:</u>** • Apomorphine pre-filled syringes (**APO-go pens** and **APO-go PFS**) (Insupen needles for pens are provided by Britannia) • Infusion lines (when apomorphine is used as an infusion) –See drug tariff for available options • Sharps bin • Tegaderm dressings **Sharps device (bins)**- The PDNS should issue the first sharps device (bin) and advise the patient on the correct disposal process (This may vary between different geographical areas). <u>The following are NOT available on FP10 but may be obtained as follows</u>: • **APO-go ambulatory infusion pumps** are available on loan from Britannia via the PDNS. • **Crono-APO-go syringes** for use in an APO-go ambulatory infusion pump can be obtained by the Community Pharmacist directly from Britannia pharmaceuticals. **If prescribing Dacepton product:** • **Contact the PDNS for specific advice as this varies between patients**
Pharmaceutical Precautions	**APO-go Pens and APO-go PFS:** ○ Should be stored below 25°C in their original outer cartons to protect from light ; they should not be used if the solution turns green. Once in use, APO-go pens have a 48h expiry. **Dacepton cartridges:** ○ Should be stored below 25°C in their original outer carton to protect from light. The product should be stored at the same conditions after opening and between withdrawals. Do not refrigerate or freeze. Do not use if the solution turns green. ○ After first opening: Chemical and physical in-use stability has been demonstrated for 15 days at 25°C. From a microbiological point of view, unless the method of opening and further handling precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user. **Dacepton 5 mg/ml solution for infusion** ○ Should be stored below 25°C in their original outer carton to protect from light. The product should be stored at the same conditions after opening and between withdrawals. Do not refrigerate or freeze. Do not use if the solution turns green. ○ The solution should be inspected visually prior to use. Only clear and colourless to slightly yellow solutions without particles in undamaged containers should be used. ○ For single use only. Any unused medicinal product or waste material should be disposed in accordance with local requirements.

	○ After opening and filling the drug product in syringes attached with infusion sets: chemical and physical in-use stability has been demonstrated for 7 days at 25 °C. From a microbiological point of view, unless the method of opening and further handling precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user .
Caution	• Apomorphine should be given with caution: to patients with renal, pulmonary or cardiovascular disease, prone to nausea and vomiting, or with pre-existing postural hypotension; in pregnant women and women of child-bearing age. Female patients should not breast feed. • Neuropsychiatric problems may be exacerbated by Apomorphine. Avoid abrupt withdrawal. • Severe allergic reactions / bronchospasm due to sodium bisulphite in APO-go preparations.
Contraindications	• Apomorphine is contra-indicated in: patients with any respiratory depression, dementia, psychotic diseases or hepatic insufficiency; children and adolescents under 18.
Side Effects **NB:**	• Apomorphine is highly emetogenic; domperidone treatment is started before and continued after apomorphine initiation; however, it may be gradually withdrawn by the GP, PDNS or Specialist. (See appendix 1 and 2 for MHRA Drug safety update and advice from the Association of British Neurologists on the use of domperidone in general and with specific reference to use with Apomorphine.) • Postural hypotension may be experienced on initiating treatment. This is transitory and should not persist after discharge. • Local induration and nodules often develop at injection sites in most patients, particularly with continuous use; counselling of patient/carer on injection technique may help. • Dopamine dysregulation syndrome (e.g. pathological gambling, increased libido, hypersexuality) have been reported in patients; generally reversible upon reduction of the dose or treatment cessation. • Apomorphine has been implicated in haemolytic anaemia (haematology monitoring required). • Apomorphine has been associated with somnolence. **Patients must be advised to exercise caution while driving or operating machines during treatment with Apomorphine. Patients who have experienced somnolence must refrain from driving or operating machines.**
Drug Interactions	• Antipsychotics may antagonise the effects of apomorphine. Apomorphine may potentiate the effects of vaso- and cardio-active medicines. Patients selected for treatment with apomorphine are almost certain to be taking concomitant medications for their Parkinson's disease. In the initial stages of apomorphine therapy the patient should be monitored for unusual side-effects or signs of potentiation of effect.

MONITORING	
The Hospital Specialist will:	• arrange monitoring of BP and response to apomorphine and side-effects during the first month after initiation of therapy • conduct regular patient review • inform patients to report nodule formation and/or ulceration, somnolence, or persistent side-effects to the GP without delay
The GP will: continue treatment, but seek advice immediately	• if WBC < $4x10^9$/L *or* neutrophils < 2 x 10^9/L *or* platelets < $150x10^9$/L • if Coomb's test positive • if creatinine > 150 µmol/L • if potassium > 5.5 mmol/L • if ALT >62 IU/L in *women or* > 80 IU/L in men
The GP will STOP treatment:	• **and** seek advice in the event of a hypersensitivity reaction

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

(Refer to Full Shared Care Guideline for full list of responsibilities and for more detailed information)

Specialist Responsibilities

- Confirm diagnosis , carry out baseline tests and check QT interval (if domperidone is to be prescribed) –(see Appendices 1&2 for ECG monitoring advice)
- Assess patient's clinical suitability for Apomorphine
- Check for any Contraindications before requesting a challenge trial.
- Check for possible drug interactions when considering Apomorphine therapy.
- Liaise with GP regarding shared care before a challenge test is considered.
- Liaise with PDNS regarding Apomorphine challenge test and arrange for the patient to receive domperidone 2 days prior to the test.
- Provide information to patient and GP about Apomorphine and the necessary monitoring requirements.
- Liaise with GP regarding shared care **before** a challenge test is considered.
- Liaise with PDNS regarding Apomorphine challenge test and arrange for the patient to receive domperidone 2 days prior to test.

Parkinson's Disease Nurse Specialist (PDNS) Responsibilities

- Ensure the patient has received domperidone for 2 days prior to apomorphine challenge test. (Check QT interval - See appendices 1 and 2 of shared care guideline for details of dosing regimen and ECG monitoring advice, as recommended by Assoc. British Neurologists and MHRA)
- Conduct the "challenge test" and determine dose of Apomorphine.
- Prescribe initial 28 days treatment, consisting of :
  - Apomorphine (continuous infusion or s/c pens, whichever is applicable)
  - Domperidone (off label use – see appendix 1& 2) if applicable)
  - Additional needles /infusion lines / sharps bin
- Train patient/carer on how to use S/C injection/infusion devices.
- Communicate with GP in writing

Specialist / PDNS Further Responsibilities

- **Review patient at regular intervals (minimum 3 monthly)**
- Optimise patient's medication.
- Monitor and evaluate adverse drug reactions
- Carry out ongoing monitoring of PD symptoms, drug response and blood pressure (and refer if applicable)
- Be a point of contact for community teams and patients and provide information and support to GPs , patient and carers.
- Arrange training for District Nurse re: Using Apomorphine infusion pumps and syringes
- Have mechanisms in place to rapidly refer deteriorating patients.
- Have mechanisms in place to deal with mechanical failure of apomorphine pump.

GP Responsibilities

- Agree to share care
- Communicate with PDNS / Specialist
- Prescribe ongoing apomorphine, needles / infusion lines and any concomitant therapy e.g. domperidone if needed. (off-label use – see Appendices 1 and 2)
- **Check QT interval if clinically indicated** if patient is prescribed apomorphine and domperidone (see Appendices 1 & 2)
- **Monitoring tests and bloods every 6-12 months.**
- Consult specialist team when appropriate (e.g. patient deteriorates, administration issues, abnormal bloods, missed blood tests)
- Dose adjustments/treatment changes as per specialist advice.

Patient Responsibilities

- Attend for blood tests and reviews.
- Inform nurse/ doctor of any adverse effects and / or concerns.
- Report any suspected pregnancy (patient or partner)
- Collect repeat prescriptions.
- Dispose of sharps appropriately.

Communication: Specialist to GP

- **Invite** GP to share care;
- Communicate baseline test results and treatment plan
- Provide details of the type of monitoring tests needed and the monitoring intervals required.
- Provide back-up advice when required

Communication: PDNS to GP

- Provide information regarding:
  - apopmorphine dose and route of administration
  - concomitant medication e.g. domperidone (if required)
  - details of additional items required e.g needles/ infusion lines
- Advise on monitoring requirements
- Inform GP of any dose changes
- Provide point of contact for GP and patient.
- Provide training and back –up advice when required.

Communication: GP to PDNS / Specialist

Contact the PDNS / Specialist if:

- Patient deteriorates
- Patient has problems administering Apomorphine
- Abnormal test results
- Patient does not attend for blood test monitoring

In the case of an urgent query, the GP should contact the PDNS or the individual Trust's Neurology

Individual Companies 24 hour Helpline for problems with pump or pens:-

Apo-Go® Britannia 08081964242 ; **Dacepton®** D-mine® Care support line on 0800 254 0175

Additional Information

Information consisting of care plans, information for ward staff and the Apomorphine Challenge Protocol documentation is available as a separate document and is also included in the embedded document below :

Please note: This care plan is for APO – Go preparation. Please contact PDNS for Dacepton specific care plan / challenge protocol.

Document History

- Publication was originally adapted with permission from 'The use of Apomorphine in Parkinson's disease' South East London & Kent PDNS team and 'Treatment of Parkinson's disease with Apomorphine, Shared care guideline', University College London Hospitals Foundation.
- **Feb 15** - Updated and agreed by the Bedfordshire & Luton Joint Prescribing Committee (JPC)
- **November 2016** -Guideline updated to include the MHRA guidance (April 16) on Apomorphine with domperidone: 'minimising risk of cardiac side-effects'. Specific guidance relating to ECG monitoring has been incorporated into the Specialist team and GP Responsibilities sections and the MHRA guidance is included in appendix 1.
- **June 19** – Updated to include information on the Dacepton® brand of apomorphine; general modifications made throughout the document.

Appendix 1 : MHRA Drug Safety Updates:

Apomorphine with domperidone: minimising risk of cardiac side effects

From: Medicines and Healthcare Products Regulatory Agency (MHRA) Published: 18 April 2016

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

1. Domperidone and the risk of cardiac side effects
2. Apomorphine with domperidone and the risk of QT-prolongation
3. Further information

Advice for healthcare professionals:

- Before starting treatment, carefully consider whether the benefits of concomitant apomorphine and domperidone treatment outweigh the small increased risk of cardiac side effects
- 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 continue to report suspected side effects to apomorphine, domperidone, or any other medicine on a Yellow Card

Apomorphine (brand names: APO-go, Dacepton) is a dopamine agonist used to treat refractory motor fluctuations in people with Parkinson's disease. Domperidone (brand names: Motilium, Dismotil) is usually started at least two days before apomorphine to control the expected side effects of nausea and vomiting.

Domperidone and the risk of cardiac side effects

In 2014, a review by EU medicines regulators concluded that domperidone is associated with a small increased risk of QT-interval prolongation, serious ventricular arrhythmias, and sudden cardiac death. A higher risk was observed in people older than 60 years, people taking daily oral doses of more than 30 mg, and in those taking other QT-prolonging medicines or cytochrome P450 3A4 inhibitors at the same time as domperidone. As a result of this review, the licensed indication for domperidone was restricted to relief of nausea and vomiting, the licensed dose was reduced, and several contraindications were introduced (see Drug Safety Update article from May 2014 and below* for further details).

Apomorphine with domperidone and the risk of QT-prolongation

Apomorphine can increase the risk of QT-prolongation at high doses.

A review by EU medicines regulators of the safety of concomitant apomorphine and domperidone use has recently finished. This review concluded that health professionals should take the precautions listed above to reduce the risk of QT-prolongation. The risk of QT-prolongation may be increased in people on concomitant apomorphine and domperidone who have certain risk factors, including:

- pre-existing QT-interval prolongation
- serious underlying cardiac disorders such as heart failure
- severe hepatic dysfunction
- significant electrolyte disturbances
- concomitant drug therapy that may increase domperidone levels (eg, cytochrome P450 3A4 inhibitors)

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 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 2

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 >30 mg/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. Pharmacoepidemiol Drug Saf 2010; 19: 881–88
- 3) Straus SM, et al. Eur Heart Journal 2005; 19: 2007–12
- 4) De Bruin ML, et al. Br J Clin Pharmacol 2007; 63: 216–23

Yours sincerely,