Oxfordshire Clinical Commissioning Group

NHS

Oxfordshire Clinical Commissioning Group, Oxford University Hospitals NHS Trust and Oxfordshire Health NHS Foundation Trust
Shared Care Protocol and Information for GPs

THE USE OF APOMORPHINE IN PARKINSON'S DISEASE

This leaflet provides the necessary information and guidance for the shared care of adult patients requiring Apomorphine therapy

This shared care agreement states how prescribing and monitoring responsibilities can be shared between the specialist and primary care. Shared care should only take place when all parties, including the patient, agree. A General Practioner should only take on the prescribing if he/she has been provided with all the necessary information from the specialist and feels that it was within his/her competency to do so. APCO have agreed that if these conditions are met then this medicine is suitable for shared care under this protocol.

Summary

The document aims to provide information and guidelines on the use of Apomorphine in patients with Parkinson's disease. It also identifies the lines of communication between primary and secondary care. It explains who holds responsibility for different aspects of Apomorphine therapy, and communicates the key aspects of treatment. Apomorphine is a directly acting dopaminergic agonist, licensed for use in patients with Parkinson's disease who have frequent and /or severe akinesia ("off periods") not controlled by levodopa or other dopamine agonists. Candidates for Apomorphine therapy are those capable of recognising and anticipating "off" episodes. They must also be capable and motivated in order to use the treatment properly.

Background

Parkinson's disease (PD) is a common neurodegenerative disorder with a prevalence of about 150/100 000 and typical onset at 50-60 years of age. Motor symptoms (bradykinesia, rigidity, and tremor) dominate the clinical picture. The etiology of PD is unknown but motor symptoms are believed to be caused by a dopamine deficit in the striatum due to progressive loss of dopamine neurons that project to the striatum from the substantia nigra (Lang & Lozano 1998). Symptomatic drug therapy with Levodopa and dopamine agonists usually provides good symptomatic relief without significant side effects early in the disease. However, after some years of treatment most patients develop motor fluctuations and dyskinesias that, with time, cause increasing disability.

Motor fluctuations are a common complication of drug treatment and it is estimated that 40% of patients with PD will develop them within 4 to 6 years of taking Levodopa (Ahlskog & Muenter 2001). The emergence of motor fluctuations marks a crucial point in the disease as it is often at this stage that patients will start to report increased difficulties with daily living, increased disability and increased dependence on others.

Motor fluctuations can have a huge impact on quality of life both for the person with PD (Dodel et al 2001, Keranen et al 2003), and on their partner or carer (O'Reilly et al 1996). Health economics

studies on the cost of PD indicate that healthcare costs increase considerably in patients with motor fluctuations and dyskinesias compared with patients without these symptoms (Dodel et al 2001). LePen and collaborators (1999) found that the amount of daily "Off" episodes was the most significant predictor of costs among patients with motor fluctuations, and it was estimated that for every 10% reduction in "Off" time, medical costs would decline by 5%. There is also a huge hidden cost to the patient in the form of lost wages, informal care-giving and changing roles (Whetten-Goldstein et al 1997).

Motor fluctuations such as 'off' periods, painful off period dystonia, peak dose or interdose/ biphasic dyskinesias can be difficult to manage even for the most experienced of movement disorder clinicians as disease progression often results in a less predictable response to oral medications. Apomorphine is an effective therapy for patients with PD who experience an unpredictable motor response to oral anti-parkinsonian medication's (Chaudhuri et al 1988; Stocchi et al 1993, Poewe et al 1993; Colzi et al, 1998; Manson et al 2002).

Indications

Apomorphine has been licensed since 1993 for use in patients with disabling motor fluctuations in patients with Parkinson's disease which persist despite individually titrated treatment with Levodopa (with a peripheral decarboxylase inhibitor) and/or other dopamine agonists. Routes of administration covered by the license are:

- Intermittent subcutaneous injection
- Continuous subcutaneous infusion

Prescribing Information

1. To provide general practitioners and primary care teams with clear information on the use of Apomorphine therapy in the treatment of idiopathic Parkinson's disease.

2. To provide a framework for co-operation and understanding between the primary care team and the hospital, so that Apomorphine and other anti-Parkinsonism therapy can be monitored and adjusted according to the patients' individual needs.

3. To establish clear lines of communication between general practitioners, community pharmacists, district nurses and other members of the multidisciplinary primary care team and the hospital team

4. To clearly highlight the specific responsibilities of the primary and the secondary care teams.

Apomorphine Therapy

Apomorphine is a potent injectable dopamine agonist which has a high affinity for D1 and D2 receptors alike and has no narcotic properties.

Apomorphine cannot be given orally because it undergoes extensive first pass metabolism to an inactive metabolite. The quality of the response from a single injection of Apomorphine is indistinguishable from the response to Levodopa (Kempster et al 1990).

Research has shown that Apomorphine reduces the daily "off" period time by up to 50% in patients with late-stage Parkinson's disease associated with refractory on-off oscillations.

The dose of Apomorphine is individually tailored and may range from a few milligrams per day by intermittent sub-cutaneous injection at the onset of an "off" period; or up to 100mg daily by continuous sub-cutaneous infusion over the 'waking day'. However, in rare cases doses up to 250mg daily have been used as have 24hr infusions.

Presentation

Apomorphine is a colorless aqueous solution for injection.

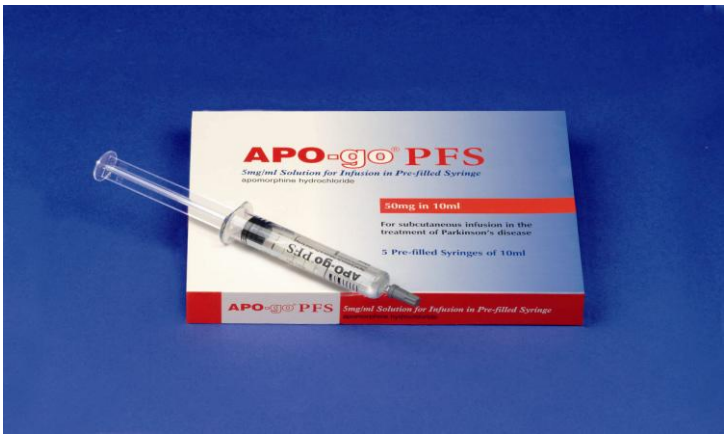
Available as:

1) **Apomorphine Pre-filled syringe 5mg/ml** (each syringe contains 10ml of pre-diluted solution ready for use. 10ml solution contains 50mg Apomorphine).

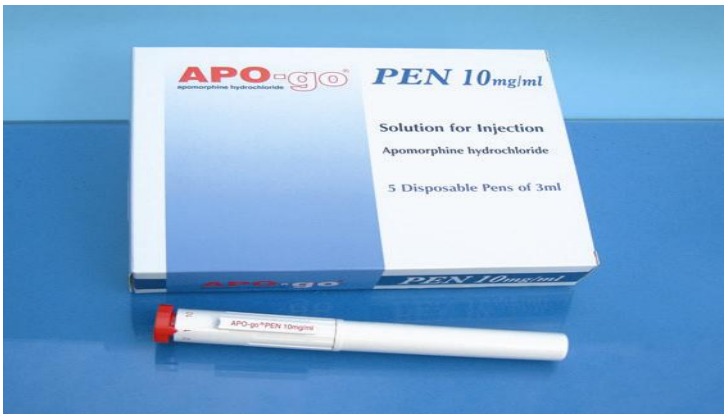
2) **Apomorphine Pre-filled multiple dose Pen 10mg/ml** (each pen contains 30mg Apomorphine in 3ml)

3) **Apomorphine 10mg/ml 2ml and 5ml Ampoules** (these require dilution 50/50 with 0.9% sodium chloride for injection prior to use with the Crono APO-go infusion pump)

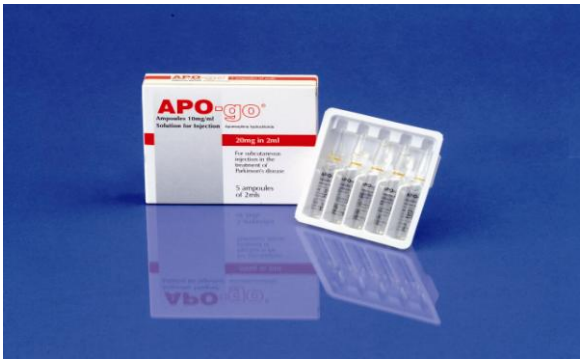
Pre-filled syringe (PFS)



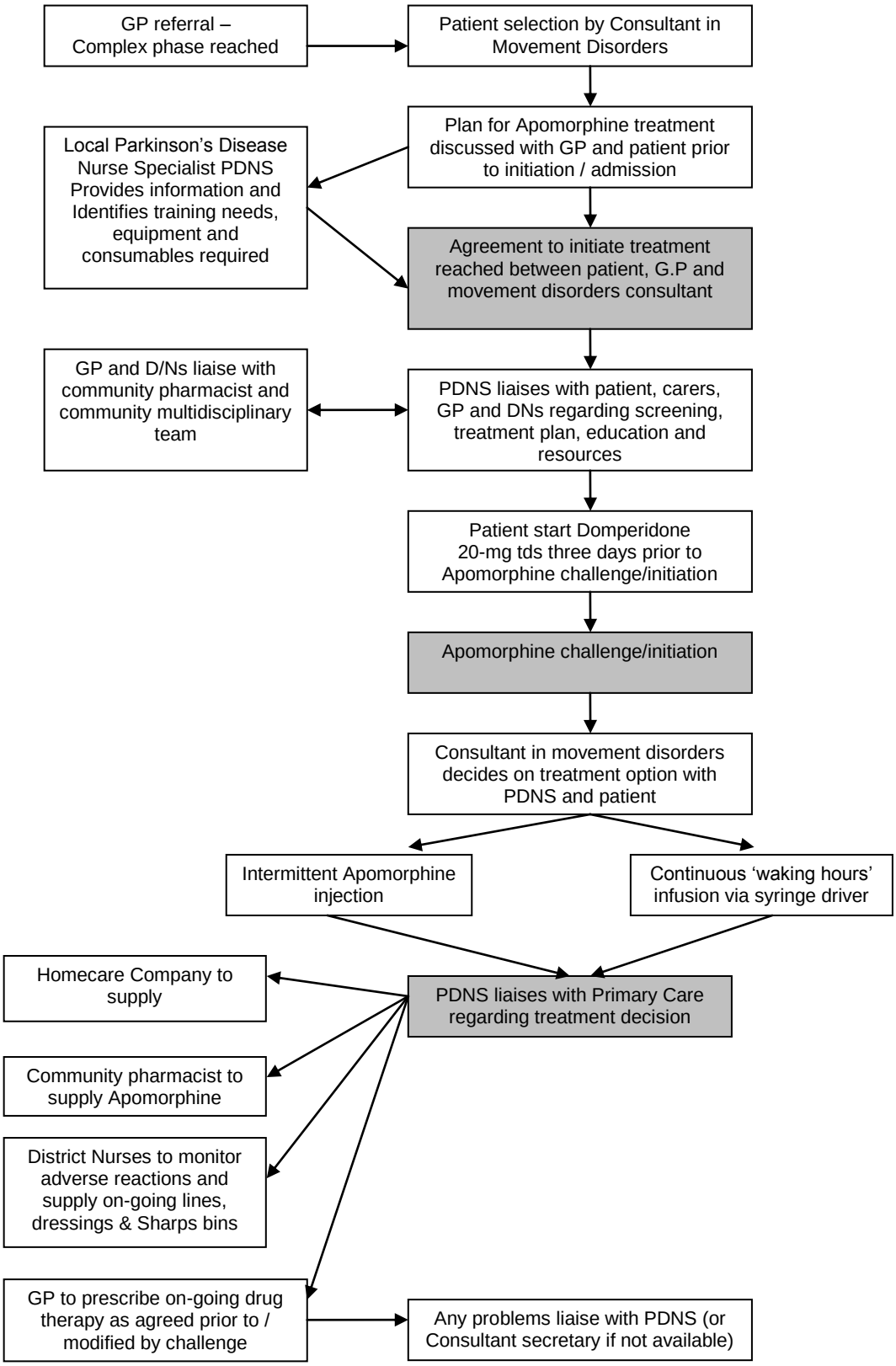
Pre-filled multiple dose Pen



Ampoules



FLOW CHART DEMONSTRATING THE USE OF APOMORPHINE IN PARKINSON'S DOSEASE SHARED CARE PROTOCOL



The Consultant Neurologist, Movement Disorders Consultant, Physician with an interest in PD and PDNS are responsible for identifying and selecting suitable patients for Apomorphine and determining the best mode of administration (i.e. intermittent sub cutaneous injection or continuous sub cutaneous infusion). The hospital team will send a copy of the shared care guidelines to the GP and also explain the specific reasons for choosing this therapy. Any GP declining to accept shared care should communicate this to the patient's neurologist in writing.

The specialist team provides the patient with information and advice, supported by written and audio information if required, explaining the treatment and use of equipment. Only when the patient and their family are satisfied with the process and the Primary care team has been made aware of their funding obligation, will the treatment proceed. Successful apomorphine therapy is initiated by secondary care and maintained in the primary care setting by sharing the responsibilities between primary and secondary care. After a successful challenge, the initiation, titration and adjustment of oral therapy will be the managed by the PDNS following discussion with the Consultant and in accordance with the clinical management plan.

The primary care team accepts responsibility for the on going prescribing of Apomorphine and will continue to act as the primary contact for general health care. The PDNS and Genus Pharmaceuticals provide training, support and advice for General Practitioners, community pharmacists and District Nurses and the patient and family. It is recommended that D/Ns receive training in the use of the Crono APO-go® pump.

Apomorphine challenge

The Apomorphine challenge is performed to establish efficacy in a person with diagnosed idiopathic Parkinson's disease.

1. To determine whether a patient experiences a positive, safe response to treatment
2. To observe the patient for potential side effects, such as postural hypotension, confusion and hallucinations. Such side effects may limit the potential for use.

The patient can have the challenge either as a day case or as an inpatient. It is necessary that the challenge is performed in a safe, clinical environment with medical support.

Prior to admission the Consultant will arrange for the patient to have an ECG, a full blood count, Coombs test, and reticulocyte count.

Challenge Procedure

(The Parkinson's disease Nurse Specialist (PDNS) is usually responsible for performing the challenge).

- Patients should be pre-treated with Domperidone 20mg three times per day, starting 72hrs prior to carrying out the Apomorphine challenge.

- Routine ECG is performed 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.

- Written patient consent is obtained. An early light breakfast is usually offered to the patient as the challenge may take several hours.

- 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 movement disorder team will provide specific instructions for each patient regarding their PD medication.

- 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 such as the Unified Parkinson's disease Rating Scale (UPDRS Part 3 Motor Sections) is often performed to provide an assessment of the patient's response to increased consecutive doses of Apomorphine.

- Single injections of increasing dosages of Apomorphine are administered (i.e. 1 mg, 3mg, 5mg and 7mg) at 30 minute intervals. 15mins after each dose has been administered the UPDRS Part 3 motor section is completed to see which dose provides a positive response (i.e. the patient switches 'On'). Non motor symptoms should also be recorded.

- If 7mg is administered without any positive effect the patient is usually considered to be a non responder. However, in rare cases the medical team may consider administering a slightly higher dose up to a maximum of 10mg.

- The patient is closely observed and monitored throughout for any side-effects. Lying and standing blood pressure is monitored throughout the challenge and the challenge stopped if the patient experiences any serious side-effects.

Positive response to the challenge

A challenge is positive if one or more of the following results are achieved:

1. An improvement in UPDRS score of 20% of baseline score
2. More than 25% improvement in walking time
3. Alleviation of specific symptoms, e.g. pain, dystonia, non-motor presentations such as urinary retention, gastric disturbances, anxiety.

Intermittent subcutaneous injections – AGO-go® Pen

Patients selected for treatment with an APO-go ® Pen should be able to recognise the onset of their 'off' symptoms and be capable of injecting themselves or else have a responsible carer to inject for them when required.

Intermittent subcutaneous injections are used to reverse disabling 'off' periods in conjunction with oral therapy. These are suitable for patients who experience unpredictable 'off' periods. 'off' symptoms can include pain, marked dystonia, freezing and immobility, swallowing and speech problems. An individual therapeutic dose is established for each patient.

For ease of administration, Apomorphine comes in a pre-filled multiple dose pen device.

The pen is discrete and easy to use. Patients and carers are trained to use the pen and administer the injection in the abdominal wall or outer aspects of the thigh.

Continuous subcutaneous infusion - Crono APO-go® Infusion Pump

The continuous infusion pump is used when patients demonstrate a good 'on' period response to Apomorphine, but whose overall motor control fluctuates between freezing and dyskinesia. Existing patients using in excess of 6 bolus injections per day may benefit from administration by continuous infusion. A continuous infusion allows for adjustment and /or reduction of oral medication (associated with motor fluctuations and dyskinesia) to provide more consistent symptom control.

Experience has shown that managing this group of patients on a combination of Apomorphine and oral dopamine agonists, and subsequently reducing or even stopping L-dopa, can dramatically reduce dyskinesia. It is thought a 30% reduction in L-dopa can be made almost immediately once an infusion is commenced.

The Crono APO-go® Infusion pump has been specifically designed for the purpose of delivering Apomorphine. It permits:

- Easy adjustment of the dose rate in small increments
- Flow rate accuracy
- Accurate bolus doses (if agreed that the patient should use the bolus button)
- Syringes and connectors for the Crono APO-go® pump are provided free of charge with the pre filled syringes.

- Neat, compact and lightweight
- Time display, so that the user knows exactly how much time the infusion will run for
- Full alarm/error warning system complying with EU standards
- Supplied on a permanent loan basis to the patient. A 24-hour help line, provided by Genus Pharmaceuticals is also available.

Patients and carers receive initial training in the use of the pump by their local PDNS before a patient is established on a continuous infusion of Apomorphine.

The Genus Pharmaceuticals sales representative can arrange for the Health Care Professional to receive training and training materials.

Pumps no longer required should be returned to Genus Pharmaceuticals. Contact details and help line numbers can be found in the back of these shared care guidelines.

Preparation of the infusion

Some patients may become independent of nursing support within a month after initiation of therapy, eliminating the need for continued district nurse visits. However, some patients may require ongoing District Nurse support. See responsibilities.

Pre-filled syringes (PFS) containing Apomorphine 5mg/ml should be stored at room temperature (not to be stored above 25ºC) and protected from the light. The PFS has an unopened shelf life of 2 years when stored within the recommended conditions. The APO-go ® Pen should be discarded 48 hours after first use.

Apomorphine turns green when exposed to oxygen and stains are difficult to remove. Lemon juice can be effective if used immediately after spillage.

Crono APO-go® Infusion pump flow rate settings for use with apomorphine 5mg/ml PFS

Mg per hour	Ml per hour
2.0	0.4
2.5	0.5
3.0	0.6
3.5	0.7
4.0	0.8
4.5	0.9
5.0	1.0
5.5	1.1
6.0	1.2
6.5	1.3
7.0	1.4
7.5	1.5
8.0	1.6
8.5	1.7

Adverse Effects

Possible adverse effects are divided into those derived from Apomorphine's pharmacology and those attributable to the mode of administration, i.e. localised reactions.

Pharmacological	At administration site
• Nausea and vomiting • Dyskinesias during 'ON' time • Neuropsychiatric complications: – Hallucinations, euphoria, increased libido, confusion, personality changes, agitation, restlessness, psychosis, sleep disturbance. • Sedation • Orthostatic hypotension • Light-headedness • Haemolytic anaemia • Thrombocytopenia • Eosinophilia	• Nodule formation at injection or infusion site • Local infection/abscess / ulceration / scarring • Localised discomfort at injection or infusion site

Drug-induced dyskinesias during 'ON' periods can be severe with intermittent injections. In contrast, continuous subcutaneous infusions of Apomorphine as monotherapy can attenuate dyskinesias.

Apomorphine is a strong, short term emetic, and all patients started on Domperidone prior to their challenge, will remain on 10-20 mg tds until established on Apomorphine therapy. Domperidone is gradually withdrawn over several weeks on the advice of the PDNS or supervising physician.

Transient, mild confusion and visual hallucinations have occurred; most commonly in patients reporting previous Levodopa (as co-beneldopa or co-careldopa) and/or dopamine agonist induced neuropsychiatric complications. Should these continue to develop, attempts should be made to identify the contributing factor under the direct supervision of the hospital team.

Skin care: how to reduce incidence of nodules and other localised complications

Cutaneous complications associated with continuous subcutaneous infusions are common, ranging from mild nodule formation to painful hard nodules and rarely skin ulceration. It is important to minimise the development of nodules as it is thought that they may reduce the absorption of Apomorphine, thus reducing the efficacy of the treatment.

It is important that patients, and those who care for them, are taught the correct technique for managing the infusion prior to initiation of Apomorphine therapy. At the moment there are no proven effective strategies to reduce or prevent nodules from occurring (Hagell & Odin 2001). However, the following may be of benefit:

Practical advice on how to reduce nodule formation

- Ensure a clean technique
- Daily rotation of injection sites
- Good insertion technique is essential. The needle must be inserted at an angle of 45 degrees to the skin; if the needle is inserted intra-dermally, the Apomorphine may irritate the skin and possibly cause ulceration.
- If possible minimise the number of people involved in setting up the infusion. The more people who are involved , the more likely it is that quality of the insertion technique will vary
- It is crucial that the needle site is rotated daily
- Use of 10mm 'Soft- set' needles
- Gentle massage of the injection sites on a daily basis, by hand or with a hand held massage device, could help to reduce nodule formation. Massage promotes healthy skin by encouraging good circulation to the adipose tissue whilst de-sloughing dead skin cells.
- Silicone gel patches can also help to reduce nodule formation and relieve itchiness. The patches are placed over the nodules and left in place overnight. The patches can be used many times if they are rinsed in warm water and dried carefully. Each packet contains instructions for use. It is not fully understood how these patches work to reduce nodule formation, although silica is known to exert a beneficial effect on scar tissue.
- There have been some anecdotal reports that therapeutic ultrasound may be used with benefit on Apomorphine nodules. Some patients have received ultrasound treatment for many years and continue to maintain good skin quality and reduction in nodules. However, ultrasound therapy has not been subject to any formal trials. There is no clinical evidence to support its use or conversely to suggest that it is harmful. **Patients with Deep Brain Stimulators in situ must not have ultra sound treatment.**

Contra-indications/Cautions

- Respiratory or CNS depression
- Neuropsychiatric problems or dementia
- Hepatic insufficiency
- Pregnancy and breast feeding

Cautions:
- Pulmonary, cardiovascular or endocrine disease
- Renal impairment
- History of postural hypotension

Pregnancy and Lactation

A) Teratogenicity / Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info Apokyn(TM), 2004f) (All Trimesters)

Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

2) Australian Drug Evaluation Committee's (ADEC) Category: B3 (Batagol, 1996)

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

3) Crosses Placenta: Unknown

4) Clinical Management

There is little data on the use of Apomorphine in pregnant women. One small study did not show any detriment of the drug use on fetuses when given before C-section. Until more information is available, Apomorphine should only be used during pregnancy if the maternal condition justifies the potential risk to the fetus.

5) Literature Reports

Apomorphine was compared with gastric tubes in emptying the stomach prior to general anaesthesia in obstetric patients.

Forty-five mothers about to undergo general anaesthesia received Apomorphine in a 3 mg dose, then received atropine 0.6 mg or hyoscine 0.6 mg IV when vomiting ceased. Apgar scores were obtained in the infants of 30 mothers who underwent C-section and had Apomorphine administered. Infant Apgar scores were not significantly different in the Apomorphine group as compared to the stomach tube group. There was no evidence that Apomorphine had any depressant effect on the babies (Holdsworth et al, 1974).

B) Breastfeeding

1) Thomson Lactation Rating: Infant risk cannot be ruled out.

Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

2) Clinical Management

No reports describing the use of Apomorphine during human lactation are available and the effects on the nursing infant from exposure to the drug in milk are unknown. It is not known if Apomorphine affects the quantity and composition of breast milk. Until more data are available, use caution when considering the use of Apomorphine in lactating women.

3) Literature Reports

No reports describing the use of Apomorphine during human lactation or measuring the amount, if any, of the drug excreted into milk have been located.

Drug Interactions (refer also to BNF or SPC; include significance of interaction)

- Antipsychotics: effects of Apomorphine antagonized by antipsychotics
- Dopaminergic: effects of Apomorphine possibly enhanced by Entacapone
- Memantine: effects of dopaminergic possibly enhanced by Memantine
- Methyldopa: antiparkinsonian effect of dopaminergic antagonized by methyldopa

Responsibilities

Consultant Neurologist / MDC

- Prior to admission arrange for the patient to have an ECG, a full blood count, Coombs test, and reticulocyte count
- Patient suitability/selection and confirms GPs agreement to prescribe
- Optimises anti-Parkinson's therapy
- Prescribes the initial Apomorphine challenge with a non-formulary form
- Establishes whether the patient should start on an infusion and/or a APO-go® Pen
- Writes the Electronic Discharge Letter (post day case admission)
- Gains patient written consent for challenge and therapy where indicated
- Arranges ongoing ECG AND 6 monthly full blood count, Coombs test and reticulocyte count monitoring for haemolytic anaemia.

General Practitioner

- Agrees to clinical responsibility for prescribing Apomorphine
- Agrees to prescribe Domperidone cover with guidance from the Neurology team (PDNS or Consultant Neurologist / MDS)
- Agrees to treat local skin problems with specialist guidance in the case of nodule formation
- Liaises with PDNS/Consultant Neurologist/DN's/Community Pharmacist

Responsibilities

PD Nurse Specialist

- Receive training prior to patient starting Apomorphine
- Provision of information to patient, carer (video, DVD and written materials)
- Arranges for provision of a pump from Genus pharmaceuticals
- Gains patients consent for his/her details to be passed to the above (for loan agreement)
- Provides patient and carer education and training with appropriate device i.e. pen or pump
- Provision of information about Apomorphine to GP and DN's – arranges training for DN's re using Apomorphine infusion pumps and Apomorphine pens
- Arranges hospital admission

- Conducts Apomorphine challenge
- Arranges follow up appointment in conjunction with Consultant neurologist / MDC
- Provide telephone support for patient
- Provide point of contact and ongoing support for GP and district nurses
- Provide specialist skin care advice (hand held massager, referral for ultrasound where indicated).
- Support patient/carer/district nurses with daily pump set up where indicated and negotiated
- Provide assessment within the first week if the patient is self-administering injections or infusion via pump to identify any issues in practice setting.
- Regular assessment of patient and inspection of infusion site for early detection of nodules
- Notify the patient's regular community pharmacist that apomorphine is being transferred to primary care (notethe similarity in name to morphine and diamorphine).

Genus Pharmaceuticals

- Provide the loan of practice pump,dummy pens and massagers
- Provide therapy support literature and Videos/DVDs for patients and carers
- Provide training to healthcare professionals for infusion pump and pen
- Provide nurse advisor support
- Provide pharmaceutical advice / literature on the product for healthcare professionals
- Provide maintenance of pump and replace pumps if faulty using their 24/7 Helpline Service (Telephone number (office hours): 08448801327 or (out of hours) 02089383951)

Patient

- Ensure that they have a clear understanding of their treatment.
- Report any adverse effects to their GP and/or specialist regarding their treatment.
- Ensure they attend for monitoring requirements as per shared care guideline.

Patient Information Leaflet

Genus pharmaceutical to provide an APO-GO® patient information pack for each new patient.

Contact Details:

Parkinson's Disease Nurse Specialist: Angela Weir: Neuroscience Offices; Level 3; John Radcliffe Hospital, OX3 9DU; 01865 234048

Consultant Neurologist: Dr Marco Bogdanovic: Neuroscience Offices; Level 3; John Radcliffe Hospital, OX3 9DU; 01865 234605

Consultant Gerontologist: Dr Sudhir Singh: Department of Geratology, Academic level 4; John Radcliffe Hospital, OX3 9DU; 01865 234878