Satellite Symposium Proceedings

A Landmark Year for Apomorphine – Advancing Parkinson's Disease Management with New Clinical Evidence

Highlights of a Britannia-sponsored symposium held at the 21st International Congress of Parkinson's Disease and Movement Disorders, Vancouver, Canada, 4–8 June 2017

Andrew Lees, Regina Katzenschlager and K Ray Chaudhuri

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It has now been almost 30 years since the publication of the pivotal clinical trial in *The Lancet* in 1988, which confirmed that subcutaneous apomorphine (APO) has equivalent antiparkinsonian efficacy to levodopa for the management of 'off' symptoms in patients with Parkinson's disease (PD). The study's findings led to subcutaneous APO (APO-go®, Britannia Pharmaceuticals Ltd, UK) being licensed initially in the UK in 1993 for PD treatment and since that time it has been used successfully in clinical practice in Europe and many other parts of the world for the management of 'off period' disability. This symposium, chaired by Professor Andrew Lees (UK), who was a key investigator in that original trial, set out to review what has been another landmark year for APO and to discuss how recent clinical evidence can help inform our daily practice and improve outcomes for our patients with PD. APO is the only other drug with an antiparkinsonian effect equal to levodopa. When used as intermittent subcutaneous injections, it is also the most rapidly effective treatment for motor fluctuations and its efficacy has been confirmed in randomised trials. Extensive clinical experience and many uncontrolled studies have shown the efficacy of APO for the relief of motor fluctuations when administered either as an intermittent injection or as a continuous subcutaneous infusion using ambulatory mini-pumps, depending on the patient's symptoms. However, unlike other therapies commonly used for these types of patients, such as levodopa/carbidopa intestinal gel and deep-brain stimulation, up to now Level 1 evidence for the efficacy and safety of APO infusion from large, randomised studies has been lacking. Professor Regina Katzenschlager (Austria) provided an overview of the clinical trial of apomorphine subcutaneous infusion in patients with advanced Parkinson's disease (TOLEDO study), the first randomised, double-blind clinical trial to investigate the efficacy, safety and tolerability of APO-go 5 mg/ml solution for infusion compared with placebo in patients with PD whose motor fluctuations are uncontrolled despite optimised PD therapy. Results from this study will fill an important knowledge gap in the currently available evidence for APO infusion. Professor K Ray Chaudhuri (UK) went on to review the clinical indications for APO infusion and other continuous dopaminergic therapies, illustrated with patient case studies and supported by his experience since the 1990s in initiating and monitoring medication to obtain the best long-term results. Recently, wearable sensors have been used to monitor patients with PD undergoing treatment to help inform clinical management. Although APO is more than 150 years old, it is apparent that there are still many important lessons to learn about its mode of action and optimum clinical application which will be of benefit to patients with PD.

Keywords

Parkinson's disease (PD), motor fluctuations, subcutaneous apomorphine infusion, randomised clinical trial

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Introduction

Andrew Lees

The National Hospital for Neurology and Neurosurgery and Reta Lila Weston Institute of Neurological Studies, Institute of Neurology, University College London, London, UK

Professor Lees introduced the symposium by highlighting that there had been several significant landmark events in the past year in the field of Parkinson's disease (PD) and its treatment. Notably, it was now exactly 200 years since the original publication by James Parkinson of his *An essay on the shaking palsy*,[1] 100 years since Tretiakoff discovered one of the most important lesions in PD, the loss of dopamine-producing cells in the substantia nigra[2] and 50 years since the Hoehn and Yahr scale was first used to describe symptom progression in PD.[3,4] In addition, 2017 was a landmark year for apomorphine (APO) as a PD therapy. One of the objectives of the symposium was to review information on a new clinical trial for this established treatment.

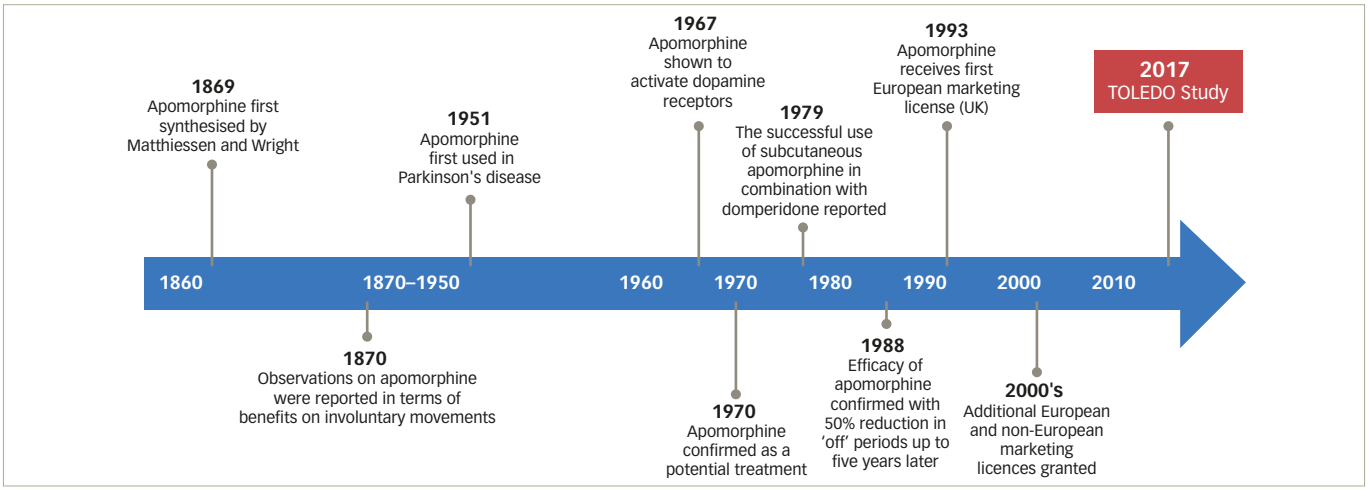
Professor Lees advised that APO had a long and interesting history in the field of neurology and PD (*Figure 1*).[5–12] For those unfamiliar with APO, he said it was important to note that despite its name, it was not a narcotic substance. Since its discovery, APO has had various clinical applications in neurology, being used in the 19th century to treat chorea and pseudo-epilepsy, and at the beginning of the 20th century to treat delirium tremens due to alcohol or drug addiction. More recently, it has been used to treat erectile dysfunction. It was first suggested in the 19th century that APO might be a valuable treatment for PD but it was not until the 1950s that Schwab and colleagues, in the USA, reported positive results with subcutaneous administration of APO in patients with PD, despite some side effects (primarily nausea, vomiting and hypotension).[5] Cotzias was instrumental in undertaking research that led to the development of levodopa as an oral therapy for PD but was aware of its limitations and so looked to investigate dopamine agonists, including APO, that could be used in combination with levodopa to augment its effects on motor symptoms; however, the focus at that time was on oral agents.[6] In 1979, following the discovery that the dopamine receptor antagonist domperidone could ameliorate the side effects of nausea and vomiting associated with the administration of subcutaneous APO, there was a renewed focus on the drug and research into its clinical benefits in patients with PD.[7] At around the same time, in other fields of medicine there were advances in technology and the use of ambulatory mini-pumps, which paved the way for the introduction of APO infusion into clinical practice.

Professor Lees advised that his own involvement in research into the use of APO in PD management began almost 30 years ago and resulted in the publication of the pivotal clinical trial in *The Lancet* in 1988, which confirmed that subcutaneous APO has equivalent antiparkinsonian efficacy to levodopa, and was a potent and effective drug for the management of 'off' symptoms in patients with PD.[10] No other oral or transdermally administered dopamine agonists have been shown to have equivalent efficacy to levodopa. The study's findings led to subcutaneous APO being licensed initially in the UK in 1993 for PD treatment (APO-go®, Britannia Pharmaceuticals Ltd, UK). Since that time, subcutaneous APO has been used successfully in clinical practice in many countries around the world for the management of 'off period' disability. However, despite extensive clinical experience and positive findings from many uncontrolled studies, Level 1 evidence from a randomised, controlled trial (RCT) had been lacking up to now.[13]

Professor Lees went on to introduce the international faculty. Professor Regina Katzenschlager, Head of the Department of Neurology and Karl Landsteiner Institute for Neuroimmunological and Neurodegenerative Disorders at the Danube Hospital in Vienna, Austria, is the principal investigator of the clinical trial of apomorphine subcutaneous infusion in patients with advanced Parkinson's disease (TOLEDO study; NCT02006121), the first double-blind RCT to investigate the efficacy, safety and tolerability of APO-go 5 mg/ml solution for infusion compared with placebo in patients with PD whose motor fluctuations are uncontrolled despite optimised PD therapy.

Professor K Ray Chaudhuri, Director of the National Parkinson Foundation Centre of Excellence at Kings College London, has considerable experience in both clinical research and practical use of APO in patients with PD. Professor Chaudhuri would share his personal experience of how clinicians can optimise patient outcomes when they are treated with APO using a combination of careful patient selection, initiation and monitoring of treatment efficacy. ❑

Figure 1: The history of apomorphine[5–12]



The TOLEDO study – the first, randomised, placebo-controlled trial of apomorphine infusion (APO-go®) therapy in Parkinson's disease

Regina Katzenschlager

Department of Neurology, Karl Landsteiner Institute for Neuroimmunological and Neurodegenerative Disorders, Danube Hospital, Vienna, Austria

Professor Katzenschlager gave an introduction to the pharmacological properties of APO, a highly potent, short-acting dopamine agonist with broad spectrum receptor affinity for D1-like (D1, D5) and D2-like (D2, D3, D4) dopamine receptors, as well as serotoninergic and adrenergic activity.[14]

When administered as an intermittent subcutaneous injection (APO-go PEN 10 mg/ml solution for injection), APO has a rapid onset of effect within 4–12 minutes and has been shown to reverse 95% of 'off' periods in patients with PD.[15] Continuous subcutaneous APO infusion (APO-go 5 mg/ml solution for infusion) is indicated for the treatment of motor fluctuations (on–off phenomena) in patients with PD that are not sufficiently controlled by oral anti-PD medication.[16] It is now licensed in 23 countries worldwide and has been used in clinical practice in the UK for more than 25 years.

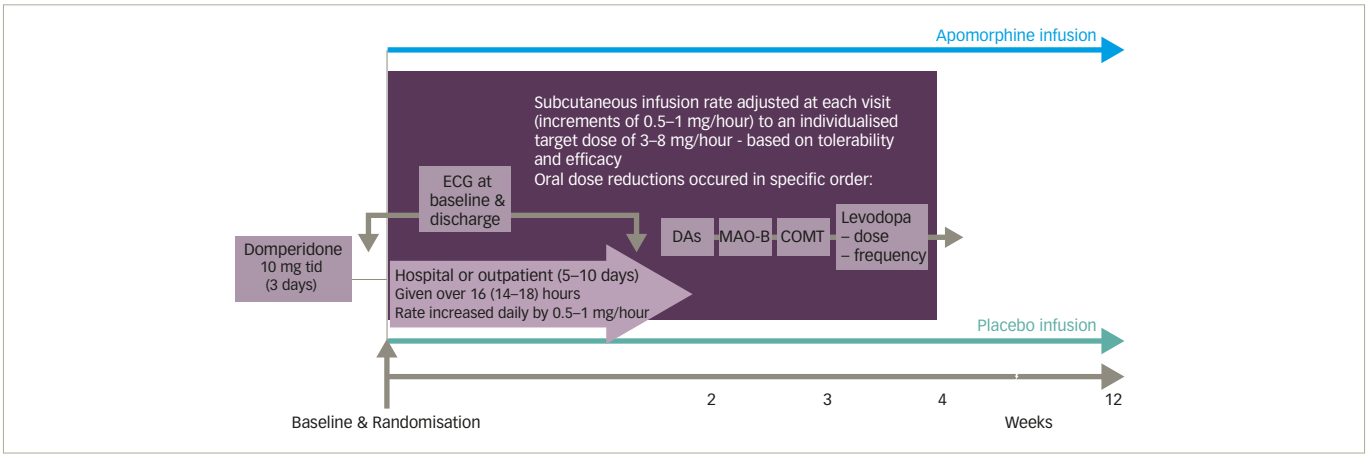
Accumulated data from a considerable number of open-label studies undertaken over the past 20 years in patients with PD have demonstrated a mean reduction in daily 'off' time of around 60% and a mean reduction in dyskinesia intensity of around 32% following treatment with APO infusion.[17] However, many clinical guidelines and systematic reviews, such as the evidence-based medicine review of treatments for the motor symptoms of PD issued by the International Parkinson and Movement Disorders Society, only include recommendations for the use of APO injection, since data from a randomised clinical trial providing Level 1 evidence for APO infusion have been lacking up to now.[13] The phase III TOLEDO study was initiated to fill this evidence gap.

Professor Katzenschlager highlighted the significance of TOLEDO as the first double-blind, randomised, placebo-controlled, phase III study of APO infusion in this setting. The objectives of the study were to evaluate the efficacy, safety and tolerability of subcutaneous APO infusion in patients with PD with motor fluctuations not well controlled on optimised medical treatment.[18] The study was undertaken in 23 centres in seven countries around Europe. Patients were eligible to participate in the study if they had had PD for >3 years (according to Queen Square Brain Bank Criteria) and an average 'off' time of ≥3 h/day with their motor fluctuations not adequately controlled on medical treatment (including ≥4 daily doses of levodopa) judged to be optimal by physician. Subjects also needed to be able to differentiate between 'on' and 'off' time, and 'on' time with troublesome dyskinesias and without troublesome dyskinesias in order to complete home diaries.

The design of the TOLEDO study is shown in *Figure 2*. A total of 107 patients were randomised 1:1 to APO infusion (n=53) or placebo infusion (n=54). After randomisation, patients underwent a treatment initiation phase of 5–10 days, followed by a dose adjustment phase (including oral medication) up to the end of week 4, and then stable treatment to the end of week 12. The target dose of APO was each patient's individual optimised dose at hourly flow rates of 3–8 mg administered for 16±2 hours of their waking day. Following completion of the 12-week, parallel-group, double-blind, placebo-controlled phase, or in the case of withdrawal due to lack of efficacy, patients could enter a 52-week open-label phase.

The initial results of the 12-week double-blind phase had been presented at the 21st International Congress of the Movement Disorders Society in Vancouver, Canada, in June 2017.[18] The open-label phase of TOLEDO is ongoing and results are expected in 2018. ❑

Figure 2: Design of the TOLEDO study[18]



COMT = catechol-O-methyl transferase inhibitor; DAs = dopamine agonists; ECG = electrocardiogram; MAO-B = monoamine oxidase-B inhibitor; tid = three times daily.

Optimising patient outcomes with apomorphine – practical approaches to patient selection, initiation and monitoring

K Ray Chaudhuri

National Parkinson Foundation Centre of Excellence, Kings College London, Denmark Hill Campus, London, UK

In his presentation, Professor Chaudhuri discussed clinical and practical approaches to the use of APO infusion based on his 30-year experience with the use of this medication. He noted that key questions related to when patients with PD should be started on continuous dopaminergic drug delivery (CDD) therapy, how we decide which CDD therapy is best for each patient and, if APO infusion is selected, how we ensure it is optimised. In his view, the future of PD management would focus on personalised medicine for each individual patient to ensure the best outcomes.

Various CDD options are available in different countries around the world and generally comprise one of three choices. Levodopa/carbidopa intestinal gel (LCIG) is the continuous administration of levodopa/carbidopa by infusion into the duodenum/jejunum. It requires a gastrostomy procedure for the placement of the infusion tube. Deep-brain stimulation (DBS) is another option but this requires stereotactic brain surgery. Subcutaneous APO infusion is the least invasive option and is administered by means of a removable infusion pump which does not require surgery and is reversible. APO infusion can be initiated during inpatient hospitalisation or in an outpatient hospital setting.

The Navigate PD survey was a summary of expert opinion that was developed to aid clinicians when making a selection of one device-aided CDD therapy over another.[19] This concluded that for patients aged <70 years with motor fluctuations or dyskinesias who are otherwise healthy, any of the device-aided therapies may be considered. For patients aged >70 years, DBS surgery should only be considered as a second-line option in preference to the other device-aided therapies (although patients can be operated on in the presence of a normal MRI and preserved cognitive function), while for patients aged >70 years with mildly or moderately impaired cognition (or other contraindications to DBS), LCIG infusions or subcutaneous APO infusion may be considered with careful cessation or reduction in oral therapy (rapid cessation of dopamine agonists may lead to withdrawal symptoms).

There is growing recognition that administration of oral therapies can be problematic for some patients with PD, due to upper gastrointestinal (GI) tract issues that can occur at all stages of the disease. Dysphagia may lead to silent aspiration, and delayed gastric emptying can lead to poor absorption of medication resulting in motor complications.[20] In addition, small intestinal bacterial overgrowth and altered gut microbiota can have an impact on drug absorption.

Many treatment guidelines have been published to aid clinicians in the selection of appropriate PD therapy at the different disease stages and for the range of presenting symptoms. Often, effective treatments, including CDD therapies such as APO infusion, are prescribed too late as they are wrongly perceived as only being suitable for patients with end-stage disease, whereas they can provide valuable benefits if prescribed earlier in the course of the disease. Collection of patient data via registries also provides supporting 'real-world' data necessary to identify patient-specific and quality-of-life benefits of the different types of therapy. However, these take a generalised approach to PD management and in recent years there has been a growing paradigm shift towards personalised medicine which aims to deliver a more precisely targeted therapy.[21–23] Personalised medicine is an approach that is already used in several other fields of medicine, such as oncology and rheumatology. The concept of personalised medicine is particularly relevant for PD, since it is a heterogeneous condition with multiple pathologies and diverse presentations. Future PD management needs to embrace the range of influences on the disease and its outcomes – genetic, therapeutic, personal and socio-economic – and APO infusion can form part of the treatment algorithm to help deliver this.

Professor Chaudhuri highlighted the importance of lifestyle considerations when treating patients with PD, including the person's work and work environment, exercise regime or recreational activities, as these external factors can influence which particular treatment can be used and the success of therapy.[23] He illustrated this point with one of his own patient case studies (*Figure 3*), a female patient with PD who worked as a musician and was involved in regular concerts. She had developed severe levodopaphobia so a personalised treatment approach was sought, taking into account her individual needs and lifestyle. She was treated successfully, initially with APO injection and subsequently with APO infusion, and was able to continue to work.

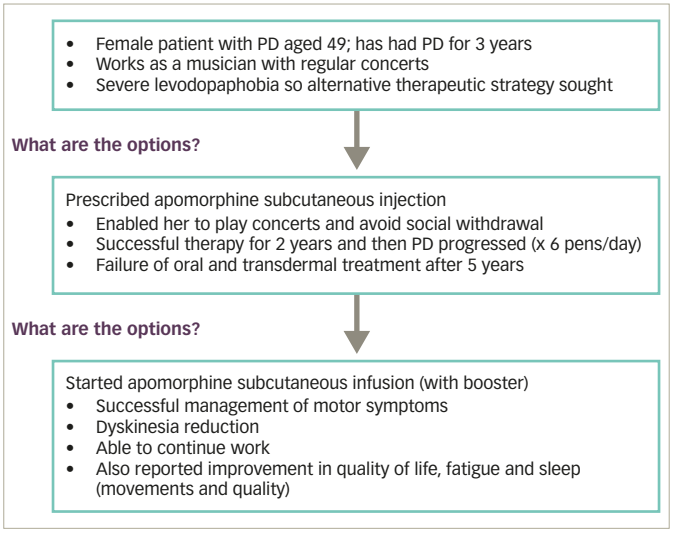
Professor Chaudhuri advised that the criteria for deciding whether patients were suitable for APO infusion had been outlined in the recent Expert Consensus Statement.[24] These experts had agreed that APO infusion was suitable for patients with PD who had troublesome 'off' periods despite optimised treatment, and particularly in the following situations – patients who felt doses of APO intermittent injection were required too frequently, where dyskinesias limit further therapy optimisation, to simplify complex PD dosing regimens, as an alternative to surgical therapy or LCIG if these are contraindicated or because of patient preference, and when absorption or oral levodopa was impaired due to GI issues.

To help guide clinicians, particularly those who may be unfamiliar with using APO infusion, the Expert Consensus Statement also summarised the stepwise initiation process for patients who were starting treatment.[24] Although there were regional variations, Professor Chaudhuri noted that APO infusion could be initiated on either an outpatient or an inpatient basis. He advised that one-day initiation was common in the UK and was a cost-effective approach with support from PD nurse specialists (PDNS). The initiation process comprised

1. patient selection and pre-treatment safety checks;
2. pre-medication, usually with domperidone;
3. treatment initiation;
4. dose optimisation/reduction of other PD medications; and
5. follow-up and monitoring.

Professor Chaudhuri considered that PDNS were key members of the multidisciplinary team involved in PD patient care, providing education, training and support to help ensure that each patient got the best from their selected therapy.[25]

Figure 3: Patient case study – a personalised approach to PD therapy



PD = Parkinson's disease

Once patients with PD were established on therapy, it was important that they were regularly monitored to ensure that treatment was effective and adjusted as necessary. Monitoring could be done in a variety of ways, including asking the patient how they feel about their therapy at clinic visits, asking them to keep a daily diary recording 'on' and 'off' periods, or using wearable monitoring devices or other sensors. Professor Chaudhuri stressed that the adjustment of any medication regimen was a dynamic process and could take time to get right, often several months.

Professor Chaudhuri concluded by saying that in his opinion, optimal outcomes with any PD therapy were best achieved with an individualised approach to treatment – selecting the right patient, giving the best treatment for them at the right time and continuing to monitor progress. He noted that PD progression was a complex process requiring personalisation of therapy to ensure patients receive the best treatment to suit their symptoms and lifestyle. Selection of treatment – aided by recommendations in treatment guidelines, supported by data from registries – should be individualised for each patient and their personal circumstances.

Wearable sensors could be used to support clinical opinion and decision-making in individual cases and help demonstrate why patients may need to change their treatment, but still require validation for use with device-aided therapies. In the case of APO infusion, optimising patient outcomes relied on careful patient selection, established stepwise initiation and continuous monitoring. ❑

Article highlights

- The dopamine agonist apomorphine (APO) has an extensive history in the field of neurology and has been licensed (APO-go®, Britannia Pharmaceuticals Ltd, UK) and used successfully in clinical practice for almost 30 years for the effective management of motor symptoms in patients with Parkinson's disease (PD).
- Positive clinical experience with APO has been supported by the results of many uncontrolled studies which showed its efficacy for the relief of motor fluctuations when administered either as an intermittent injection or as a continuous infusion.
- Until recently, Level 1 evidence from a randomised, blinded clinical trial to confirm the efficacy of APO infusion has been lacking.
- The clinical trial of APO subcutaneous infusion in patients with advanced Parkinson's disease (TOLEDO study) is the first randomised, double-blind clinical trial to investigate the efficacy, safety and tolerability of APO-go 5 mg/ml solution for infusion compared with placebo in patients with PD whose motor fluctuations are uncontrolled despite optimised PD therapy.
- In clinical practice, optimal outcomes with APO infusion, or any other form of continuous dopaminergic stimulation, are best achieved with a personalised approach to therapy – selecting the right patient and continuing to monitor progress. ❑

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When the increasing frequency and severity of daily 'OFFs', dyskinesias or pill burden threaten everything they live for,[1,2,6] it's time to prescribe APO-go PUMP[3] – continuous subcutaneous infusion of apomorphine, delivering smooth, predictable control of motor fluctuations.[3-5]

APO-go® PUMP

apomorphine hydrochloride

Continuous, reliable 'ON'[3-5]

APO-go® Apomorphine hydrochloride. **PRESCRIBING INFORMATION**. Consult Summary of Product Characteristics before prescribing. **Uses:** Treatment of motor fluctuations ('ON-OFF' phenomena) in patients with Parkinson's disease which are not sufficiently controlled by oral anti-Parkinson medication. **Dosage and Administration:** Apomorphine hydrochloride is administered subcutaneously either as an intermittent bolus injection or by continuous subcutaneous infusion. Its rapid onset (4-12 mins) and duration of action (about 1 hour) may prevent an 'OFF' episode which is refractory to other treatments. Apomorphine should be initiated in the controlled environment of a specialist clinic. The patient should be supervised by a physician experienced in the treatment of Parkinson's disease (e.g. neurologist). Please refer to the Summary of Product Characteristics for full details before initiating therapy. Patients treated with apomorphine will usually need to start domperidone at least two days prior to initiation of therapy. The domperidone dose should be titrated to the lowest effective dose and discontinued as soon as possible. Before the decision to initiate domperidone and apomorphine treatment, risk factors for QT interval prolongation in the individual patient should be carefully assessed to ensure that the benefit outweighs the risk. The optimal dosage of apomorphine HCl has to be determined on an individual patient basis; individual bolus injections should not exceed 10mg and the total daily dose should not exceed 100mg. Do not use if the solution has turned green. The solution should be inspected visually prior to use. Only clear, colourless and particle free solution should be used. **Contraindications:** Children and adolescents (up to 18 years of age). Known sensitivity to apomorphine or any other ingredients of the product. Respiratory depression, dementia, psychotic disease or hepatic insufficiency. Intermittent apomorphine HCl treatment is not suitable for patients who have an 'ON' response to levodopa which is marred by severe dyskinesia or dystonia. **Pregnancy and lactation:** Apomorphine should not be used in pregnancy unless clearly necessary. Breast-feeding should be avoided during apomorphine HCl therapy. **Interactions:** Patients should be monitored for potential interactions during initial stages of apomorphine therapy. Particular caution should be given when apomorphine is used with other medications that have a narrow therapeutic window. It should be noted that there is potential for interaction with neuroleptic and antihypertensive agents. It is recommended to avoid the administration of apomorphine with other drugs known to prolong the QT interval. Apomorphine can increase the antihypertensive effects of domperidone. **Precautions:** Use with caution in patients with renal, pulmonary or cardiovascular disease, or who are prone to nausea or vomiting. Extra caution is recommended during initiation of therapy in elderly and/or debilitated patients. Since apomorphine may produce hypotension, care should be exercised in patients with cardiac disease or who are taking vasoactive drugs, particularly when pre-existing postural hypotension is present. Neuropsychiatric problems co-exist in many patients with advanced Parkinson's disease. There is evidence that for some patients neuropsychiatric disturbances may be exacerbated by apomorphine. Special care should be exercised when apomorphine is used in these patients. Apomorphine has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution whilst driving or operating machines during treatment with apomorphine. Haematology tests should be undertaken at regular intervals, as with levodopa, when given concomitantly with apomorphine. Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders, including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating, can occur in patients treated with dopamine agonists, including apomorphine. Dose reduction/tapered discontinuation should be considered if such symptoms develop. Dopamine dysregulation Syndrome (DDS) is an addictive disorder resulting in excessive use of the product seen in some patients treated with apomorphine. Before initiation of treatment, patients and caregivers should be warned of the potential risk of developing DDS. Since apomorphine, especially at high dose, may have the potential for QT prolongation, caution should be exercised when treating patients at risk for torsades de pointes arrhythmia. When used in combination with domperidone, risk factors in the individual patient should be carefully assessed. This should be done before treatment initiation, and during treatment. Important risk factors include serious underlying heart conditions such as congestive cardiac failure, severe hepatic impairment or significant electrolyte disturbance. Also medication possibly affecting electrolyte balance, CYP3A4 metabolism or QT interval should be assessed. Monitoring for an effect on the QTc interval is advisable. An ECG should be performed prior to treatment with domperidone, during the treatment initiation phase and as clinically indicated thereafter. The patient should be instructed to report possible cardiac symptoms including palpitations, syncope, or near-syncope. They should also report clinical changes that could lead to hypokalaemia, such as gastroenteritis or the initiation of diuretic therapy. At each medical visit, risk factors should be revisited. Apomorphine has been associated with local subcutaneous effects that can be reduced by rotation of injection sites or use of ultrasound on areas of nodularity and induration. Contains sodium metabisulphite which rarely causes severe allergic reactions and bronchospasm. **Side Effects:** Local induration and nodules (usually asymptomatic) often develop at subcutaneous site of injection, leading to areas of erythema, tenderness, induration and panniculitus. Irritation, itching, bruising and pain may also occur. Rarely, injection site necrosis and ulceration have been reported. Pruritus may occur at the site of injection. Drug-induced dyskinesias during 'ON' periods can be severe, and in a few patients may result in cessation of therapy. Postural hypotension is seen infrequently and is usually transient. Transient sedation following each dose of apomorphine may occur at the start of therapy, but this usually resolves after a few weeks of treatment. Dizziness and light-headedness have also been reported. Nausea and vomiting may occur, particularly when APO-go treatment is initiated, usually as a result of the omission of domperidone. Neuropsychiatric disturbances including transient mild confusion and hallucinations – seeing, hearing or feeling things that are not there have occurred during apomorphine therapy and neuropsychiatric disturbances may be exacerbated by apomorphine. Positive Coombs' tests, haemolytic anaemia and thrombocytopenia have been reported in patients receiving apomorphine. Local and generalised rashes have been reported. Eosinophilia has occurred in only a few patients during treatment with apomorphine HCl. Patients treated with dopamine agonists, including apomorphine, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, compulsive spending or buying, binge eating or compulsive eating, (especially at high doses), syncope (fainting), aggression and agitation. Apomorphine is associated with somnolence. Yawning and breathing difficulties have been reported, as has peripheral oedema. Apomorphine has been associated with sudden sleep onset episodes. Prescribers should consult the Summary of Product Characteristics in relation to other side effects. **Presentation and Basic NHS Cost:** APO-go PENs (disposable multiple dosage injector system) contain apomorphine hydrochloride 10mg/ml, as follows: 30mg in 3ml – basic NHS cost £123.91 per carton of 5 pens. APO-go Pre-filled syringes contain apomorphine hydrochloride 5mg/ml, as follows: 50mg in 10ml – basic NHS cost £73.11 per carton of 5 syringes. APO-go ampoules contain apomorphine hydrochloride 10mg/ml as follows: 50mg in 5ml – basic NHS cost £73.11 per carton of 5 ampoules. **Marketing Authorisation Numbers:** APO-go Ampoules: PL 04483/0072. APO-go Pens: PL 04483/0073. APO-go Pre filled syringes: PL 04483/0074. **Legal Category:** POM. **Date of last revision:** November 2016. For further information please contact: Britannia Pharmaceuticals, 200 Longwater Avenue, Green Park, READING, Berkshire, RG2 6GP. Version Number: APG.PI.V25

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Medical Information on 0870 851 0207 or dso@britannia-pharm.com

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