SAFETY

Crono® APO-go III Pump was well tolerated and no unexpected safety signals were observed.

Most events were mild or moderate in intensity, and no deaths occurred during the study.

Six patients had adverse events that led to study discontinuation; in all but one, the event was considered related to apomorphine and all these events resolved after the drug was discontinued.

Summary of adverse events by week 12†

	Apomorphine (n=54)	Placebo (n=53)
At least one TEAE	50 (93%)	30 (57%)
Skin nodules at infusion site	24 (44%)	0
Nausea	12 (22%)	5 (9%)
Somnolence	12 (22%)	5 (9%)
Infusion site erythema	9 (17%)	2 (4%)
Dyskinesia	8 (15%)	2 (4%)
Headache	7 (13%)	2 (4%)
Insomnia	6 (11%)	1 (2%)
At least one AE with local intolerability (skin changes at injection site)	32 (59%)	8 (15%)
Serious AEs	5 (9%)	2 (4%)
AEs leading to study discontinuation	6 (11%)	0
AEs leading to dose modification	26 (48%)	6 (11%)

AE, adverse event; TEAE, treatmeat-emergent adverse event.
†Only treatment-emergent adverse events that occurred in ≥10% of patients in each group are shown.

APO-go® INFUSION
apomorphine hydrochloride

BRITANNIA PHARMACEUTICALS LTD
STADA GROUP

PRESCRIBING INFORMATION

APO-go® Apomorphine hydrochloride. PRESCRIBING INFORMATION.
Consult Summary of Product Characteristics before prescribing.

Indications 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. 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). The patient's treatment with levodopa, with or without dopamine agonists, should be optimised before starting APO-go treatment. The appropriate dose for each patient is established by incremental dosing schedules. For bolus injection it is suggested to start with 1 mg of apomorphine (0.1 ml) during a hypokinetic or 'off' period. If no response or an inadequate response is obtained after 30 minutes, a second dose of 2 mg is injected and the patient is observed for a further 30 minutes. The dosage may be increased by incremental injections with at least a forty minute interval between succeeding injections, until a satisfactory motor response is obtained. Patients who have shown a good 'on' period response during the initiation stage of apomorphine therapy, but whose overall control remains unsatisfactory using intermittent injections, or who require many and frequent injections (more than 10 per day), may be commenced on or transferred to continuous subcutaneous infusion by minipump and/or syringe driver. Continuous infusion is started at a rate of 1 mg apomorphine HCl (0.1 ml) per hour then increased according to the individual response. Increases in the infusion rate should not exceed 0.5 mg per hour at intervals of not less than 4 hours. Hourly infusion rates may range between 1 mg and 4 mg (0.1 ml and 0.4 ml), equivalent to 0.015 - 0.06 mg/kg/hour. Infusions should run for waking hours only. 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 10 mg and the total daily dose should not exceed 100 mg. 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. Apomorphine must not be used via the intravenous route.

Contraindications Children and adolescents (up to 18 years of age). Known hypersensitivity to apomorphine or any excipients of the medicinal 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. Breastfeeding: It is not known whether apomorphine is excreted in breast milk. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with APO-go should be made taking into account the benefit of breast-feeding to the child and the benefit of APO-go to the woman.

Ability to drive and operate machinery Apomorphine has minor or moderate influence on the ability to drive and use machines. Patients being treated with apomorphine and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities (e.g. operating machines) where impaired alertness may put them or others at risk of serious injury or death until such recurrent episodes and somnolence have resolved.

Interactions Patients should be monitored during initiation with apomorphine therapy particularly when used with other medications that have a narrow therapeutic window. There is potential for interaction with neuroleptic and antihypertensive agents and cardiac active medicinal products. It is recommended to avoid the administration of apomorphine with other drugs known to prolong the QT interval.

Precautions Use with caution in patients with renal, pulmonary or cardiovascular disease, or who are prone to nausea or vomiting. Apomorphine may produce hypotension, exercise care in patients with cardiac disease or who are taking vasoactive drugs. Neuropsychiatric disturbances may be exacerbated by apomorphine. Apomorphine has been associated with somnolence and episodes of sudden sleep onset (see advice on driving above). Haematology tests should be undertaken at regular intervals as haemolytic anaemia and thrombocytopenia have been reported. Monitor patients for the development of impulse control disorders. 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; patients and caregivers should be warned of the potential risk of developing DDS. Apomorphine may have the potential for QT prolongation, exercise caution when treating patients at risk for torsades de pointes arrhythmia. Risk factors for use with domperidone include serious underlying heart conditions such as congestive cardiac failure, severe hepatic impairment or significant electrolyte disturbance. An ECG should be performed prior to treatment with domperidone, during the treatment initiation phase and as clinically indicated thereafter to monitor prolongation of QT interval. Patients should report possible cardiac symptoms; palpitations, syncope, or near-syncope and clinical changes that could lead to hypokalaemia, e.g. gastroenteritis or initiation of diuretic therapy. At each medical visit, risk factors should be revisited. Apomorphine has been associated with local subcutaneous effects that can be sometimes reduced by rotation of injection sites in order to avoid nodularity and induration. Contains sodium metabisulphite which may rarely cause severe allergic reactions and bronchospasm.

Side Effects: Very common: Hallucinations and injection site reactions. Common: Neuropsychiatric disturbances, somnolence, transient sedation, dizziness, yawning, nausea and vomiting. Rarely, injection site necrosis and ulceration have been reported. Severe drug-induced dyskinesias during "on" periods may require discontinuation. Postural hypotension is usually transient and infrequent. Positive Coombs' tests, haemolytic anaemia and thrombocytopenia have been reported. Eosinophilia occurs rarely. Dopamine agonists, including apomorphine, may cause impulse control disorders such as pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating or compulsive eating. Rarely, allergic reactions (including anaphylaxis and bronchospasm) due to sodium metabisulphite. Symptoms of overdose like excessive emesis, respiratory depression, hypotension and bradycardia may be treated empirically.

Prescribers should consult the Summary of Product Characteristics in relation to other adverse reactions.

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® Pen: PL 04483/0073
APO-go® Pre Filled Syringes: PL 04483/0074

Legal Category POM

SmPC Revision Date January 2020

API Revision date April 2020

Marketing Authorisation Holder in the UK Britannia Pharmaceuticals, 200 Longwater Avenue, Green Park, Reading, Berkshire, RG2 6GP

Full prescribing information and further information is available from Britannia Pharmaceuticals at Britannia@medinformation.co.uk or 01483 920 763.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Britannia Pharmaceuticals Ltd at dso@britannia-pharm.com or 01483 920 763.

Version Number: APG.PI.V28

Reference
1. Olanow CE, *et al. Lancet Neurol.* 2014;13(2):141–149

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APO-go® INFUSION
apomorphine hydrochloride

BRITANNIA PHARMACEUTICALS LTD
STADA GROUP

KATZENSCHLAGER R, *et al.*

TOLEDO: HIGH-LEVEL EVIDENCE PROVING THE CLINICAL BENEFIT OF CRONO® APO-go III Pump

ADAPTED FROM: **APOMORPHINE SUBCUTANEOUS INFUSION IN PATIENTS WITH PARKINSON'S DISEASE WITH PERSISTENT MOTOR FLUCTUATIONS (TOLEDO): A MULTICENTRE, DOUBLE-BLIND, RANDOMISED, PLACEBO-CONTROLLED TRIAL**
Katzenschlager R, Poewe W, Rascol O, Trenkwalder C, Deuschl G, Chaudhuri KR, Henriksen T, van Laar T, Spivey K, Vel S, Staines H, and Lees A.

AUTHORS' CONCLUSIONS

- Crono® APO-go III Pump has beneficial clinical effects on motor fluctuations in patients with Parkinson's disease that persist despite optimisation of oral or transdermal medication
- TOLEDO provides high-level evidence that the Crono® APO-go III Pump leads to a pronounced improvement in 'OFF' time, which is associated with an increase in good 'ON' time and is clinically meaningful from the patient's perspective
- The 1.9-hour treatment difference in 'OFF' time with apomorphine infusion vs. placebo in TOLEDO is comparable to controlled trials of other infusion therapies (–3.05 vs. –0.76; p=0.0015)[1]

Prescribing information can be found on the back page

APO-go® INFUSION
apomorphine hydrochloride

INTRODUCTION

Over time, motor fluctuations usually worsen, leading to long and troublesome periods of immobility and non-motor symptoms, and attempts to control fluctuations with oral medication can lead to disabling dyskinesia.

Although the efficacy of apomorphine infusion in PD patients with advanced motor fluctuations is well established in clinical practice, the lack of evidence from Level 1 (randomised, controlled) studies has limited its place in evidence-based reviews and guidelines.

PATIENTS AND METHODS

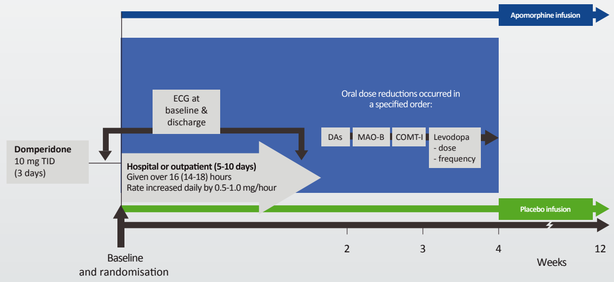
107 patients were enrolled and randomly assigned to a treatment group (apomorphine=53, placebo=54; 1 subsequently excluded from the analysis).

The target dose of apomorphine was each patient's individual optimised dose at hourly flow rates of 3–8 mg administered for 16±2 hours of their waking day.

If applicable, oral medication was reduced in a hierarchical manner, with the aim to reduce and discontinue oral or transdermal dopamine agonists first, followed by MAO-B inhibitors. For levodopa or combined levodopa and COMT inhibitors, doses were to be reduced first, followed by an increase in the intervals between doses. COMT inhibitors could be discontinued. Amantadine and anticholinergics were left unchanged.

Using diaries, patients recorded the time they spent in the 'OFF' and 'ON' states.

TOLEDO double-blind phase study design



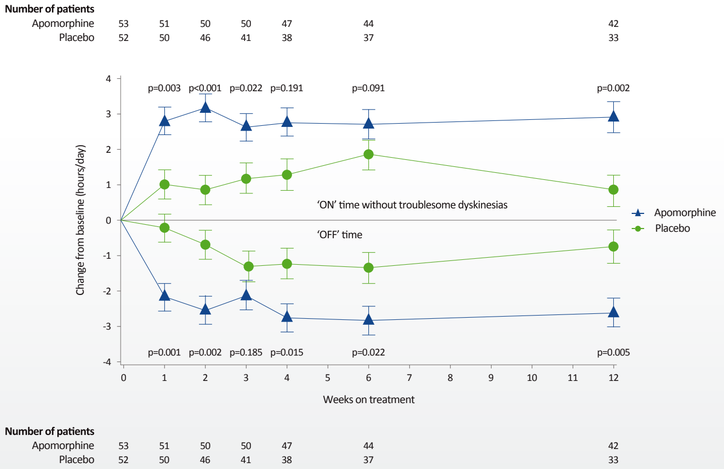
COMT-I, catechol-O-methyltransferase inhibitor; DAs, dopamine receptor agonists; ECG, electrocardiogram; MAO-B, monoamine oxidase B; TID, three times daily

REDUCTION IN 'OFF' TIME

Crono® APO-go III Pump significantly decreased 'OFF' time: mean change from baseline to Week 12 in 'OFF' time was –2.47 hours per day for the Crono® APO-go III Pump group vs. –0.58 hours per day for the placebo group (treatment difference –1.89 hours per day, 95% CI –3.16 to –0.62; p=0.0025).

Crono® APO-go III Pump significantly increased 'ON' time without troublesome dyskinesia: mean change was 2.77 hours per day in the Crono® APO-go III Pump group vs. 0.80 hours per day in the placebo group (treatment difference 1.97 hours per day, 95% CI 0.69–3.24; p=0.0008).

Change in 'ON' time without troublesome dyskinesias and 'OFF' time between baseline and Week 12



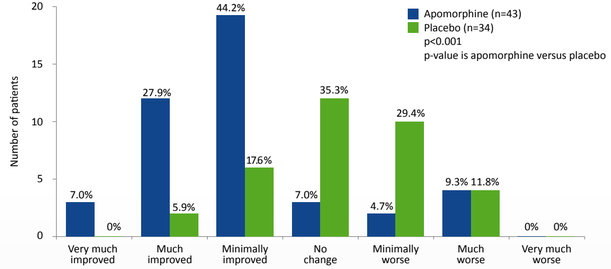
CI, confidence interval.
Error bars indicate 95% CIs.
*Analysis excludes as-needed use and missing data from three sites.

PATIENT GLOBAL IMPRESSION OF CHANGE

Crono® APO-go III Pump significantly improved PGIC scores at Week 12: mean change was 3.23 in the Crono® APO-go III Pump group vs. 4.43 in the placebo group (treatment difference –1.20, 95% CI –1.71 to –0.69; p<0.0001).

At Week 12, 34 (71%) of 48 patients in the Crono® APO-go III Pump group thought that their general health state was improved compared with nine (18%) of 51 patients in the placebo group.

PGIC from baseline to Week 12



PGIC, Patients Global Impressions of Change.

ORAL LEVODOPA-EQUIVALENT DOSE

Mean oral levodopa dose was reduced during the study in both groups. However, the difference between the study groups was not significant (–113.5 mg; p=0.0615).

The reduction in oral levodopa-equivalent dose between baseline and Week 12 was significantly greater in the Crono® APO-go III Pump group vs. the placebo group (p=0.0014), and this difference was significant at all visits from Week 4.

Mean change in levodopa-equivalent dose from baseline to Week 12*