APOMORPHINE PENJECT – EMERGING EVIDENCE AND TREATMENT STRATEGIES FOR DELAYED ON AND OFF PERIODS IN PARKINSON'S DISEASE

Summary of Presentations from the Britannia-sponsored Symposium, held at the Joint Congress of European Neurology (EFNS–ENS), Istanbul, Turkey, on 1st June 2014

Chairperson

Olivier Rascol[1]

Speakers

Fabrizio Stocchi,[2] Stuart Isaacson,[3] William Ondo[4]

1. Professor, Toulouse University Hospital Clinical Investigation Centre, Toulouse, France
2. Professor, Institute of Research and Medical Care, IRCCS San Raffaele, Rome, Italy
3. Associate Professor, Florida International University, Herbert Wertheim College School of Medicine, Miami; Director, Parkinson's Disease and Movement Disorders Center of Boca Raton; Research Director, Marcus Neuroscience Institute, Boca Raton Regional Hospital, Florida, USA
4. Professor, University of Texas Health Science Center, Houston, Texas, USA

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MEETING SUMMARY

This educational symposium was held during the Joint Congress of European Neurology (EFNS–ENS), which took place from 31st May to 3rd June 2014 in Istanbul, Turkey, and was sponsored by Britannia Pharmaceuticals Limited. The symposium debated the problem of delayed ON and OFF periods in Parkinson's disease that can occur even in patients optimised on oral medication. Emerging evidence for the rapid and effective resolution of such complications using apomorphine intermittent injection (penject) was reviewed with particular reference to the positive results of the recent AM IMPAKT trial in patients with morning akinaesia. The discussions were illustrated with examples of 'real life' patient case studies to help determine which patients might be best suited for treatment with apomorphine injection.

Delayed ON and Wearing OFF – Complications

Professor Fabrizio Stocchi

Prof Stocchi described how the management of patients with Parkinson's disease (PD) is frequently complicated by the development of motor fluctuations and dyskinaesias, which occur as a result of alterations in levodopa responsiveness following long-term therapy. Prof Stocchi considered that these motor complications represented a therapeutic challenge to the effective long-term treatment of PD and had a significant negative impact on the patient's quality of life (QoL).[1] Motor fluctuations comprise end-of-dose 'wearing-off' phenomena, peripheral problems such as 'delayed ON' (for example morning akinaesia) or 'no ON' (dose failure), and unpredictable 'ON–OFF' periods. Dyskinaesias may be peak-dose effects, distressing and painful diphasic dyskinaesias, or painful OFF-period dystonia. Prof Stocchi presented compelling

video evidence of real patient cases showing just how debilitating and distressing these different motor complications could be, underlining the need for effective management.

Prof Stocchi highlighted the results of the recent DEEP Study (Early DEtection of wEaring off in Parkinson disease), which had been undertaken to assess the frequency of wearing off in PD patients and its impact on QoL using a validated screening tool, WOQ-19.[2] These results showed that the frequency of wearing off increased with duration of disease such that, after 10 years, around 80% of PD patients experienced wearing-off phenomena.

Prof Stocchi outlined the results of a secondary analysis of the STalevo Reduction In Dyskinesia Evaluation in Parkinson's Disease (STRIDE-PD) study that had investigated the effect of levodopa dose and other risk factors on the development of dyskinaesias and wearing off. The results demonstrated that time to the development of dyskinaesias and time to wearing off both correlated with the dose of oral levodopa.[3] Multivariate analyses showed that factors predictive of dyskinaesia included young age at onset, higher levodopa dose, low body weight, female gender, and more severe Unified Parkinson's Disease Rating Scale (UPDRS) Part III scores. Predictors of wearing off included baseline UPDRS scores but excluded weight.

Evidence suggests that many of these motor complications directly reflect variations in levodopa plasma levels and the rate of levodopa transport to the brain. Standard oral formulations of levodopa result in pulsatile dopaminergic stimulation and are not able to maintain steady plasma levels throughout the day. Within the basal ganglia, striatal dopamine concentrations are normally maintained at a relatively constant level and dopamine receptors are continuously activated.[4] Continuous dopaminergic stimulation (CDS) is therefore thought to more closely mimic the physiological situation, and has been proposed to help overcome the motor complications that occur with standard oral therapy.[5-8]

The benefits of the CDS approach compared with oral levodopa were initially demonstrated with the dopamine agonist lisuride.[9] This double-blind, double-dummy, randomised, controlled trial comparing levodopa + lisuride subcutaneous infusion versus levodopa + high-dose oral pramipexole confirmed the benefits of infusion therapy on UPDRS motor scores and in reducing OFF time and ON time with troublesome dyskinaesias in PD patients.

Prof Stocchi also recognised the contribution of peripheral factors to delayed ON and dose failure with oral levodopa. He illustrated the journey of an oral levodopa dose from mouth to brain and the many possible hurdles it might encounter including swallowing difficulties, delayed emptying from the stomach, absorption in the small intestine, and crossing the blood-brain barrier – a process that takes between 60 and 90 minutes in total. Gastrointestinal (GI) dysfunction, including gastroparesis (delayed gastric emptying), is common in PD, and gastroparesis is a recognised contributing factor to the delay in levodopa time to ON (TTO).[10] Recently, delayed TTO and dose failures have been recognised as a significant proportion of total OFF time, comprising more than twice the duration of wearing off.[11] This was illustrated clearly in a pharmacokinetic study, undertaken by Prof Stocchi, of levodopa given every 4 hours, which revealed a substantial proportion of OFF time over the day, particularly delayed ON (Figure 1) [unpublished data].

Prof Stocchi went on to discuss the role of apomorphine in the management of PD. Apomorphine is a non-ergot dopamine agonist first synthesised in 1845 by heating morphine with hydrochloric acid. Unlike morphine, it has no opioid analgesic effects. It is predominantly a dopamine D1 and D2 receptor agonist, in contrast to most other dopamine agonists which are of the D2 family. The D1 agonist effects of apomorphine are thought to result in less psychosis and less dyskinaesia compared with other dopamine agonist compounds. When injected subcutaneously, apomorphine has a very rapid onset of action within 7.5–10 minutes and duration of effect of around 90 minutes. Subcutaneous apomorphine is available in two formulations for clinical use – an intermittent injection (penject) and a continuous infusion – giving the clinician different therapeutic options depending on the patient's symptoms.

The apomorphine penject is an easy to use injection device that has been shown in a range of clinical studies to reduce OFF time by as much as 65% in PD patients with motor fluctuations when used as an adjunct to the patient's usual oral medication. Patients with more advanced or complex disease who require frequent daily apomorphine injections to control their OFF periods may be more suited

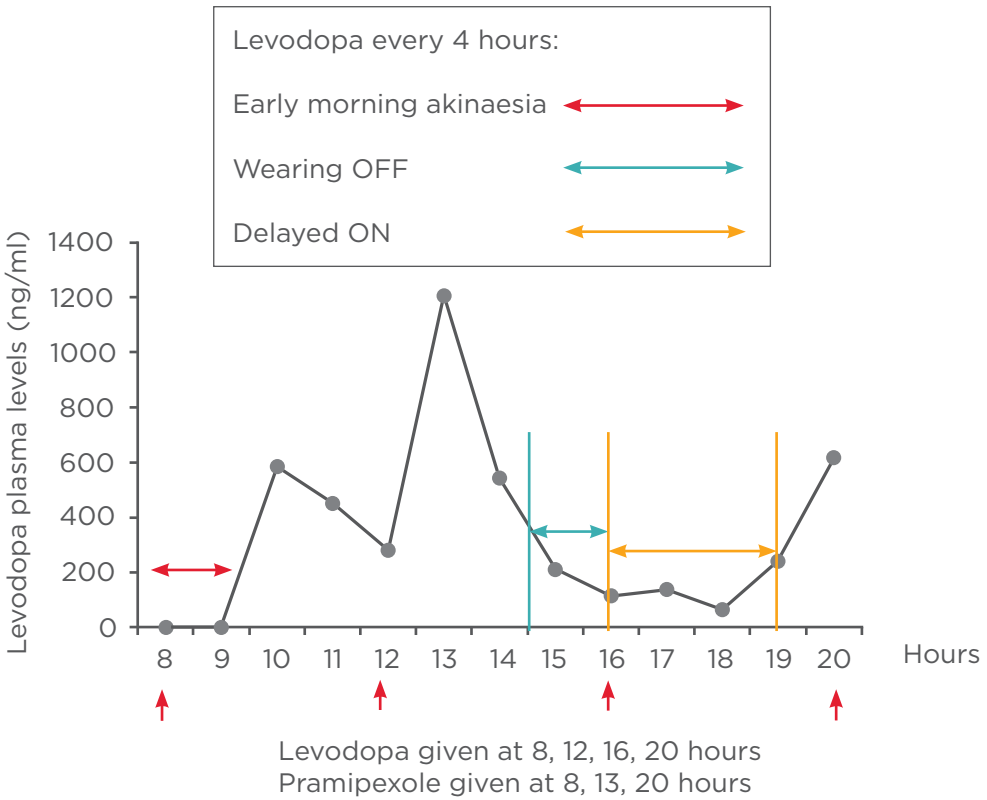


Figure 1: Proportion of OFF time following oral doses of levodopa [unpublished data].

to apomorphine continuous infusion which provide CDS. The efficacy of the infusion formulation has also been demonstrated in clinical trials with reductions in OFF time, oral levodopa dose, and the severity of dyskinaesia being reported.[12-16] In addition, the efficacy of apomorphine in PD patients has been shown to be sustained over several years without the development of tolerance.[13]

Prof Stocchi noted that in addition to classical motor fluctuations, many PD patients also experience non-motor fluctuations, such as anxiety, panic attacks, pain, fatigue, mood changes, urinary urgency, and swallowing difficulties,[17] which, in his clinical experience, could also be resolved rapidly with apomorphine intermittent injection.

Prof Stocchi considered that the types of PD patient most suited to apomorphine penject were generally those with disabling motor and non-motor fluctuations despite optimised oral therapy, and those (or those with carers) who can clearly recognise their OFF periods and who are able to inject themselves (with help if it is available). It might not be suitable for those who have a poor response to levodopa, those with severe cognitive impairment, or those with excessive skin problems.

In clinical studies apomorphine had been shown to be well tolerated, but there were commonly-reported adverse events in the form of local reactions and skin nodules at the injection site. However, these rarely necessitate cessation of apomorphine therapy and can be easily managed.

Prof Stocchi concluded that apomorphine is a very effective treatment for PD patients with motor and non-motor fluctuations, in particular for those with advanced PD whose motor fluctuations are uncontrolled by conventional oral or transdermal medication. Apomorphine penject offers an effective therapy for the rapid and reliable resolution of delayed ON and no ON phenomena, such as early morning akinaesia.

AM IMPAKT: Apomorphine for Morning Akinaesia Trial – Results

Professor Stuart Isaacson

Prof Isaacson continued to debate the problem faced by many clinicians: getting oral levodopa, acknowledged as the mainstay of PD therapy, to work reliably in their patients. Initially, the

therapeutic effect of each levodopa dose is rapid, reliable, and sustained with an onset of around 20 minutes and a long duration response. However, after several years of levodopa treatment the long duration response is replaced by a short duration response and OFF periods emerge, comprising both end-of-dose wearing off and delayed TTO. Despite attempts to optimise oral therapy and the use of multiple medications, many patients still experience OFF time. Both motor and non-motor symptoms are frequent during these OFF periods, especially when the next levodopa dose has a delayed onset of action; when this occurs upon awakening it is known as morning akinaesia. Morning akinaesia is in fact a very common but under-recognised symptom of PD for which treatment appears to be suboptimal despite the availability of a rapid and effective therapy in the form of subcutaneous apomorphine pen injection. Prof Isaacson considered that there should be a renewed focus on the importance of delayed TTO and its management, including not only morning akinaesia but also nocturnal akinaesia and postprandial akinaesia. Studies have shown that delayed TTO is a major contributor to OFF time, being more than twice the duration of wearing off.[11]

There is increasing evidence in PD that the GI system is dysfunctional and that this can occur almost a decade or more before PD is clinically diagnosed. Medications used to treat PD may also contribute to GI dysfunction, including levodopa, dopamine agonists, anticholinergics, amantadine, and inhibitors of monoamine oxidase B (MAO-B) and catechol-O-methyltransferase (COMT). A survey of PD patients found that 24% reported nausea and 45% reported bloating, both symptoms of gastroparesis.[18] The most common gastroparesis symptoms comprise postprandial bloating, early satiety, nausea, vomiting, weight loss, and malnutrition; however, Prof Isaacson considered that in PD patients delayed ON and dose failure, manifesting as OFF periods such as morning akinaesia, were also suggestive of gastroparesis. Studies of the incidence of motor fluctuations in PD patients show that morning akinaesia is indeed extremely common, occurring in around 58% of subjects.[1]

Treatment strategies to improve morning akinaesia focus on reducing early morning OFF time through the use of long-acting dopamine agonists or by inhibiting MAO-B, or on attempts to hasten TTO by enhancing delivery of levodopa to the proximal small intestine (through the use of liquid, dispersible, modified, or higher-dose levodopa). However, in PD patients who have gastroparesis, emptying of both solids and liquids may be impaired[19] so delayed TTO may still occur. The phenomenon of delayed TTO is one that may not always be well described by patients in the clinic but it is important that clinicians try to identify it to be able to effectively manage it.

Recently, the EUROPAR Study Group investigated the prevalence and characteristics of early morning OFF (EMO) periods in 320 PD patients.[20] EMO periods were present in 59.7% of patients, and of these, 88.0% had EMO with mixed motor and non-motor symptoms while 12.0% had pure motor EMO. EMO also occurred throughout the course of the disease in mild, moderate, and severe PD patients. The motor component of these EMO periods was morning akinaesia, while the most common non-motor symptoms comprised urinary urgency, anxiety, pain, dribbling, low mood, and paresthaesia. Many of the patients in the EUROPAR study were taking dopaminergic therapy but although the addition of prolonged release dopamine agonists appeared to result in less EMO periods compared with levodopa alone, EMO periods still occurred.

Having identified the inherent problems with levodopa therapy, Prof Isaacson considered that it was important to find an effective solution. Since subcutaneous injection avoids the oral route of administration with its associated challenges, apomorphine penject may be a valuable option for the management of morning akinaesia; TTO will not be affected by delayed gastric emptying or impaired intestinal absorption. Prof Isaacson described how this hypothesis formed the rationale for the ongoing Phase IV, multicentre (12 sites), open-label, efficacy and safety study - AM IMPAKT (Apokyn for Motor IMProvement of Morning AKinesia Trial).[21-23] AM IMPAKT is investigating whether subcutaneous apomorphine injection upon awakening can provide rapid and reliable improvement in motor symptoms in PD patients with morning akinaesia. Enrolment is now complete (10 patients) and the full results are expected towards the end of 2014.

Interim analysis of the initial 50 patients in the AM IMPAKT trial has revealed that morning akinaesia is common and occurs throughout the course of PD, even in the early stages; many patients in the study had experienced it for an average of four years even though they were taking adjunctive

therapies. In addition, they had never been offered apomorphine injection to manage their symptoms despite it having been available for decades.

Optimal apomorphine doses were identified by the investigator as the dose replicating the levodopa effect after 15 minutes. In 38% of patients, the optimal dose level was 4 mg but around 18% needed a higher dose. Patients recorded their time to ON after their first morning levodopa or apomorphine injection dose in a diary every 5 minutes by checking boxes either 'yes' or 'no' until onset of ON up to 60 minutes.

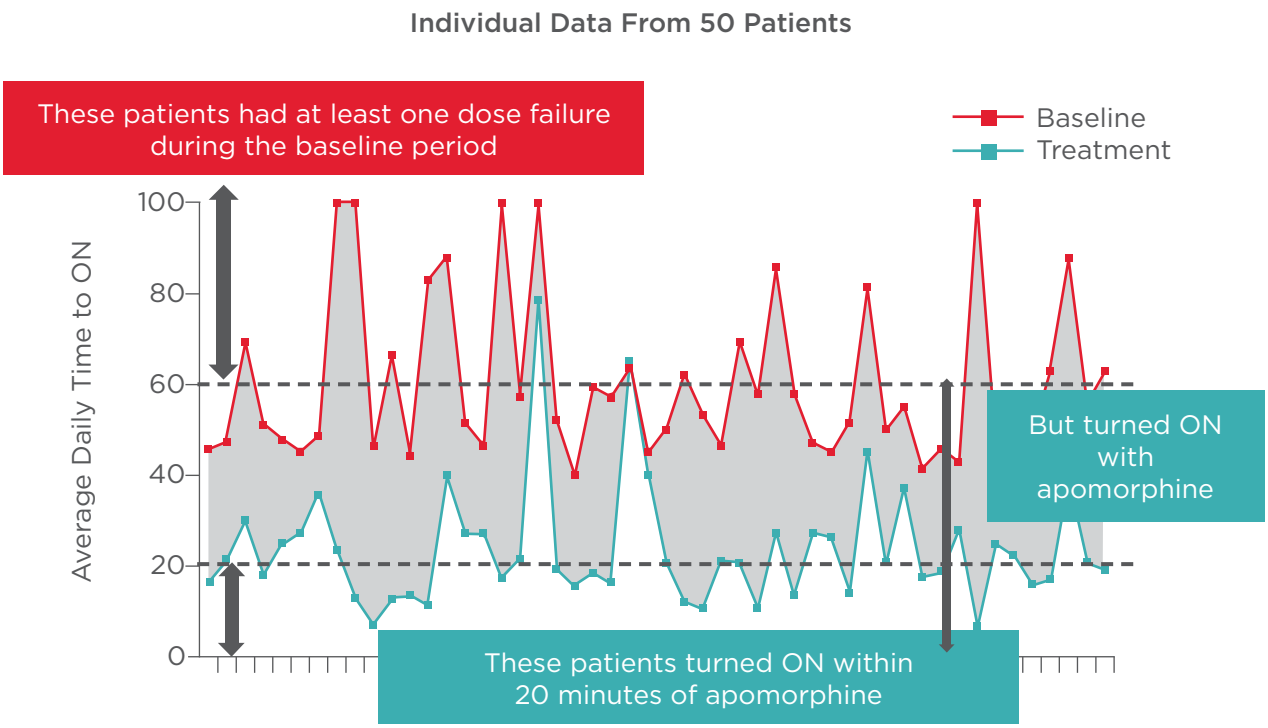
The results of the study so far have found that apomorphine pen injection significantly improved the primary endpoint of TTO, and was rapid and reliable with 95% of patients achieving at least a 20-minute reduction in TTO with an average reduction of 40 minutes. Mean baseline TTO with levodopa was 60.26 minutes which reduced significantly to 23.59 minutes with apomorphine injection.

Analysis of individual data for each patient clearly illustrates the reliability of the response to apomorphine; 48 of the 50 patients had a rapid and reliable clinical improvement in TTO. Surprisingly, when patients were taking their usual levodopa dose, dose failures were found to be common with 40% having at least one during the study period. In contrast, with apomorphine penject all but two patients achieved an ON state, 60% of these within 20 minutes (Figure 2).

UPDRS motor scores were also significantly reduced within 15 minutes of apomorphine compared with baseline (33.6 versus 14.9; $p<0.0001$) as was the Hoehn and Yahr (H&Y) Stage (2.8 versus 2.3; $p<0.0001$). Prof Isaacson considered that the H&Y Stage was an indicator of postural instability and the risk of falling so this change represented an improvement in balance.

Patients and investigators were asked to rate their global impression of severity of illness relative to akinaesia/motor function before and after apomorphine therapy, measured on a 7-point scale from 'normal' to 'extremely ill'. In both cases significant improvements were recorded.

Motor symptom improvements were also reflected in measures of health-related QoL. EQ-5D-3L index scores were significantly reduced from a mean of



Subject recorded their time to "ON" after their L-dopa or APOKYN dose in a diary every 5 minutes by checking boxes either "yes" or "no" until onset of "ON," up to 60 minutes. A value of 100 was imputed for subjects that did not report turning "ON" within 60 minutes.

Figure 2: Reliable reduction in average daily time-to-ON in individual patients following apomorphine injection.

3.50 at baseline to a mean of 2.31 at the end of the 1-week apomorphine treatment period (p<0.0001). EQ-5D-3L is a patient-reported health outcome scale related to mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, in which each dimension is ranked from 1 (no problem) to 5 (extreme problem), so lower scores indicate a more favourable rating. Similarly, EQ-5D VAS scores significantly improved from a mean of 48.02 at baseline to 65.25 at the end of the treatment period (p=0.0001). Using this scale, subjects rate their health state relative to akinaesia on a scale of 0 (worst imaginable] to 100 (best imaginable) so higher scores indicate a more favourable rating. Overall, apomorphine pen injection was well tolerated, the most common side-effects being nausea and somnolence. As expected, more adverse effects were seen at higher doses.

Prof Isaacson concluded that the interim results from the AM IMPAKT study suggest that morning akinaesia is a common but under-recognised symptom of PD and that subcutaneous apomorphine pen injection results in a rapid and reliable TTO in such patients. Importantly, the reduction in TTO is clinically relevant – significant improvements were observed in motor score, H&Y Stage, measures of QoL, and global impression of severity.

Clinical Case Considerations

Professor William Ondo

Prof Ondo reviewed several PD patient cases, illustrated with videos, to determine what type of patient or disease features could potentially benefit from subcutaneous apomorphine injection, and also where it might not be an appropriate therapy.

Case 1

- 54-year-old working male with an 8-year history of PD
- Has been taking levodopa for 6 years: 150 mg, 4–5 times/day with entacapone
- Latency to onset 60 minutes despite crushing and taking with orange juice
- He experiences painful dystonia in the morning
- Duration of levodopa action was 3–4 hours with variable wearing off and unpredictable dose failures
- He experiences mild dyskinaesia, usually when under stress
- Modest non-motor signs: constipation
- No dementia, psychosis, depression, or postural problems
- No fear of needles

Prof Ondo illustrated this case with a video of the patient commenting that painful OFF-period dystonia was often a common presenting feature of young-onset PD. The majority of the audience considered that this patient would be a good candidate for apomorphine injection. Prof Ondo agreed that this was very much a 'typical' apomorphine pen injection patient – relatively young and needs to be turned ON rapidly, particularly as he is working.

Case 2

- 84-year-old female with a 22-year history of PD
- Advanced PD: H&Y Stage 4 (not ambulating); no tremor
- Moderate-to-severely demented: MMSE 14/30
- Positive visual hallucinations
- Marked sialorrhoea, urinary incontinence
- Lives in nursing facility
- Takes levodopa 25/250, 1.5 tablets, 4 times/day
- Has difficulty determining if her medication is helping or not but feels worse when not taking it
- ON examination: has mild dyskinaesia with some doses but still has severe gait/balance issues, marked dysarthria/dysphagia, and dementia

Prof Ondo commented that the fact that this patient has dyskinaesia when she is turned ON demonstrates that the levodopa is in fact being absorbed. He noted that many cases of levodopa non-responsiveness are due to the fact the patient is not taking a sufficient dose, but in this case the dyskinaesias show that the dose is adequate. In this patient, even in the ON state she experiences significant non-levodopa responsive morbidity and is unable to walk easily. The majority of the audience considered that for this reason she was not a suitable candidate for apomorphine penject. Prof Ondo agreed that using apomorphine injection might give the patient a longer ON time but due to the disability she experiences when ON, it is unlikely to improve her overall QoL.

Case 3

- 78-year-old male with an 18-year history of PD
- Fluctuations for 14 years
- Takes levodopa 25/250, 6 times/day
- 30–40 minutes to onset of levodopa effect
- Frequent dose failures
- When OFF, unable to walk
- Marked benefit complicated by mild dyskinaesia
- History of marked nausea and mild hallucinations with trials of dopamine agonists in the past
- Mild orthostatic hypotension
- Very bad constipation
- Cognitively good

The audience was somewhat divided about whether this patient would be a suitable candidate for apomorphine injection – about 60/40 in favour. Prof Ondo illustrated the case with a video of the patient showing rapid resolution of his OFF symptoms with apomorphine injection within about 10 minutes highlighting that it can be an extremely beneficial therapy even in relatively advanced disease presenting with complex symptoms.

Prof Ondo went on to discuss two studies of possible predictors of response to apomorphine injection. A single-site study had prospectively assessed orthostatic blood pressure, nausea (assessed using a visual analogue scale), and other adverse events (AEs), while a sub-analysis of a recent clinical trial for PD subjects with problematic morning akinaesia had assessed all AEs and apomorphine dose.[24,25]

In terms of AEs, there was very limited correlation with previous response to other dopaminergics: response did not correlate with a history of nausea with dopamine agonists, a history of orthostatic hypotension, age, dose of medications, a history of dyskinaesia, or gender. Younger patients appeared to have more hypotension and, in this study, surprisingly the anti-nausea medication trimethobenzamide was associated with a greater degree of nausea.

In the second study, higher doses of apomorphine were found to be required in patients with a longer duration of disease. However, there was no correlation of response with individual levodopa dose, total daily dose, PD severity, use of dopamine agonists, or gender. There does not appear to be a 'shortcut' to predicting what apomorphine dose will work best to turn a patient ON, so it is important that the clinician titrates the dose in each patient to find what suits that individual. Prof Ondo concluded that the utility of apomorphine injection is greatest in patients who experience OFF periods and need to turn ON rapidly.

Panel Discussion – Apomorphine Injection in PD: When, Who, Why?

The Panel considered that it was not possible to predict the response to apomorphine injection based on a patient's response to other dopamine agonists. Prof Stocchi noted that apomorphine was associated with fewer psychiatric AEs than other dopamine agonists; however, the experience of nausea might vary between compounds. Prof Isaacson commented that patients already taking a dopamine agonist when they start apomorphine might have some degree of peripheral dopaminergic tolerance, and therefore fewer AEs might be expected, but this had not been investigated in clinical trials. He added that the relatively short half-life of apomorphine meant that any AEs also tended to be short-lived and tolerable.

It was agreed that doses of apomorphine needed to be titrated individually for each patient – a higher dose was not necessarily better and some patients might have symptoms that were not responsive to levodopa therapy. Prof Isaacson commented that clinical data show that apomorphine injection is effective almost every time in suitable patients, and often it is the case of adjusting therapy to find the right dose.

Prof Rascol considered that apomorphine injection should be considered as a suitable treatment much earlier in the disease course in patients who experience OFF periods with optimised oral medication, whether early in the morning or during the day. It is able to rapidly and reliably resolve OFF symptoms that occur due to the delay in the levodopa effect. This restored confidence and independence to patients who previously may have been reluctant to socialise for fear of experiencing a debilitating OFF period.

Statement

APO2-0614-0489 Date of preparation: June 2014. Prescribing information can be found on page 35.

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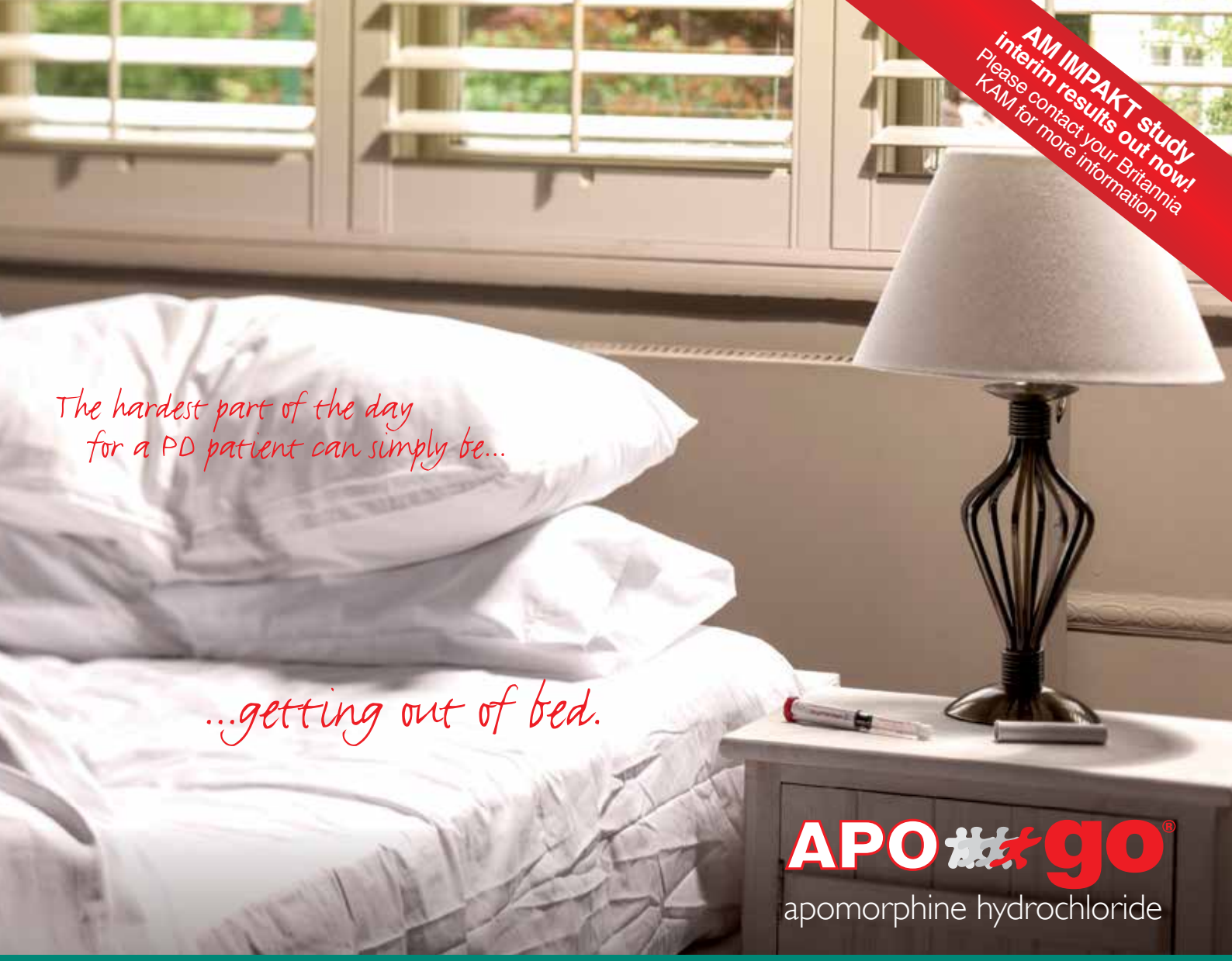

Rapid reliable 'on' for Parkinson's disease

APO-go PEN provides rapid and reliable 'on' **for patients with morning akinesia**, reducing time to on by an average of 40 minutes[1]

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 (5-10 mins) and duration of action (about 1 hour) may prevent an "off" episode which is refractory to other treatments. Hospital admission under appropriate specialist supervision is necessary during patient selection and when establishing a patient's therapeutic regime. Please refer to the Summary of Product Characteristics for full details before initiating therapy. Treatment with domperidone (typical dosage 20mg three times a day) before and during apomorphine HCl therapy is essential. 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 disturbances are common in Parkinsonian patients. APO-go should be used with special caution 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 with 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. 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. 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 broncospasm. **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 intransient. 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 visual hallucinations) have occurred during apomorphine therapy and neuropsychiatric disturbances may be exacerbated by apomorphine. Positive Coombs' tests and haemolytic anaemia and thrombocytopenia have been reported in patients receiving apomorphine and levodopa. 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 (especially at high doses). Apomorphine is associated with somnolence. Yawning and breathing difficulties have been reported as has peripheral oedema. *Prescribers should consult the Summary of Product Characteristics in relation to other side effects* **Presentation and Basic NHS Cost** APO-go ampoules contain apomorphine hydrochloride 10mg/ml, as follows: 20mg in 2ml – basic NHS cost £37.96 per carton of 5 ampoules. 50mg in 5ml – basic NHS cost £73.11 per carton of 5 ampoules. 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. **Marketing Authorisation Numbers**: APO-go Ampoules: PL 06831/0245 APO-go Pens: PL 06831/0246 APO-go Pre filled syringes: PL 06831/0247 **Legal Category** POM **Date of last revision**: March 2014 For further information please contact: Genus Pharmaceuticals, Park View House, 65 London Road, Newbury, Berkshire, RG14 1JN, UK

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@genuspharma.com

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1. AM IMPAKT Study interim results. Presented at International Parkinson and Movement Disorder Society. Treatment of Parkinson's Disease: Past, Present and Future. March 2014, Miami, Florida, USA.

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