There is evident clinical data demonstrating that apomorphine injections significantly reduce Time-to-"On" in advanced Parkinson´s disease.

There are two important aspects to apomorphine treatment: (Trenkwalder et al., 2015)

1. **The speed of drug effect onset after intermittent apomorphine injection, making it desirable for the patient who has a predictable but delayed response to levodopa of 15-30 min or longer; and the reliability of its effect at recovering an "On" state (as compared to the effects of oral dosing with levodopa).**

2. **The short half-life of apomorphine induces a response of about 45-60 min, which does not generally interfere with the basal drug regimen, but fills the gaps in motor functioning.**

Intermittent injections on demand are useful for patients who experience refractory "Off" periods due to a marked delay in the onset of clinical benefit from oral medication. (Trenkwalder et al., 2015)

Subcutaneous Apomorphine injections provide a rapid and reliable "On" state for patients with morning akinesia, as a result of avoiding gastrointestinal delivery and absorption.

Reasons for considering s.c. Apomorphine bolus injections on demand:

- → To treat morning problems like akinesia and dystonia
- → Problems with gastric emptying (gastroparesis)
- → When rapid and reliable relief is required during both predictable and non-predictable"Off" periods
- → To bridge delayed "On"
- → Prevent from dose failures
- → To treat non-motoric "Off" (e.g. pain)

Apomorphine for subcutaneous injection on demand can be administered with Dacepton® 10 mg/ml in 3 ml cartridges and D-*mine*® Pen.

Literature:

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7. Stuart H. Isaacson, Fernando L. Pagan, Mark F. Lew, Rajesh Pahwa. Should "on-demand" treatments for Parkinson's disease OFF episodes beused earlier? Clin Park Relat Disord. 2022 Aug 12;7:100161

EVER PHARMA

ABBREVIATED PRESCRIBING INFORMATION: Dacepton 10 mg/ml solution for injection in cartridge. QUALITATIVE AND QUANTITATIVE COMPOSITION: 1 ml contains 10 mg apomorphine hydrochloride hemihydrate. Each 3 ml cartridge contains 30 mg apomorphine hydrochloride hemihydrate. Excipients with known effect: Sodium metabisulphite (E223) 1 mg per ml, Sodium less than 2.3 mg per ml. PHARMACEUTICAL FORM: Solution for injection in cartridge. The solution is clear and colourless or almost colourless to slightly yellow and free from visible particles. pH of 3.3 – 4.0. Osmolality: 62,5 mOsm/kg. THERAPEUTIC INDICATIONS: Treatment of motor fluctuations ("on-off" phenomena) in patients with Parkinson's disease which are not sufficiently controlled by oral anti-Parkinson medication. POSOLOGY AND METHOD OF ADMINISTRATION: Selection of patients suitable for Dacepton 10 mg/ml solution for injection in cartridge: Patients selected for treatment with Dacepton 10 mg/ml solution for injection should be able to recognise the onset of their "off" symptoms and be capable of injecting themselves or else have a responsible carer able to inject for them when required. 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. 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 treatment with Dacepton 10 mg/ml solution for injection. Adults: Method of administration: Dacepton 10 mg/ml solution for injection in cartridge is intended for multidose use by subcutaneous intermittent bolus injection using only the dedicated D-mine Pen. Patients and caregivers must receive detailed instructions in the preparation and injection of doses, with particular attention paid to the correct use of the required dosing pen (see instructions for use included with the dosing pen). There are differences in the dosing pen of this product and other apomorphine products on the market. Therefore when a patient has received a particular pen and is trained on it, a switch to a different product should be accompanied by re-training under the supervision of a health care professional. Any remaining air in the cartridge should be removed before use (see Instructions for Use of the dosing pen). Apomorphine must not be used via the intravenous route. 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. DETERMINATION OF THE THRESHOLD DOSE: The appropriate dose for each patient is established by incremental dosing schedules. The following schedule is suggested: 1 mg of apomorphine hydrochloride hemihydrate (0.1 ml), that is approximately 15-20 micrograms/kg, may be injected subcutaneously during a hypokinetic, or "off" period and the patient is observed over 30 minutes for a motor response. If no response, or an inadequate response, is obtained a second dose of 2 mg of apomorphine hydrochloride hemihydrate (0.2 ml) is injected subcutaneously and the patient observed for an adequate response 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. ESTABLISHMENT OF TREATMENT: Once the appropriate dose is determined a single subcutaneous injection may be given into the lower abdomen or outer thigh at the first signs of an ‚off' episode. It cannot be excluded that absorption may differ with different injection sites within a single individual. Accordingly, the patient should then be observed for the next hour to assess the quality of their response to treatment. Alterations in dosage may be made according to the patient's response. The optimal dosage of apomorphine hydrochloride hemihydrate varies between individuals but, once established, remains relatively constant for each patient. Precautions on continuing treatment The daily dose of Dacepton 10 mg/ml solution for injection varies widely between patients, typically within the range of 3-30 mg, given as 1-10 injections and sometimes as many as 12 separate injections per day. It is recommended that the total daily dose of apomorphine hydrochloride hemihydrate should not exceed 100 mg and that individual bolus injections should not exceed 10 mg. The D-mine Pen that is required for the application of Dacepton 10 mg/ml solution for injection in cartridge is not suitable for patients needing doses above 6 mg/bolus. For these patients, other products have to be used. In clinical studies it has usually been possible to make some reduction in the dose of levodopa; this effect varies considerably between patients and needs to be carefully managed by an experienced physician. Once treatment has been established, domperidone therapy may be gradually reduced in some patients but successfully eliminated only in a few, without any vomiting or hypotension. Paediatric population: Dacepton 10 mg/ml solution for injection in cartridge is contraindicated for children and adolescents under 18 years of age. Elderly: The elderly are well represented in the population of patients with Parkinson's disease and constitute a high proportion of those studied in clinical trials of apomorphine. The management of elderly patients treated with apomorphine has not differed from that of younger patients. However, extra caution is recommended during initiation of therapy in elderly patients because of the risk of postural hypotension. Renal impairment: A dose schedule similar to that recommended for adults, and the elderly, can be followed for patients with renal impairment. CONTRAINDICATIONS: Hypersensitivity to the active substance or to any of the excipients listed. In patients with respiratory depression, dementia, psychotic diseases or hepatic insufficiency. Apomorphine hydrochloride hemihydrate must not be administered to patients who have an "on" response to levodopa which is marred by severe dyskinesia or dystonia. Concomitant use with ondansetron. Dacepton 10 mg/ml solution for injection is contraindicated for children and adolescents under 18 years of age. SPECIAL WARNINGS AND PRECAUTIONS FOR USE: Apomorphine hydrochloride hemihydrate should be given with caution to patients with renal, pulmonary or cardiovascular disease and persons prone to nausea and vomiting. Extra caution is recommended during initiation of therapy in elderly and/or debilitated patients. Since apomorphine may produce hypotension, even when given with domperidone pre-treatment, care should be exercised in patients with pre-existing cardiac disease or in patients taking vasoactive medicinal products such as antihypertensives, and especially in patients with pre-existing postural hypotension. 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, 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 is associated with local subcutaneous effects. These can sometimes be reduced by the rotation of injection sites or possibly by the use of ultrasound (if available) in order to avoid areas of nodularity and induration. Haemolytic anaemia and thrombocytopenia have been reported in patients treated with apomorphine. Haematology tests should be undertaken at regular intervals as with levodopa, when given concomitantly with apomorphine. Caution is advised when combining apomorphine with other medicinal products, especially those with a narrow therapeutic range. 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 while driving or operating machines during treatment with apomorphine. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore, a reduction of dos age or termination of therapy may be considered. Impulse control disorders: 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. Dacepton 10 mg/ml solution for injection in cartridge contains sodium metabisulphite which may rarely cause severe hypersensitivity reactions and bronchospasm. This medicinal product contains less than 1 mmol sodium (23 mg) per 10 ml, i.e. essentially "sodium-free". Interaction with other medicinal products and other forms of interaction: Patients selected for treatment with apomorphine hydrochloride hemihydrate are almost certain to be taking concomitant medications for their Parkinson's disease. In the initial stages of apomorphine hydrochloride hemihydrate therapy, the patient should be monitored for unusual side-effects or signs of potentiation of effect. Neuroleptic medicinal products may have an antagonistic effect if used with apomorphine. There is a potential interaction between clozapine and apomorphine, however clozapine may also be used to reduce the symptoms of neuropsychiatric complications. The possible effects of apomorphine on the plasma concentrations of other medicinal products have not been studied. Therefore caution is advised when combining apomorphine with other medicinal products, especially those with a narrow therapeutic range. Antihypertensive and Cardiac Active Medicinal Products: Even when co-administered with domperidone, apomorphine may potentiate the antihypertensive effects of these medicinal products. It is recommended to avoid the administration of apomorphine with other drugs known to prolong the QT interval. Concomitant use of apomorphine with ondansetron may lead to severe hypotension and loss of consciousness and is therefore contraindicated (see section 4.3). Such effects might also occur with other 5-HT3 antagonists. Fertility, pregnancy and lactation: There is no experience of apomorphine usage in pregnant women. Animal reproduction studies do not indicate any teratogenic effects, but doses given to rats which are toxic to the mother can lead to failure to breathe in the newborn. The potential risk for humans is unknown. Dacepton 10 mg/ml solution for injection should not be used during pregnancy unless clearly necessary. It is not known whether apomorphine is excreted in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Dacepton 10 mg/ml solution for injection should be made taking into account the benefit of breast-feeding to the child and the benefit of Dacepton 10 mg/ml solution for injection to the woman. Effects on ability to drive and use machines: Apomorphine hydrochloride hemihydrate 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 themselves or others at risk of serious injury or death until such recurrent episodes and somnolence have resolved. UNDESIRABLE EFFECTS: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). Blood and lymphatic system disorders: Uncommon: Haemolytic anaemia and thrombocytopenia have been reported in patients treated with apomorphine. Rare: Eosinophilia has rarely occurred during treatment with apomorphine hydrochloride hemihydrate. Immune system disorders rare: Due to the presence of sodium metabisulphite, allergic reactions (including anaphylaxis and bronchospasm) may occur. Psychiatric disorders very common: Hallucinations. Common: Neuropsychiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine hydrochloride hemihydrate therapy. Not known: Impulse control disorders: Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including apomorphine. Aggression, agitation. Nervous system disorders common: Transient sedation with each dose of apomorphine hydrochloride hemihydrate at the start of therapy may occur; this usually resolves over the first few weeks. Apomorphine is associated with somnolence. Dizziness/light-headedness have also been reported. Uncommon: Apomorphine may induce dyskinesias during "on" periods which can be severe in some cases, and in a few patients may result in cessation of therapy. Apomorphine has been associated with sudden sleep onset episodes. Unknown: Syncope, headache. Vascular disorders uncommon: Postural hypotension is seen infrequently and is usually transient. Respiratory, thoracic and mediastinal disorders common: yawning has been reported during apomorphine therapy. Uncommon: Breathing difficulties have been reported. Gastrointestinal disorders. Common: Nausea and vomiting, particularly when apomorphine treatment is first initiated, usually as a result of the omission of domperidon. Skin and subcutaneous tissue disorders uncommon: Local and generalised rashes have been reported. General disorders and administration site conditions very common: Most patients experience injection site reactions, particularly with continuous use. These may include subcutaneous nodules, induration, erythema, tenderness and panniculitis. Various other local reactions (such as irritation, itching, bruising and pain) may also occur. Uncommon: Injection site necrosis and ulceration have been reported. Not Known: Peripheral oedema has been reported. Investigations uncommon: Positive Coombs' tests have been reported for patients receiving apomorphine. Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system. Overdose: There is little clinical experience of overdose with apomorphine by this route of administration. Symptoms of overdose may be treated empirically as suggested below: Excessive emesis may be treated with domperidone. Respiratory depression may be treated with naloxone. Hypotension: appropriate measures should be taken, e.g. raising the foot of the bed. Bradycardia may be treated with atropine. PHARMACODYNAMIC PROPERTIES: Pharmacotherapeutic group: Anti-Parkinson drugs, dopaminergic agents, dopamine agonists, ATC code: N04B C07. Mechanism of action. Apomorphine is a direct stimulant of dopamine receptors and while possessing both D1 and D2 receptor agonist properties does not share transport or metabolic pathways with levodopa. Although in intact experimental animals, administration of apomorphine suppresses the rate of firing of nigro-striatal cells and in low dose has been found to produce a reduction in locomotor activity (thought to represent pre-synaptic inhibition of endogenous dopamine release) its actions on parkinsonian motor disability are likely to be mediated at post-synaptic receptor sites. This biphasic effect is also seen in humans. Pharmacokinetic properties: After subcutaneous injection of apomorphine its fate can be described by a two-compartment model, with a distribution half-life of 5 (±1.1) minutes and an elimination half-life of 33 (±3.9) minutes. Clinical response correlates well with levels of apomorphine in the cerebrospinal fluid; the active substance distribution being best described by a two-compartment model. Apomorphine is rapidly and completely absorbed from subcutaneous tissue, correlating with the rapid onset of clinical effects (4-12 minutes), and that the brief duration of clinical action of the active substance (about 1 hour) is explained by its rapid clearance. The metabolism of apomorphine is by glucuronidation and sulphonation to at least ten per cent of the total; other pathways have not been described. Preclinical safety data: Repeat dose subcutaneous toxicity studies reveal no special hazard for humans, beyond the information included in other sections of the SmPC. In vitro genotoxicity studies demonstrated mutagenic and clastogenic effects, most likely due to products formed by oxidation of apomorphine. However, apomorphine was not genotoxic in the in vivo studies performed. The effect of apomorphine on reproduction has been investigated in rats. Apomorphine was not teratogenic in this species, but it was noted that doses which are toxic to the mother can cause loss of maternal care and failure to breathe in the newborn. No carcinogenicity studies have been performed. LIST OF EXCIPIENTS: Sodium metabisulphite (E223), Hydrochloric acid (for pH-adjustment), odium hydroxide (for pH-adjustment), Water for injections. Incompatibilities: This medicinal product must not be mixed with other medicinal products. SHELF LIFE: Unopened: 24 months, after first opening: Chemical and physical in-use stability has been demonstrated for 15 days at 25°C. From a microbiological point of view, unless the method of opening and further handling precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user. Special precautions for storage: Do not store above 25°C. Do not refrigerate or freeze.Keep the container in the outer carton in order to protect from light. The product should be stored at the same conditions after opening and between withdrawals. NATURE AND CONTENTS OF CONTAINER: Clear glass cartridges, type I with bromobutyl rubber stopper and an aluminium flip-off cap with bromobutyl rubber seal, containing a clear solution for injection. Each cartridge contains 3 ml of solution for injection. Packs containing: 5, 10, 30, 2 x 5 (bundle pack), 6 x 5 (bundle pack) and 3 x 10 (bundle pack) of 3 ml cartridges in a moulded plastic tray in an outer cardboard carton. Not all pack sizes may be marketed. Special precautions for disposal and other handling: Do not use if the solution has turned green. The solution should be inspected visually prior to use. Only clear and colourless to slightly yellow solutions without particles in undamaged containers should be used. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Discard each cartridge with any unused content not later than 15 days after first opening. The patient should be advised how to safely discard the needle after each injection. Dacepton 10 mg/ml solution for injection cartridges are designed to be used only with the dedicated D-mine Pen and disposable pen-needles as specified in the Instructions for Use of the pen. MARKETING AUTHORISATION HOLDER: EVER Neuro Pharma GmbH, Oberburgau 3, 4866 Unterach, Österreich. MARKETING AUTHORISATION NUMBER: AT/H/0524/001/DC. Legal Category: POM. Date of last revision: October 2023.

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WHEN TO START INTERMITTENT ON DEMAND PEN INJECTIONS

EARLY MORNING OFF, WEARING-OFF AND DELAYED ON IN PARKINSON`S DISEASE

Dacepton®
Apomorphine Hydrochloride

INTRODUCTION

Chronic levodopa therapy for Parkinson's disease (PD) is often complicated by the subsequent development of motor fluctuations ("Wearing-Off" and related phenomena) and dyskinesias. These are typically not present when levodopa therapy is initiated, but become an increasing problem with ongoing treatment.

The inconsistent anti-parkinsonian effect that typifies motor fluctuations may severely compromise lifestyle. Awareness of these levodopa complications influences medication treatment strategies not only when these problems develop, but also early, when medical therapy is initiated. In hopes of forestalling these problems, a variety of strategies has been proposed, such as delaying levodopa therapy, limiting the levodopa dose, or early administration of a dopamine agonist medication.
(Ahlskog et al., 2001)

Delays in turning "On" reflect a delay in the absorption of Levodopa and a subsequent delay in crossing the blood–brain barrier. This may be a result of delayed gastric emptying (gastroparesis) or presence of intestinal protein that competes with L-dopa absorption. (Stocchi et al., 2008)

A treatment paradigm shift to consider "on-demand" treatments earlier and throughout the disease course is supported by the persistence of "Off" despite adjunctive treatment, the emerging understanding of gastrointestinal dysmotility and variability of oral levodopa absorption, and the impact of "Off"on daily activities and quality of life measures. Shared clinical decisionmaking should routinely incorporate "on-demand" treatments as a therapeutic option when OFF episodes emerge. (Isaacson et al., 2022)

CLINICAL LIMITATIONS OF ORAL MEDICATION

Merims et al., 2003 compared two portions of "Off" period in patients with PD and response fluctuations:

- Time to "On" (the latency from Levodopa intake to turning "On")
- "Wearing-Off" (time from termination of the beneficial dose effect until the time when the next dose was taken).
-

Time to "On" was more than twice the duration of "Wearing-Off". Although underrecognized, time to "On" is the major component of total daily "Off".

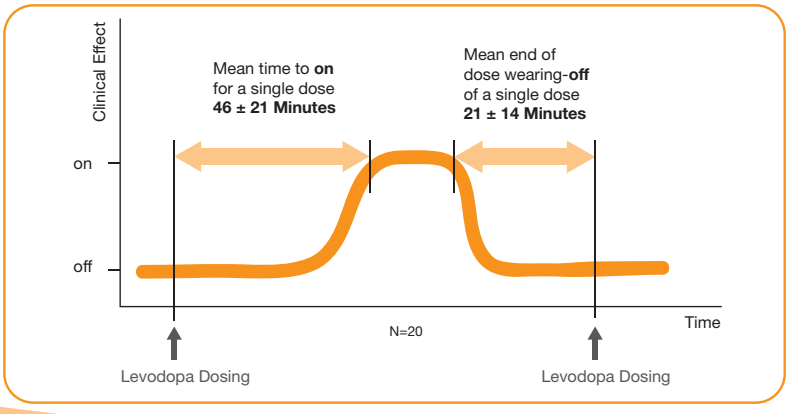

Figure 1: Time to "On": the latency from taking a levodopa dose until the patient turns on. "Wearing-off": the time from termination of the beneficial effect of the dose until the time when the next dose is taken. (Adapted from Merims et al., 2003)

WHICH THERAPEUTIC STRATEGY MAY BRIDGE THE TIME SPENT IN "OFF" UNTIL ORAL MEDICATION TAKES EFFECT?

RESULTS

Merello et al., 1997 compared the mean time of subcutaneous Apomorpine injections and oral Levodopa medication until it took effect.

The mean time for subcutaneous Apomorphine injections to take effect is significantly shorter than Levodopa.

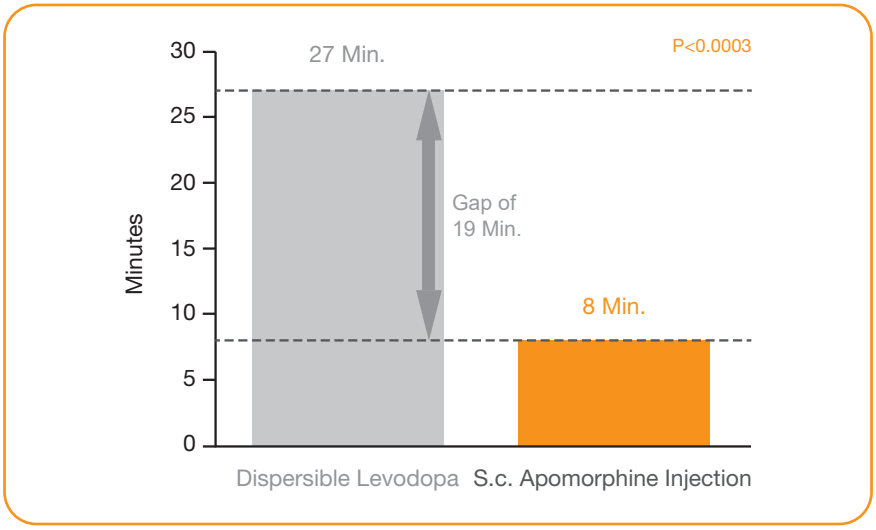

Figure 2: Comparison of Subcutaneous Apomorphine versus dispersible Levodopa and effect duration in Parkinson's Disease Patients. Double-blind study comparing subcutaneous Apomorphine Pen injections vs. Levodopa dispersible; n=12; 12-hour drug-free period before patients received study treatment at 9:00 am; patients received study drug over 2 consecutive days.
Merello et al., 1997

Isaacson et al., 2016 investigated motor symptoms in Parkinson's disease patients who experienced delayed onset of their oral Levodopa medication taken upon awakening (Early Morning "Off" = EMO) before and after treatment with subcutaneous Apomorpine Pen injections.

The average time to "On" was recorded over 7 days of all patients on Levodopa at baseline, before switching all patients to subcutaneous Apomorphine Pen injections and re-recording their average time to "On" over 7 days. If an "On" state had not been achieved within 60 minutes (dose failure), a value of 100 was imputed for that day. A very low rate of failed dosing while taking subcutaneous Apomorpine injections Pen vs. levodopa baseline, as measured by diary entries, was demonstrated.

Almost all subjects (95.5%) showed improvement in Time-to-"On", which mirrors the 95% response rate in previous studies.

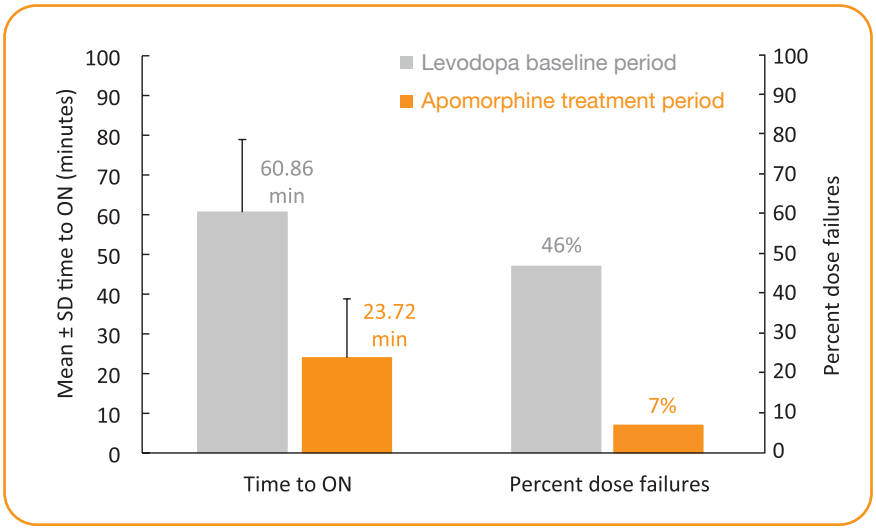

Figure 3: Apomorphine Subcutaneous Injection for the Management of Morning Akinesia in Parkinson's disease. Time to "On" and percent of dose failures during the L-dopa baseline period and Apomorphine treatment period (FAS; n = 88). Patients recorded their time to "On" after their L-dopa or Apomorphine dose in a diary every 5 minutes by marking either "yes" or "no" until onset of "On" ≤ 60 minutes. A value of 100 was imputed for patients that did not report turning "On" within 60 minutes. (Phase IV, multicenter, open label study with subcutaneous Apomorphine injections patients with morning akinesia resulting from delayed or unreliable onset of oral L-dopa took place in 12 U.S. centres with a patient population of n=88 (Safety population = 127). Isaacson et al., 2016

Objective assessments of motor function confirmed that subcutaneous apomorphine injections significantly improved motor function as assessed by improvements in Hoehn and Yahr staging and UPDRS motor scores.

Subcutaneous Apomorphine injections demonstrated a greater reliability of turning "On"

- Nearly all patients did show improvement compared to baseline
- Fewer dose failures than baseline treatment with levodopa
- Quicker time to "On" in nearly all patients than baseline treatment with levodopa

Patients with morning akinesia may well benefit from a combination of subcutaneous Apomorphine injection (for rapid relief) with oral L-dopa (for longer duration of effect).
Prolonged morning akinesia, during which time patients remain in an "Off" state in advance of a therapeutic response from their first morning Levodopa dose, is a common clinical manifestation in patients with delayed "On". (Isaacson et al., 2016)

CONCLUSION

Delays in turning "On" reflect a delay in the absorption of L-dopa and a subsequent delay in crossing the blood–brain barrier. This may be a result of delayed gastric emptying. Prolonged morning akinesia, during which time patients remain in an "Off" state in advance of a therapeutic response from their first taken morning dose may severely compromise quality of life.

Because subcutaneous injections of apomophine bypass gastrointestinal dysmotility (and other intestinal absorption-related factors), they can reliably and rapidly switch patients from "Off" to "On", effectively shortening the "Off" episode duration. (Isaacson et al., 2022)

Rapid and reliable efficacy can be achieved with subcutaneous Apomorphine injections and lead to significant clinical benefits.