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Dacepton®
Dopaceptin®

Apomorphine Hydrochloride

Drug Profile

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1. INTRODUCTION & OVERVIEW

About This Monograph

This Product Monograph is a factual, scientific document about the drug “Dacepton®” (or Dopaceptin® or Apomine® - apomorphine hydrochloride) from EVER Neuro Pharma. The “Dacepton®” Product Monograph describes the properties, indications, and conditions of use for the drug. Furthermore, it also contains other information that may be required for optimal, safe, and effective use of the drug. Some of the topics covered in this monograph are:

- Apomorphine - mechanism of action, indications, administration & dosage
- Contraindications
- Pharmacology, pharmacokinetics & pharmacodynamics
- Side effects
- Overdosage
- Scientific information

The “Dacepton®” Product Monograph gives an overview and a summarized picture of efficacy and therapy in moderate/intermediate and advanced Parkinson’s disease.

Sporadic Idiopathic Parkinson’s Disease

Sporadic idiopathic Parkinson’s disease (in the following called PD) belongs to a group of conditions called motor system disorders, which are the result of the loss of dopamine-producing brain cells. The four primary motor symptoms of PD are bradykinesia, rigidity, tremor and postural instability (AAN, 2014).

In contrast to other etiologies for Parkinsonism, patients with Parkinson’s disease typically have asymmetric motor symptoms such as tremor at rest, rigidity and akinesia/bradykinesia (Levodopa motor complications in Parkinson‘s disease, 2000), levodopa responsiveness, slow progression and lack of so-called “atypical” symptoms, such as ataxia and apraxia (Brookes, 2002).

Pathologically, PD patients suffer from loss of dopaminergic projections from the substantia nigra to the striatum. There are many symptomatic treatments for PD, most of which increase the concentration of dopamine or activate dopamine receptors in the striatum (Gunzler, 2009).

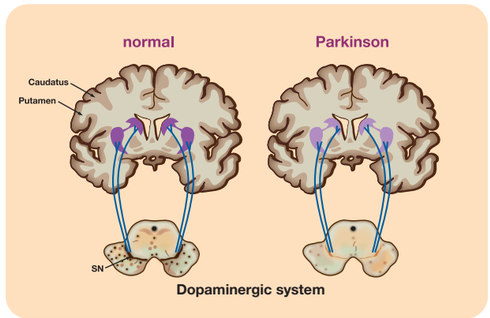

Fig.1: Idiopathic PD

PD is divided into the early phase, the moderate/intermediate phase and the advanced phase. Therapies start, depending on the age of the patient, either with levodopa and/or dopamine agonists. In the moderate/intermediate phase additional therapies are added. Frequently, a combination including two or more of the following therapies is used; levodopa, dopamine agonists, COMT-inhibitors, optional MAO-B-inhibitors and/or anticholinergics. The moderate/intermediate and advanced phases often become more complicated to treat as patients have increasing periods of “off” time and levodopa-induced dyskinesias. In addition to the motor fluctuations during long term levodopa there may also be cognitive and/or psychiatric symptoms (Chaudhuri et al., 2013).

In the advanced phase of the disease Continuous Dopaminergic Stimulation (CDS) is a commonly used therapeutic approach, while intermittent injection or subcutaneous infusion of apomorphine, continuous enteral levodopa and deep brain stimulation have also been used.

The continuous infusion of a dopamine agonist is cumbersome for the patient and caregiver. However, it avoids the need for an intracranial operation and seems to provide benefits that are comparable with surgical therapies (Stocchi et al., 2008).

Apomorphine is a potent, non-ergoline, non-selective and direct-acting dopamine-receptor agonist. Given subcutaneously, it has a rapid onset of antiparkinsonian action, qualitatively compared to that of levodopa. Although apomorphine has been known to treat symptoms of PD for many years, its use has been limited due to dopaminergic side effects like nausea and vomiting.

While several routes have been explored, subcutaneous administration, both as intermittent injections or continuous infusion, is so far the best and most applied method in the treatment of moderate/intermediate and advanced PD. Clinical trials have shown stable efficacy with markedly reduced time spent in „off“ phases as well as, for infusion therapy, reduced oral levodopa requirements. In the most successful cases, motor fluctuations disappear and the need for oral medication is significantly reduced. Adverse effects are usually mild and predominantly involve skin reactions. Neuropsychiatric side effects have occurred, but it is often not possible to differentiate between the influence of dopamine agonists and concomitant medication with levodopa. Controlled long-term clinical trials are highly warranted to appreciate the full potential of this treatment approach. Careful patient selection and follow-up, where the specialized PD nurse has a crucial role, are paramount for a successful long-term outcome. It has been suggested in the literature that apomorphine therapy warrants a wider application in the treatment of moderate/intermediate and advanced PD and should be seriously considered before surgical interventions (Hagell et al., 2001).
In addition, the potential of Apomorphine as a disease-modifying therapy deserves to be investigated, as well as its ability to induce brain plasticity through chronic infusion (Auffret et al. 2018).

2. MOTOR FLUCTUATIONS

Motor fluctuations occur at moderate/intermediate and advanced stages of PD (see Fig. 2). They are characterized by end of dose phenomenon or “wearing-off”, where patients have to reduce the interval between doses of oral medication.

In addition to the known side effects of levodopa therapy patients are subject to “on” and “off” periods. During “off” periods, patients are less able to control motor function. During “on” periods, motor function is “normal” and the blood plasma concentration of levodopa is optimal. Dyskinesias (i.e. involuntary movements) may be related to excessive concentrations of levodopa in plasma.

Motor fluctuations impair quality of life and cause significant disability (Chapuis et al., 2005). Risk factors for motor complications include younger age at onset of PD, disease severity, higher levodopa dosage, and longer disease duration. These problems are often addressed by adjusting the levodopa dose and the addition of adjunctive medications (Pahwa, et al., 2006). LePen et al. found that the number and duration of “off” periods had the strongest influence on cost of care. They estimated that a reduction in “off” periods of 10% could lead to a reduction in disease-associated costs of 5% (LePen et al., 1999).

Patients typically experience a very good response to levodopa during the early stages of treatment. As the disease progresses, however, the effect of levodopa starts to wear off. This phenomenon may be explained by the observation that dopaminergic nerve terminals are able to store and release dopamine early in the course of the disease but, with more advanced stages of the disease and increasing degeneration of dopamine terminals, the concentration of dopamine in the basal ganglia is much more dependent upon plasma levodopa levels. Plasma levels may fluctuate erratically because of the short

minute half-life of levodopa and the frequently unpredictable intestinal absorption of this medication. Patients with moderate/intermediate and advanced PD start to be aware of a wearing-off or end-of-dose effect. This phase is characterized by the need to reduce the time interval between doses of oral medication.

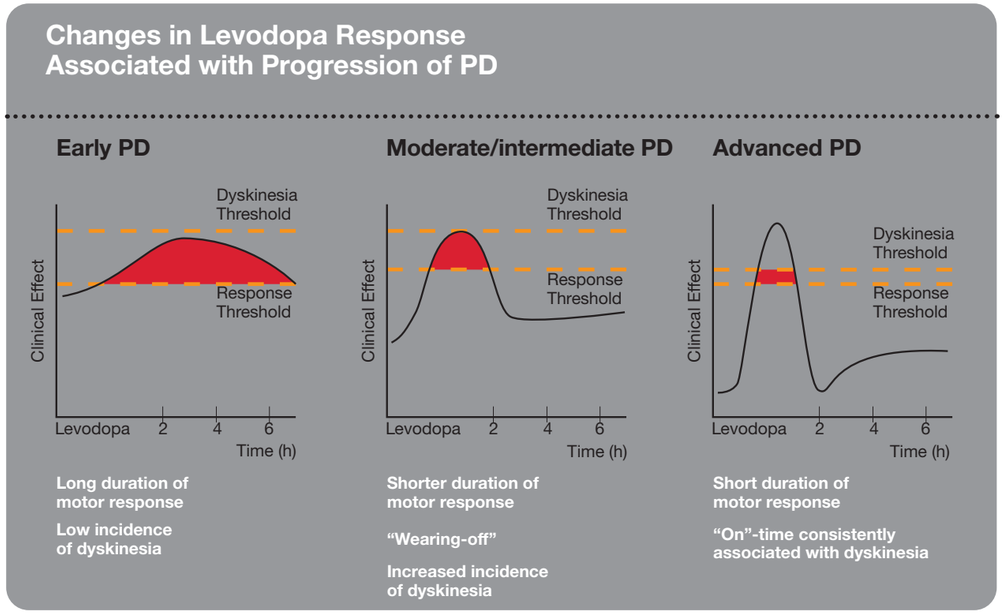

Fig. 2 (adapted): Levodopa response associated with progression of PD (Obeso et al., 2000)

Intermittent or pulsatile stimulation of dopamine receptors is thought to be responsible for the development of the motor fluctuations and dyskinesias that complicate the long-term use of levodopa therapy in Parkinson's disease (Nutt et al., 2000).

Dopaminergic neurons in the basal ganglia normally fire in a continuous manner. But, in a dopamine depleted state, intermittent oral doses of levodopa induce discontinuous stimulation of the striatal dopamine receptors leading to physiological changes in basal ganglia and development of motor complications. These effects are reduced when dopaminergic therapies are delivered in a more continuous and physiological manner (Olanow et al., 2006).

Motor complications occur in approximately 50 to 90% of patients with PD who have received levodopa for 5 to 10 years and constitute a major source of disability.

These symptoms are especially common in patients with young-onset PD and tend to be seen more frequently in association with high doses of Levodopa (Olanow et al., 2001).
Patients with dyskinesia experience involuntary movements that are usually choreatic or dystonic but, when more severe, may be ballistic or myoclonic. Dyskinesia usually appears in periods of „on". It may occasionally occur in the form of painful dystonia when the patient is „off", especially in the morning hours, because of the long interval after the last intake of medication.

Several reports and clinical trials have shown that when a loss of physiological dopamine is compensated for by levodopa, the resulting pulsatile stimulation causes alterations in the firing patterns of basal ganglia output neurons and leads to complications such as motor fluctuations and dyskinesia. Based on this, continuous drug delivery (CDD) represents an important strategy in regulating therapeutic efficacy for novel antiparkinsonian medications (Rascol, 2011).

3. APOMORPHINE - MECHANISM OF ACTION

Apomorphine hydrochloride is derived by heating morphine with concentrated hydrochloric acid. However, it has completely different pharmacological properties to morphine: apomorphine has no opiate properties and no direct pain-killing properties. (Menon et al., 2007)
In addition, apomorphine acts as an antagonist for adreno- and histamine-receptors (Boyle et al., 2015).

Apomorphine directly activates postsynaptic dopamine receptors in the striatum. In contrast to levodopa it is independent of the presynaptic dopaminergic terminals for storage and release (Hagell et al., 2001).

In contrast to levodopa, the therapeutic efficacy of apomorphine in PD is executed through direct stimulation of striatal postsynaptic dopamine receptors. It is independent of the presynaptic dopaminergic terminals for storage and release (Hagell et al., 2001). Although the precise mechanism of action of apomorphine is not known, it is assumed to involve stimulation of the postsynaptic D1 and D2 receptors within the striatum (i.e. caudate nucleus and putamen). (LeWitt, 2004). The dopamine D2 receptor is dominant in the striatum, a brain structure that plays an important role in controlling motor behaviour, and those agents that are most noted for their production of extrapyramidal side effects and tardive dyskinesia have the highest affinity for this receptor. Therefore, it is assumed that dopamine D2 receptor blockade may be linked to extrapyramidal side effects and tardive dyskinesia (Lahti et al., 1993).

Apomorphine is a strong lipophilic compound and its positive motor effect depends on its concentration in the cerebrospinal fluid.

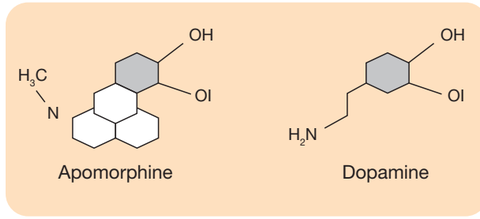

Fig. 3: Molecular structures of dopamine and apomorphine. Note the common dopaminergic moiety (Hagell, et al., 2001)

Due to the high first pass effect of apomorphine, the bioavailability of the oral formulation is very low. Apomorphine is a substance with a high hepatic clearance, only 3 – 4% is eliminated unmodified with urine (Neef, et al., 1999). After a subcutaneous (s.c.) injection, the absorption rate depends on the local blood circulation at the injection site and amounts to almost 100%. 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 absor-

bed 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 (SmPC, 2023). The variation in absorption of apomorphine after s.c. injection can differ between individuals, but remains low within individual subjects (Gancher et al., 1989). Hence the lowest effective dose can differ significantly between patients therefore the doses have to be titrated individually.
Apomorphine is currently used for the management of sudden, unexpected and refractory levodopa-induced “off” states in fluctuating PD either during the moderate/intermediate stage as intermittent rescue injections or during the advanced stage as continuous infusions. Direct stimulation of dopamine receptors is assumed as a primary and the most important mechanism of action of apomorphine in PD. Some studies suggest that the therapeutic effect of apomorphine results from a normalization of the imbalance of neuronal activity in the direct and indirect pathways. Secondary pharmacodynamic effects can play some role in the mechanism of action. The examination of the effect of apomorphine on the firing activity of neurons in the subthalamic nucleus (STN) and internal segment of the globus pallidus (GPi) in patients with PD revealed that the apomorphine-induced amelioration of parkinsonian symptoms is not solely due to a decrease in overall activity in the GPi or STN.
Apomorphine was found to act principally as a radical scavenger. It suppressed the level of Reactive Oxygen Species (ROS) and ROS-stimulated apoptotic signaling pathways. Moreover, the function of apomorphine as a nuclear erythroid 2-related factor 2-Antioxidant Response Element (Nrf2-ARE) pathway activator may be involved in the neuroprotective effects of apomorphine.

Significant metabolic changes were observed, with overall increases in the right fusiform gyrus and hippocampus, alongside a decrease in the left middle frontal gyrus. Consistent correlations between significant changes in clinical scores and metabolism were established (Auffret et al., 2017).
The chemical structure accounts for most of its properties, (ii) the pharmacokinetics and pharmacodynamics of Apomorphine are complex and subject to interindividual variability, (iii) Apomorphine acts both on DA and non-DA pathways, and (iv) this compound is extremely useful in the diagnosis and treatment of PD (Auffret et al. 2018).

Results show that the primary mechanism of action of apomorphine in patients with Parkinson’s disease is the stimulation of dopamine receptors. Some additional effects which can lead to the neurons’ protection are antioxidative and Nrf2-ARE pathway activating events which can add to neuroprotection (Hara, et al., 2006). The other known mechanisms seem to have minimal or no additional therapeutic efficacy.

The anti-parkinsonian effect of apomorphine can be described as an “All or Nothing” effect. That means the effect starts after reaching a therapeutic threshold value and the improvement in motoric reaction stabilizes quantitatively and qualitatively with further increase in dosage. Higher doses lead to a reduction of the dose efficacy latency and to an extension of the effective window (Manson et al., 2001).

Biphasic effect, with low doses (< 0.5 mg) acting preferentially on presynaptic receptors (high affinity for autoreceptors), yielding reductions in DA transmission, TH activity and associated inhibitory behavior such as sedation. At higher doses (1 mg), Apomorphine is a partial agonist of postsynaptic receptors,leading to increased DA transmission. The DA pharmacodynamic effects of Apomorphine closely match those of dopamine, and the induced motor responses are virtually indistinguishable from those of L-dopa in individual patients. Apomorphine also decreases DA biosynthesis, interferes with DA turnover, and inhibits dopamine metabolism (Auffret et al., 2018).

4. INDICATIONS, ADMINISTRATION & DOSAGE

Dacepton® is indicated for the treatment of motor fluctuations (“on-off” phenomena) in patients with Parkinson’s disease which are not sufficiently controlled by oral anti-Parkinson medication (SmPC, 2023).
Apomorphine may be administered by either intermittent s.c. injection at the beginning of “off“ phases, or by continuous s.c. infusion.
Dacepton® 10 mg/ml is for subcutaneous use by intermittent bolus injection. Dacepton® 10 mg/ml may also be administered as a continuous subcutaneous infusion by minipump and/or syringe-driver (SmPC, 2023).
Dacepton® 5 mg/ml solution for infusion is a pre-diluted vial intended for use without dilution for subcutaneous use and to be administered as a continuous subcutaneous infusion by minipump and/or syringe-driver. It is not intended to be used for intermittent injection (SmPC, 2023).
The aim of treatment is to reduce “off” period duration and frequency and not necessarily to improve motor functions during “on” phases.
In general, it is recommended that the patient or carer create a diary in which to record daily “on-off” periods.

4.1 Intermittent Therapy

Intermittent s.c. injections are used as intermittent bolus injections on demand for disabling refractory ”off” periods, in patients already treated with an optimized oral anti-Parkinson therapy (Lees et al., 2002). Data from North American clinical trials examining s.c. injection of apomorphine in PD patients demonstrated a benefit as early as 7.5 minutes after injection with a duration of up to 90 minutes (Stacy, 2004).
Optimal outcome for successful therapy with apomorphine was observed particularly in younger patients with motor fluctuations of the “wearing-off” type and normal cognitive abilities.
In general, s.c. administration of a drug with a high bioavailability has the advantage of a faster distribution, independent of the timing for food uptake and gastrointestinal functioning.
The short half-life of apomorphine induces a response of about 45-60 min, does not generally interfere with the basal drug regimen, but fills the gaps in motor functioning. Intermittent injections 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).

The daily dose can be highly variable between patients, however once the optimal dose has been found for one patient, this dose will remain fairly constant over time (low intra-patient variability). If no apomorphine test has been performed, treatment should start with 1-2 mg. If no significant motor effect is observed, increase dose by 0.5-1 mg to a maximum of 6mg in incremental steps until a clinically effective dose is observed.

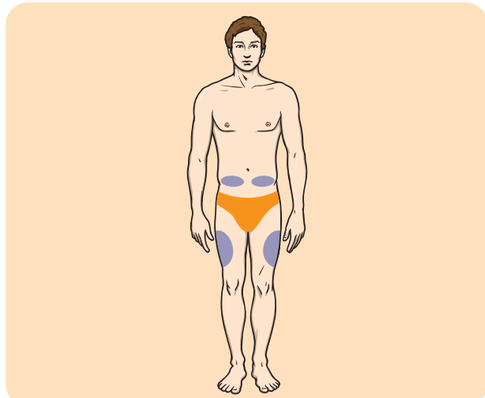

Fig. 4: Recommended injection sites for s.c. application

Delayed ‘Time-To-On’ (TTO) and morning akinesia are known to occur in patients taking oral medication for PD. It is suggested that this is due, in part, to gastroparesis. The AM-IMPAKT trial set out to assess the effect of apomorphine s.c. injection in patients with morning akinesia resulting from delayed or unreliable onset of effect of first morning dose of levodopa. The primary outcome was to compare the patient self-reported, diary-recorded TTO following first morning dose of levodopa at baseline for one week compared to TTO when using apomorphine. 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 were demonstrated and quicker time to “On” in nearly all patients

than baseline treatment with levodopa. The authors concluded that apomorphine s.c. injection significantly reduced Time-To-On in patients with delayed onset of their morning levodopa dose (Isaacson et al., 2017).

Selection Criteria for Apomorphine Intermittent Bolus Injection Therapy

- **Morning problems like akinesia and dystonia**
- **Problems with gastric emptying (gastroparesis)**
- **To bridge delayed “On”**
- **When rapid and reliable relief is required during predictable and/or non-predictable“Off” periods**
- **Prevent from dose failures**
- **To treat non-motoric “Off ” (e.g. pain)**

Table 1: Possible reasons for considering s.c. apomorphine bolus injections on demand

S.c. intermittent administrations of apomorphine should be considered as an add-on bridging therapy for patients not sufficiently controlled by oral anti-Parkinson medication. 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 s.c. infusion by minipump and/or syringe-driver. In addition apomorphine is also effective for painful and disabling dystonias.
Intermittent s.c. injections can be self-administered, do not require medical supervision and can be followed up, after proper training, by primary health care centres.
Apomorphine injections have the shortest time to clinical improvement and are ideal for patients who need a quick time-to-on.
Most of the reports dealing with on-demand treatment have found a dose range between 2-5 mg to provide well-tolerated „on“ effects in a reliable manner.
The best treatment option for every patient remains to be determined based not only on cost but also factors of efficacy and tolerability (Martinez-Nunez et al., 2023).

Considerations before administering Intermittent Bolus Injections

- **Symptom response to levodopa**
- **Neuropsychatric and cognitive status**
- **Diary showing repeated “on-off” periods even with optimized oral medication**
- **Presence of orthostatic hypotension**
- **ECG status**
- **Blood count (RBC, WBC)**
- **Renal function**
- **Care-giver and specialized PD nurse to support application**

Table 2: Considerations before administering intermittent apomorphine therapy. (Adapted from Hagel, et al., 2014)

4.2 Continuous Therapy

Continuous s.c. apomorphine infusion is indicated for patients, normally responding to levodopa, but suffering from long lasting or frequently unpredictable “off” phases, which cannot be adequately treated with optimized oral medication. Patients, who developed PD at a relatively young age (MacMahon, 1999) and who suffer daily from restrictive “peak-dose” dyskinesias are particularly well suited for this therapy.

Many patients starting on intermittent bolus injection therapy on demand later require infusions (69.6%). Tyne et al. have reported the average time for this transition to be 21.4 months (Tyne et al., 2004).
For patients with complex fluctuations and dyskinesias, as well as therapy refractory non-motor off-associated symptoms like sensory phenomena, pain and autonomic or psychotic symptoms, continuous treatment with an infusion pump system should be considered. For patients on intermittent apomorphine injection therapy with a frequency of more than 6 to 10 injections per day, a switch to continuous infusions using a s.c. infusion pump system should be considered.
Furthermore, the patient or the care-giver must be able to evaluate the “on” and “off” periods and acquire the necessary skills to use the infusion pump. The adherence of the patient to the infusion pump system in order to improve his or her independence is the first and most important requirement for therapy.

Selection Criteria for Apomorphine Continous s.c. Therapy

- **Moderate/intermediate and advanced PD**
- **Good symptom response to levodopa**
- **Long and unpredictable “off” periods**
- **Peak dose dyskinesias**
- **More than 6 to 10 apomorphine injections per day**
- **Early onset of disease**
- **No significant cognitive limitation**
- **Care-giver and specialized PD nurse available to support administration**

Table 2a: Selection criteria for continuous s.c. apomorphine infusion. (Adapted from Hagell, et al., 2008)

There are different protocols for the administration of continuous apomorphine infusion: 1) administration during daytime and 2) administration over a 24-hour period. The indication for one infusion regimen over the other has to be made by the treating physician and is primarily based on clinical efficacy. Commonly, oral anti-Parkinson medication can be reduced and in some cases even discontinued completely.

Various long-term open label studies have observed continuous efficacy of apomorphine infusions for up to five years (see table 3). In general, the duration of efficacy and dosage remains the same.
Early intervention ideally would target patients as soon as motor complications begin rather than at late stage (Antonini et al., 2018).

Apomorphine infusion significantly reduce „off“ time compared with placebo. Apomorphine infusion results in a clinically meaningful reduction in „off“ time in patients with Parkinson’s disease with persistent motor fluctuations despite optimised oral or transdermal therapy (Katzenschlager et al., 2018).

Clinical Studies on Continuous s.c. Apomorphine Infusions

	Chaudhuri et al., 1988	Pollak et al., 1990	Kreczy-Kleedorfer et al., 1993	Stocchi et al., 1993	Hughes et al., 1993	Gancher et al., 1995	Pietz et al., 1998	Chaudhuri et al., 1999	Vanderheyden et al., 1999	Kanovsky et al., 2002	Morgante et al., 2004	Katzenschlager et al., 2005	De Gaspari et al., 2006	Garcia Ruiz et al., 2008	Antonini et al., 2011	Drapier et al., 2012	Auffret et al., 2017	Katzenschlager et al., 2018	Isaacson et al., 2025
Number of patients	7	9	14	10	22	7	25	34	11	12	12	12	13	82	12	23	12	53 Apo	99
Duration of disease (years)	17	15	12.4	11.5	19.2	17.6	16	10	13	14.4	10	14.5	19	14.3	9	13.9	13.8	11.8	13,6
Follow-up (months)	11	10	26	12	36	3	44	30	12	24	24	6	12	19.9	30	12	6	3	12
Average total dose (mg/day)	29.7	93	151.7	38.4	70	50.4	112.5	70	48	31.4	100	77.7	74.8	72	83.4	62.6	57.7	74,9	55,7
Decrease of "off" periods (%)	-85	-67	-77	-57	-59	-58	-50	-42	-40	-80	-60	-38	-51	-79.4	-49	-36	-35	-36.9	-48,5
Reduction of levodopa dose per day (%)	-39	-53	-81	-48	15.7	-50	-50	-18	-30	-23	-52	-55	-29*	-32.9	nr	-26	-32	-22,6	-18,5

Table 3

In addition Antonini et al. made a 5-year prospective assessment of advanced PD patients treated with s.c. apomorphine infusion or deep brain stimulation. The dosage of continuous s.c. apomorphine infusion (CSAI) ranged from 70 to 112.5 mg, with a grand-mean dose of 83.4 mg (SD ± 19.2) and ran over a mean time of 14 h each day. On average, time on CSAI was 30 months. Results confirm that CSAI is an effective treatment option for patients with PD and severe fluctuations that are poorly controlled by oral drug treatment (Antonini et al., 2010).

Continuous s.c. administration of apomorphine has been shown to decrease levodopa-induced dyskinesias with subsequent improvement in quality of life measures for those with moderate to advanced disease. Desensitisation of dopamine receptors via constant pulsatile levodopa treatment and the decrease of the storage capacity of dopaminergic terminals play an important role in the development of motor complications. In addition, the resorption of oral dopamine uptake decreases during the course of the disease.

In a prospective follow-up study for a period of two years, the effectiveness and decrease of dyskinesias using mono- and polytherapy with apomorphine during the waking period was investigated (see Table 3). Twelve patients with levodopa-induced dyskinesias were treated with continuous s.c. apomorphine. A markedly significant reduction in peak-dose dyskinesias occurred over a two-year follow-up period. The reduction of dyskinesias in those patients was achieved at the same time as the stabilization of L-dopa doses and daily doses of apomorphine, i.e., within 2–3 months. All patients showed substantial improvement in their dyskinesias by month 6 (Kanovský et al., 2002).

In another prospective study involving 12 patients with on-off fluctuations and disabling diskinesias, apomorphine challenges showed significant reductions of 39% in Abnormal Involuntary Movement Scale (AIMS) and 36% in Goetz scores compared to baseline at 6 months $p<0.01$. Patients' self-assessment scores reflected these significant changes. Dyskinesia improvement correlated with a reduction in oral medication and with the final apomorphine dose. This study confirms marked dyskinesia reduction on continuous s.c. apomorphine therapy, paralleled by reduced dyskinesias during dopaminergic challenge tests. It supports the concept that replacement of short-acting oral anti-Parkinson medication with continuous dopamine receptor stimulation may reverse, at least partially, the sensitization process believed to mediate the development of drug-induced dyskinesias in Parkinson's diseas (Katzenschlager et al., 2005).

In a case control, comparative, 6-month multicentre study, significant improvements in motor, quality of life and total Non Motor Symptoms Scale (NMSS) scores were reported with s.c. apomorphine infusion. In addition, apomorphine improved mood dysfunction and did not worsen hallucinations (Reddy et al., 2013).

The outcome of the InfusON trial supports the clinical utility of apomorphine infusion to reduce OFF time and increase Good ON time in patients with motor fluctuations inadequately controlled with oral therapy (Isaacson et al., 2025).

Decrease of Dyskinesias under Continuous s.c. Apomorphine Therapy

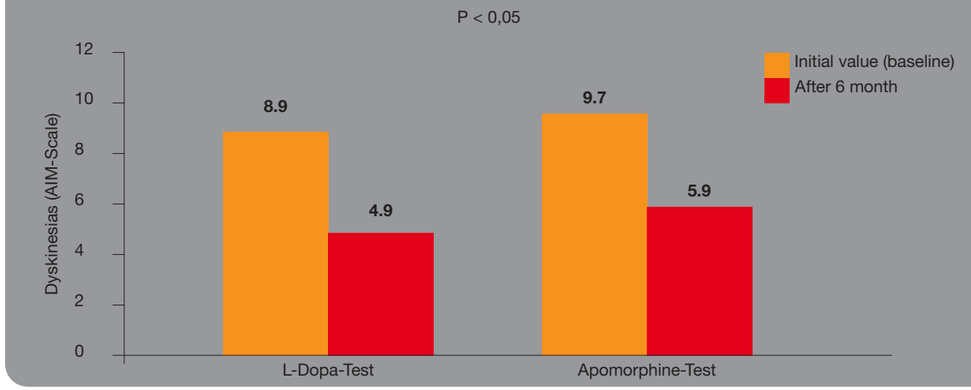

Fig. 4: Objective measures of dyskinesias during L-dopa and continuous s.c. apomorphine challenges. (Adapted from Katzenschlager et al., 2005)

4.3 The Apomorphine Test

4.3.1 Additional Diagnostic Tool for PD

The response to levodopa has been used as a diagnostic tool for PD. Both levodopa and the apomorphine tests can be performed as specific functional tests for PD. A positive effect on motor control likely indicates that a nigrostriatal dysfunction is present and thus PD. These tests can be useful during initial diagnosis but may also be important during moderate/ intermediate and advanced phases of the disease.

Results obtained after the s.c. apomorphine challenge test seem to indicate that the oral levodopa test more reliably predicts the diagnosis of PD, whereas the apomorphine test may more specifically predict chronic dopaminergic responsiveness. Therefore, a positive response to the apomorphine test increases the likelihood of PD diagnosis, but is not diagnostic on its own.

A positive pharmacological test reinforces the clinical diagnosis, however a negative acute challenge test to apomorphine still justifies an appropriate therapeutic intervention in newly diagnosed patients. Although there may be a marginally superior predictive advantage to the levodopa test in de novo parkinsonian patients, the s.c. apomorphine and oral levodopa challenge test have a high concordance and comparable predictive accuracy (Deleu et al., 2004).

Advantages of the apomorphine test versus levodopa:

- Test not affected by metabolism of food intake
- Short effective time window provides an easy control
- Fast and significant motor effect
- Short half-life allows repeating the test to prove reliability and to adjust the effective dose
- Very low risk of induction of dyskinesias
- The patient is not required to fast

During the apomorphine test, side effects such as nausea, vomiting, sedation and hypotension may occur. (Gasser, et al., 1992). Pre-treatment with domperidone is strongly recommended before starting an apomorphine test.

An apomorphine test may be carried out in the outpatient or inpatient setting, but in both cases the evaluation period has to be long enough to evaluate the motor functions and potential side effects. The apomorphine test may be administered in different doses:

Apomorphine Test Scheme

Preparation

- Premedication with domperidone: 72 hours before and 1 hour before starting the apomorphine test.[a)]
- Discontinuation of anti-parkinsonian medication

Dosage Scheme[b)]

Option A: Starting dosage: 1.0mg apomorphine s.c.
Stepwise increase of the dosage by 1.0 to 1.5 mg to a maximum dosage of 10 mg every 45 minutes.

Option B: Starting dosage : 1.5 mg apomorphine s.c.
Stepwise increase of the dosage by 1.0 to 2.0 mg to a maximum dosage of 10 mg every 45 minutes.

Option C: (sometimes practiced): Single dosage of 3 mg apomorphine s.c.

Criteria for Significant Response[c)]

At least two of the following criterias should be present:
- UPDRS part III: motor assessment: ≥ 20% improvement versus baseline
- Hand-arm-movement between two distant points of 30cm: ≥ 15% improvement versus baseline
- 2x7m walk: ≥ 20% improvement versus baseline

Testing Procedure

1. Baseline-assessment without medication UPDRS part III, motor assessment (Fahn et al., 1987)
   Hand-arm-movement between two distant points of 30cm: counting of cycles within 20 seconds (Defer et al., 1999)
   7m walk, turn around, walk back: measuring time in seconds, number of steps, including turns; if the patient is not able to walk 7m within 90 seconds measuring the distance and the number of steps within 90 seconds (Hagell, 2000)
2. Injection of apomorphine s.c. (abdominal wall) according to dosage scheme A or B
3. Assessment of the motor function (UPDRS part III, hand-arm-movements, 2x7m walk) 20 minutes after apomorphine s.c. application[b)]

Test Results

- After significant motor response (see criteria): stop test
- After negative or insignificant motor response: repeat the test (step 2 and 3 of the testing procedure if side effects are not too severe after 45 minutes)
- If side effects after 1.5 mg apomorphine s.c. are too severe: repeat the test at a dosage of 1.0 mg apomorphine s.c.
- Option C: If side effects after 3.0 mg apomorphine s.c. are too severe (despite motor response): stop test

[a)] A lower dosage and shorter interval of the premedication (e.g. 10 mg domperidone 3x daily for 24 hours) is adequate in most cases (Pietz et al., 1998), but a higher dosage may reduce the risk of peripheral dopaminergic side effects (Rascol et al., 1990). If domperidone is not available, 200 to 300 mg trimethobenzamide may be given 3x daily (Bowron, 2004).

[b)] Shorter dosage intervals (e.g. 30 minutes) after second assessment after injection and/or higher dosage steps may be considered (Lees et al., 1998).

[c)] UPDRS part III shows the best sensitivity and specificity of dopaminergic response when a reduction between 15% and 20% versus condition without medication is monitored (Roosi et al., 2000). A threshold of 15% for hand-arm-movements between two distant points in a given period of time has turned out to be an adequate assessment of the dopaminergic response of bradykinesia (van Hilten et al., 1997). Walking in a given period of time has a good correlation with other clinical assessments like e.g. the motor assessment using the UPDRS (Martínez-Martín et al.,1997).

Table 4: Adapted from protocol of the apomorphine test scheme (Hagell et al., 2014)

If the apomorphine test does not show a response, the following should be considered:
In the early stage of PD the lack of a short-term effect of apomorphine may be related to short treatment duration and does not allow any conclusions regarding the long-term efficacy of apomorphine treatment. If a positive response is not shown, repeating the test is recommended. In the event that no positive effect from apomorphine has been shown, a levodopa test may be considered to support the diagnosis.

4.3.2 The Apomorphine Test to Start Therapy

An apomorphine test before starting therapy is not essential but recommended. As preparation for the apomorphine treatment the test can give valuable information about:

- Latency until the motor effect is present
- Minimum required dosage
- Assessment of potential side effects on individual basis

4.3.3 Quick Titration Protocol for Apomorphine

When performed for dose-finding purposes, a quicker testing protocol has successfully been tried in during the past few years.

Pulse and blood pressure (supine and standing) and motor response should be monitored every 10-12 minutes. Suggested quick and reliable motor tests to quantify therapeutic motor response include hand/arm movements between two points, timed walking test, and selected items from the motor exam section of the UPDRS part III, e.g., tremor, rigidity, and pronation/supination ratings (Hagell et al., 2014).

4.4 Premedication/Co-medication

Since apomorphine has a strong emetic effect, premedication with domperidone is essential. Domperidone has been used successfully at a lower dosage and for a shorter time period before apomorphine administration, e.g. 10 mg domperidone three times daily for 12-24 hours before apomorphine administration (Pietz, et al., 1998).
While these reduced dosages and time intervals have been cited in the literature the marketing authorisation holder recommends to start domperidone at least two days prior to initiation of therapy. The domperidone dose should be titrated to the lowest effective dose and gradually discontinued as soon as possible (SmPC, 2023).
A higher dosage may reduce the risk of peripheral dopaminergic side effects (Rascol et al., 1990).

Time Intervals	Start	15 min	30 min	45 min	60 min	75 min	90 min
Injected Dose	1 mg	2 mg	2 mg	2 mg	3 mg	3 mg	3 mg
Bioavailable Dose	1 mg	3 mg	4 mg	5 mg	6 mg	7 mg	8 mg

Table 4a: Quick dose-finding protocol (Hagell et al., 2014)

According to this protocol, s.c. apomorphine injections are administered with brief intervals (15 minutes) until a satisfactory effect is gained or unacceptable side effects occur. This protocol is based on the pharmacokinetics of apomorphine and takes ad- vantage of residual plasma apomorphine levels by building up the bioavailable dose.

The pro-emetic effect of apomorphine exhibits tachyphylaxis and 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 (SmPC, 2023).

If domperidone is not available, trimethobenzamide may be given at 300 mg three or four times daily (Bowron, 2004).

5. CONTRAINDICATIONS, SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Before starting apomorphine therapy, systolic and diastolic blood pressure measurements in standing and supine positions, as well as kidney and liver function tests, are required.

Contraindications:
- Hypersensitivity to apomorphine or to any of the excipients.
- In patients with respiratory depression, dementia, psychotic diseases or hepatic insufficiency.
- In patients who have an “on” response to levodopa that is accompanied by severe dyskinesia or dystonia.
- In children or adolescents under 18 years.

Special warnings and precautions:
- Caution is advised in patients with renal, pulmonary or cardiovascular disease, those prone to nausea and vomiting and when combining with other medicinal products (especially those with a narrow therapeutic range).
- Apomorphine may produce hypotension. Exercise caution in patients with pre-existing cardiac disease or orthostatic hypotension.
- Based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron, the concomitant use of apomorphine with ondansetron is contraindicated.
- Dacepton® may induce QT prolongation, especially at high dose. Caution in those patients at risk for torsades de pointes arrhythmia.
- Extra caution is recommended in the elderly or debilitated.
- Haemolytic anaemia and thrombocytopenia have been reported. Regular haematology tests should be carried out.
- Local injection site reactions may occur. These can sometimes be reduced by rotation of injection sites.
- Pre-existing neuropsychiatric disturbances may be exacerbated by apomorphine.
- Patients may develop impulse control disorders. A reduction/tapered discontinuation of apomorphine is advised.
- Before initiation of treatment, patients and caregivers should be warned of the potential risk of developing Dopamine dysregulation Syndrome (DDS).
- Somnolence has been reported including episodes of sudden sleep onset. Patients should be informed and advised not to drive or operate machinery if affected.
- Dacepton® contains sodium. Caution is advised in those on a controlled sodium diet.
- Dacepton® contains sodium metabisulphite which may rarely cause severe hypersensitivity reactions and bronchospasm.

(SmPC, 2023)

6. PHARMACOLOGICAL AND CHEMICAL PROPERTIES OF APOMORPHINE

Apomorphine (10,11-Dihydroxyaporphin) was first synthesized as early as 1869 by the dehydration of morphine with hydrochloric acid. It is one the oldest compounds in clinical use today (Hagell et al., 2008).

Although its use in PD was described in 1884, the first documented therapy tests took place in 1951 (Schwab et al., 1951). At the end of the 1960s, the mode of action of apomorphine, acting as a non-ergoline dopamine receptor agonist, was discovered and pilot studies using s.c. injected apomorphine were carried out. These initial clinical observations showed a temporary change in the neurological manifestations of the disease similar to that of levodopa (Cotzias et al., 1970).

6.1 Chemical Structure and Characteristics

INN name:	Apomorphine hydrochloride hemihydrate
CAS number:	41372 - 20 - 7
Chemical name:	6a-ß-aporphine-10,11-diol
Molecular formula:	C17H17NO2.HCl.1/2H2O

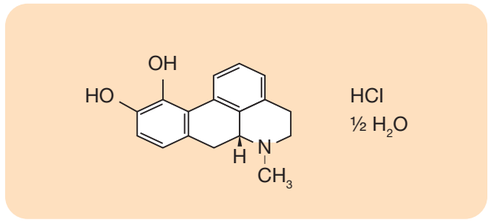

Fig. 5: Structural formula of apomorphine

General Properties: Apomorphine is produced by chemical modification of morphine and the various marketed preparations of apomorphine may vary in their potency and stability (LeWitt, 2004). It is generally formulated as a hydrochloride salt. It is a lipophilic molecule and still water soluble. Apomorphine requires protection from light due to its tendency for spontaneous oxidation (Gancher et al., 1995); (SmPC, 2023).

6.2 Pharmacokinetics

The most widely used method of delivery is the s.c. route. Apomorphine must not be used via the intravenous route. The bioavailability of the s.c. route of administration is 100%. The site of injection and skin temperature influence the kinetics of apomorphine. A rapid onset of its motor effect is related to the lipophilic properties of apomorphine, resulting in a rapid distribution from the injection site into the blood and a rapid passage through the blood-brain barrier (Gancher et al., 1989). After s.c. 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 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 sulfation to at least ten per cent of the total; other pathways have not been described (SmPC, 2023).

Apomorphine is metabolized preferentially by sulfation and glucuronidation. In humans, sulfation is the major metabolic pathway of this drug. Sulfotransferase 1A1 was confirmed to be the primary enzyme responsible for hepatic apomorphine sulfation (Thomas et al., 2003).

It was also shown that the sulfation rate of apomorphine was higher in the duodenum than in the liver (Thomas et al., 2003). In patients with PD the majority of apomorphine is not detectable and identified, which may potentially be due to its extensive (auto) oxidation. The clearance of apomorphine has not been studied in detail. However, the elimination half-life time calculated after intermittent bolus injection and continuous infusion were similar. Pharmacokinetic interactions of apomorphine with mefenamic acid, salicylic acid and quercetin have shown that these compounds are less effective inhibitors of apomorphine sulfation in the duodenum. Similarly, the administration of entacapone did not change the pharmacokinetic effects of apomorphine in patients with PD or prolong the clinical effect of apomorphine. (Safety of entacapone and apomorphine coadministration in levodopa-treated Parkinson‘s disease patients: pharmacokinetic and pharmacodynamic results of a multicenter, double-blind, placebo-controlled, cross-over study, 2004)
In summary, the drug absorption, volume of distribution, plasma clearance, and half-life times were similar for both intermittent s.c. injection and continuous s.c. infusion. Apomorphine is rapidly and completely absorbed from s.c. tissue, correlating with the rapid onset of clinical effects. The brief duration of clinical action of the drug may be explained by its strong auto-oxidation and rapid clearance.

6.3 Pharmacodynamics

Apomorphine is a direct stimulant of dopamine receptors and while possessing both D1 and D2 receptor agonist properties, does not share metabolic pathways with levodopa. Apomorphine has a high in vitro binding affinity for D4 dopamine receptors, moderate affinity for D2, D3 and D5 receptors, and low affinity for D1 receptors (Lahti et al., 1993).

Antipsychotic drugs are known to be dopamine antagonists and it is this activity at the dopamine D2 receptor that is thought to be responsible for their therapeutic action. However, clozapine for example, an antipsychotic agent that does not produce extrapyramidal side effects or tardive dyskinesias has been found to be selective for the D4 receptor vs. the D2 receptor by a factor of 2.8. This has led some to suggest that D2 receptor occupancy is equated with extrapyramidal side effects and dopamine D4 occupancy to antipsychotic efficacy (Lahti et al., 1993).

The difference in mRNA localisation and structure activity relationship for dopamine D2, D3 and D4 receptors presents some interesting concepts. The dopamine D2 receptor is dominant in the striatum, a brain structure that plays an important role in controlling motor behaviour and those agents that are most noted for their production of extrapyramidal side effects and tardive dyskinesia. Therefore, it is supposed that dopamine D2 receptor blockade may be linked to extrapyramidal side effects and tardive dyskinesia (Lahti et al., 1993); (Kolls et al., 2006).

Apomorphine affinity for D2-like receptors is ten times higher than for D1-like receptors. In PD, the quality of motor responses to apomorphine and levodopa is indistinguishable, but a more rapid onset, shorter duration of anti-parkinson effects, and fewer motor fluctuations following apomorphine make it particularly useful as a treatment option. Systemic administration of apomorphine increases locomotor activity in a dose-dependent manner, and the increase can be blocked by pre-treatment with D2-like receptor antagonists (Scarselli et al., 2001).

In the central nervous system, apomorphine works by enhancing signals in supraspinal neuronal pathways that control penile erection. At the periphery, the sympathetic pathways play a major role in flaccidity and detumescence through the stimulation by norepinephrine of postjunctional α1–adrenoreceptors found in corpus cavernosum smooth muscle cells (Mayoux et al., 2004).

The most important pharmacodynamic interaction exists with the effect of anti-dopaminergic drugs (e.g. domperidone) suppressing apomorphine-induced nausea and vomiting as the result of dopaminergic apomorphine stimulation.

The use of intermittent s.c. apomorphine injection offers an effective approach to solve the problems arising from other oral anti-Parkinson therapy. Intermittent s.c. injections are used as a rescue strategy for debilitating refractory “off” periods, in patients already receiving an optimized oral anti-Parkinson therapy. This method of administration was shown to be effective for outpatient usage and it is able to reverse “off” periods that occur despite optimized oral therapy. The improvement after intermittent s.c. administration is highly dose dependent. Moreover, treatment with s.c. apomorphine allows the modification of anti-Parkinson medication. It may result in the disappearance or reduction of neuropsychiatric side effects in patients treated. Apomorphine s.c. is also suitable for the long-term treatment of “off” periods in patients with moderate/intermediate and advanced PD.

6.4 Storage and Stability

Do not store above 25°C (77°F).
Keep in the outer carton, in order to protect from light.
Do not refrigerate or freeze.
Do not use if the solution has turned green.

(SmPC, 2023)

6.5 Special Handling Instructions

6.5.1 Dacepton® 10 mg/ml ampoules

Nature and contents of container Dacepton® 10 mg/ml ampoules
Clear, colourless type I glass ampoules containing 5 ml solution for injection.

Composition Dacepton® 10 mg/ml ampoules
1ml contains 10 mg apomorphine hydrochloride.
5ml contain 50 mg apomorphine hydrochloride.

Shelf life Dacepton® 10 mg/ml ampoules
Unopened: 30 months
For single use only. Any unused product should be discarded.

Continuous infusion and the use of a minipump and or syringe-driver
The choice of which minipump and or syringe-driver to use, and the dosage settings required, will be determined by the physician in accordance with the particular needs of the patient.
Dacepton® 10 mg/ml is compatible with sodium chloride solution 0.9 % (9 mg/ml).

(SmPC, 2023)

6.5.2 Dacepton® 5 mg/ml vials

Nature and contents of container Dacepton® 5 mg/ml vials
Clear glass vials, type I with bromobutyl rubber stopper and a flip-off cap, containing 20 ml solution for infusion.

Composition Dacepton® 5 mg/ml vials
1 ml contains 5 mg apomorphine hydrochloride hemihydrate.
20 ml contain 100 mg apomorphine hydrochloride hemihydrate.

For subcutaneous (s.c.) use. Must not be used via intravenous route. Read the package leaflet before use.

Shelf life Dacepton® 5 mg/ml vials
Unopened: 30 months
After opening and filling the drug product in syringes attached with infusion sets: chemical and physical in-use stability has been demonstrated for 7 days at 25 °C.

For single use only. Any unused medicinal product or waste material should be disposed in accordance with local requirements.

Continuous infusion and the use of a minipump and/or syringe-driver
The choice of which minipump and or syringe-driver to use, and the dosage settings required, will be determined by the physician in accordance with the particular needs of the patient.

(SmPC, 2023)

6.5.3 Dacepton® 10 mg/ml cartridges

Nature and contents of container Dacepton® 10 mg/ml cartridges
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.

Composition Dacepton® 10 mg/ml cartridges
1 ml contains 10 mg apomorphine hydrochloride hemihydrate.
3 ml contain 30 mg apomorphine hydrochloride hemihydrate.

Shelf life Dacepton® 10 mg/ml cartridges
Unopened: 24 months
After first opening: Chemical and physical in-use stability has been demonstrated for 15 days at 25°C.

Dacepton® 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.

(SmPC, 2023)

7. SIDE EFFECTS

7.1 Local reactions

Amongst the most frequent side effects of apomorphine therapy are sclerosis and subcutaneous nodules at the injection site. These nodules are frequently observed and are mostly without any significant side effects. The reaction appears to be dependent on the daily apomorphine dosage regimen but also skin types, injection technique or weight of the patient.
Apomorphine dose is likely to be a risk factor because people receiving continuous infusions, rather than (lower dose) intermittent injections, tend to experience the most significant cutaneous reactions (Hughes, et al., 1993), (Deleu, et al., 2004).
Skin nodules and irritation are rarely a cause for discontinuation. Massaging the insertion site after needle withdrawal, using finer or Teflon needles, antiseptic insertion techniques, therapeutic abdominal wall ultrasound, or, in selected cases, hydrocortisone injections can all reduce troublesome skin nodules (Bhidayasiri et al. 2016).

Measures against Subcutaneous Nodules

Injection Preparation	
Hygiene	• Washing and disinfecting hands • Cleaning and disinfecting injection site
Injections/infusions	• Selection of different injection sites • Change of needle before each injection/infusion • Sufficient subcutaneous fat at the injection site. A minimum of 10mm is best
Infusion	• Lower apomorphine concentration (not more than 5 mg/ml)
Post Injection/Infusion	
Prophylactic	• Massage the skin after injection/infusion. If necessary con sult a pysiotherapist
Rash and pain on the injection site	• Retract the needle and puncture at different site
If infection is suspected	• Appropriate medical intervention
Existing papules	• Heparine ointment • Treatment with Ultrasound • Silicon patch • TENS (transcutaneous electrical nerve stimulation)

Table 5: Measures to avoid subcutaneous nodules (Pietz et al., 1998); (Hagell et al., 2014)

7.2 Nausea and Vomiting

Nausea is frequent especially at initiation of apomorphine therapy. It is essential that the patient is established on domperidone for at least 2 days prior to intiation of Dacepton®. See section 4.3.1 of this monograph for suggested dosing recommendations. As some patients develop tolerance to these side effects a stepwise reduction in domperidone usage may be possible.

7.3 Neuropsychiatric Side Effects

In general at least one symptom, such as vivid dreams, hallucinations, psychoses or confusion, has been observed in about 61% of patients undergoing dopaminergic therapy. With apomorphine therapy, however, due to the short half-life, these symptoms are of shorter duration and easier to control. The risk of developing neuropsychiatric side effects is highest with a 24h s.c. infusion protocol, with s.c. infusion therapy associated with moderate risk and s.c. injection therapy providing the lowest risk. Studies do not show any significant relationship between the severity of neuropsychiatric side effects and age, duration of disease, dosage of levodopa, dyskinesia, or on-off phenomena (Aarsland, et al., 1999). The frequency of cognitive side effects is increased in those also developing neuropsychiatric symptoms (Pietz, et al., 1998).

In the case of neuropsychiatric symptoms, the total dosage of apomorphine should be reduced – after excluding other possible reasons – and treatment dose titrated to a minimum to maintain motor function. 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. 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. If neuroleptic medicinal products have to be used in patients with Parkinson‘s disease treated by dopamine agonists, a gradual reduction in apomorphine dose may be considered when administration is by minipump and or syringe-driver. Furthermore, a reduction of dosage or termination of therapy may be considered (SmPC, 2023).

Effects on mood and cognition have not been extensively investigated. In an observational controlled study, patients receiving subcutaneous continuous apomorphine infusions (n=12) and a control group receiving oral levodopa medication (n=18), the mood of the apomorphine group improved significantly (measured by Beck Depression Inventory) while the neuropsychiatric symptoms in both groups remained the same (Di Rosa et al., 2003).

Growing evidence tends to suggest that apomorphine is safe, and could even be beneficial for mood and apathy, as well as induce a decrease in visual hallucinations caused by visual problems, possibly through an action on the serotonin 2A receptor (Auffret et al., 2018).

7.4 Sedation

Transient sedation as well as yawning have been reported commonly after s.c. injection with apomorphine. During continuous s.c. apomorphine infusion therapy a few patients report daytime sleepiness. Similar to other comparable dopamine agonists sleep attacks may occur without prior warning signals. Care should be taken to avoid driving or operating machinery if these symptoms have occurred previously (Homann et al., 2003).

7.5 Dyskinesias

S.c. apomorphine may lead to an increase of dyskinesias during “on” periods. The dyskinesias may be severe and lead to a discontinuation of treatment. Although apomorphine has been associated with antidyskinetic effects, some patients with pre-existing, levodopa-induced dyskinesias may show a deterioration in symptoms of both duration and intensity. Hence, a gradual withdrawal of levodopa is advised while on continuous s.c. apomorphine infusions. This reduction in levodopa often results in substantial reduction of dyskinesias without loss of motor control (Colzi et al., 1998).

7.6 Impulse Control Disorders

While impulse control disorders (ICDs) are associated with all dopamine agonists, evidence suggests that the frequency is greater in those with preferential affinity to the dopamine D3 receptor and lower for apomorphine (Seeman 2015). Overall, the risk of developing ICDs is reported to be relatively low for infusion therapies, including apomorphine (Todorova et al., 2015). It is recommended that patients and carers be advised such symptoms may occur before initiating treatment.
Findings of a real-life cohort suggest that ICDs tend to improve following continuous apomorphine infusion initiation in patients, likely due to a reduction of oral dopamine agonists or the effect of continuous dopaminergic stimulation provided by the pump (Desjardins et al., 2025).

7.7 Haemolytic Anaemia

In about 0.1 to 1% of cases, a Coombs’-positive haemolytic anaemia occurs, which is reversible after discontinuation of apomorphine or by treatment with corticosteroids. Red blood cell counts, the Coombs’ test and in some cases a haematological co-treatment should be undertaken before treatment is started and the patient regularly tested during apomorphine treatment. Coombs’-positive haemolytic anaemia has rarely been reported in patients treated with levodopa, and the incidence in patients taking levodopa and apomorphine is similar. Coombs’ direct antibody test is occasionally positive, and haemolytic anaemia has occasionally been reported in patients treated with apomorphine (Hughes et al., 1993); (Pietz et al., 1998); (Bowron, 2004).

7.8 Orthostatic Hypotension

Orthostatic hypotension has been observed in as few as 0.1%-1% of patients receiving apomorphine, while other clinical trials have reported 4% to 7% of those treated with apomorphin s.c. either as intermittent injections or as continuous infusion. In those patients with pre-existing cardiac disease or arterial hypertension requiring treatment, orthostatic blood pressure should be closely monitored during an apomorphine test. Domperidone has been helpful in counteracting this side effect (Hagell et al., 2001); (Hagell et al., 2014).

7.9 Eosinophilia

Mild eosinophilia has been observed after starting treatment with apomorphine but often resolves with continued treatment (O‘Sullivan et al., 1999).

8. OVERDOSAGE

There is little clinical experience of overdose with apomorphine by this route of administration. Symptoms of overdose may be treated empirically as suggested:

Symptom	Treatment
Excessive vomiting	Domperidone
Respiratory depression	Naloxone
Hypotension	Appropriate measures should be taken, e.g. raising the foot of the bed
Bradycardia	Atropine

Table 6: Possible treatments in case of overdose with apomorphine (SmPC, 2023).

9. SCIENTIFIC INFORMATION

9.1 Pre-clinical Data

The dopaminergic system has been implicated in a number of neurological and psychiatric disorders. Behavioural studies are commonly employed when studying dopaminergic neurotransmitter systems in laboratory animals. Parkinson's disease is characterized by progressive dopaminergic neuronal cell death in the substantia nigra, resulting in severe loss of motor control.

Evidence suggests that many substances including growth factor support the survival and differentiation of dopamine neurons both in vitro and in vivo.

Apomorphine has been shown to be a highly potent iron chelator, a free-radical scavenger and an inhibitor of membrane lipid peroxidation (Youdim et al., 1999).
It is suggested, that apomorphine acts as a radical scavenger and that its iron chelating properties may not be of major importance. Since oxidative stress has been implicated in Parkinson's disease, the role of apomorphine as a neuroprotective is worthy of examination (Gassen et al., 1996).

Apomorphine has also been implicated in the inhibition of brain and mitochondrial protein oxidation. The neuroprotection observed with apomorphine does not seem to be related to its dopamine agonist properties; instead, it appears to be due to the antioxidant and free radical scavenging effects of the compounds. Guo et al. demonstrated that treatment of foetal rat ventral mesencephalic cultures with apomorphine caused a marked increase in the number of dopaminergic neurons (Guo et al., 2002).

The action of apomorphine can be mimicked by dopamine receptor D1 and D2 agonists or blocked by preincubation with D1-D2 receptor agonists. Incubation of recipient mesencephalic cultures with the conditioned medium derived from apomorphine-stimulated donor mesencephalic cultures elicited a 3.72-fold increase in the number of TH-positive neurons. Increased mRNA expression levels of brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor were also found in the apomorphine-treated mesencephalic cells along with concomitant protein expression increases in the conditioned medium. Moreover, the trophic activity observed could be partially neutralised by antibodies against either brain-derived neurotrophic factor or glial cell line-derived neurotrophic factor. Cultured foetal striatal cells, but not hippocampal cells, also responded to apomorphine treatment. These results suggest that the apomorphine-modulated development of dopaminergic neurons may be mediated by activation of dopamine receptor subtypes D1 and D2 thereby increasing the production of multiple growth factor.

Parkinson's disease is characterised by a selective degeneration of the dopaminergic neurons in the substantia nigra pars compacta, resulting in a reduction of the dopamine levels in the striatum. Maňáková et al. studied the mechanism of action of neurotoxin hydroxydopamine (6 -OHDA) to involve the generation of free radicals and subsequent apoptic processes in vitro. They demonstrated that daily administration of neuroimmunophilin FK506 (tacrolimus) for 7 days to rats (0.5, 1.0, and 3.0 mg/kg i.p.) did not significantly prevent the apomorphine-induced contralateral circling, measured 2 weeks after unilateral nigral lesioning. Moreover, FK506 pretreatment did not significantly lower the toxin elevated lipid peroxidation levels, indicating that oxidative stress was present even after the FK506 treatment in the lesioned striatum (Maňáková et al., 2005).

Many animal models have demonstrated a neuroprotective effect of apomorphine. It is known that continuous subcutaneous infusion of apomorphine rescues nigrostriatal dopaminergic neurons from toxicity induced by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in mice. In addition, in vitro studies have shown that apomorphine is an iron chelator, reduces the oxidation of polyunsaturated fatty acids and is a potent free radical scavenger that protects pheochromocytoma PC12 cells from oxidative stress. While the neuroprotective effect of apomorphine is yet to be fully understood, current medical opinion suggests it to be based on its antioxidant and free radical scavenging properties (Picada et al., 2005).

9.2 Clinical Trials - Intermittent Injections

Intermittent administration of apomorphine as subcutaneous injections offers a valuable and effective treatment alternative for patients with Parkinson's disease who have "off" periods and who are resistant to optimized oral medication. In long-term use apomorphine remains effective with few signs of patient tolerance. Adverse events are usually mild.
The best results are obtained with relatively young patients who remain active and are not cognitively impaired. Intermittent s. c. apomorphine therapy can improve the ability of the patient to live a normal social life, continue to work and may also provide freedom and self-confidence through a reliable, quick rescue from the disabling medication-resistant "off" periods (Odin et al., 2011).

A large number of clinical studies have evaluated the efficacy of apomorphine in patients with Parkinson's disease. Results reported in the following section are mostly derived from randomised clinical trials.

Five patients with idiopathic Parkinson's disease with severe response fluctuations were selected for a randomised double-blind placebo-controlled study, concerning the clinical effects of s.c. apomorphine and its assessment in "off" periods. The study was designed as five (n = 1) studies, in which every patient was his own control. The effect of apomorphine was studied by using the Columbia rating scale and quantitative assessments, using tapping, walking and pinboard. There was a significant positive effect of apomorphine, in a mean optimal dose of 2.7 mg, with a mean latency of onset of 7.3 min and a mean duration of response of 96 min. After pre-treatment with domperidone, no significant adverse effects were observed. Tapping showed the highest correlation with rigidity and bradykinesia. Walking showed a high correlation with stability and gait. Pinboard testing did not give additional information. The results revealed that apomorphine proved to be a significantly effective dopamine agonist (van Laar et al., 1993).

The effect of apomorphine on neuropsychiatric side effects of oral anti-Parkinsonian drugs was investigated in 12 non-demented patients with Parkinson's disease with previous oral drug-related neuropsychiatric problems. Apomorphine was administered by s.c. injection to the anterior abdominal wall at a dose of 1 mg, increasing by 1 mg increments every 20 min until a maximum dose of 10 mg or a clinical effect (greater than 50% improvement in motor activity scores using a standard apomorphine and levodopa challenge protocol) was obtained. Treatment with apomorphine allowed alteration of anti-parkinsonian medication and led to the abolition or reduction of neuropsychiatric complications in all patients. The mechanism is not clear but may be due, in part, to a reduction in concomitant oral medication or a psychotropic action of apomorphine (Ellis et al., 1997).

Intermittent s.c. injections are used as a rescue strategy for disabling refractory "off" periods, in patients already receiving optimum oral anti-parkinsonian therapy (Lees, et al., 2002). Data from North American clinical trials examining s.c. injection of apomorphine in PD patients demonstrated a benefit as early as 7.5 minutes with a duration of benefit as long as 90 minutes (Stacy, 2004).

In a review of 9 clinical studies (see table 7) the average time in "off" periods could be reduced by 44% (Odin et al., 2011).

Subcutaneous apomorphine, administered by continuous waking-day infusion with boluses (93.2 mg/day after 1 year of use), or by repeated intermittent injection (15.0 mg/day after 1 year of use), was given to 71 parkinsonian patients with severe refractory levodopa related "on-off" fluctuations for 1 - 5 years. Forty-nine patients (29 men, 20 women) had been treated with intermittent injections of apomorphine for more than a year. Their mean age was 62.6 (range 42-78) years. The duration of disease ranged

Data s.c. Apomorphine Intermittent Injection Therapy on demand

	1	2	3	4	5	6	7	8	9	10
Patient Characteristics										
Number of patients	12	5	6	49	16	22	11	24	20	88
Age (years)	57.4	57	59.5	62.6	59.7	59	57	58.9	66	65,2
Duration of disease (years)	10.8	9.6	15	15.2	13.9	9.8	13.5	11.5	9.2	11,63
Hoehn & Yahr stage	3.6	4.8	nr	nr	3.8	nr	3.8	4	nr	nr
Duraton of study (months)	6.5	11	6.5	27	12	2	23	22	1	0,23
Apomorphine Therapy										
Dosage/injections (mg)	4	2.1	2.8	nr	3.7	3.4	3	1.9	5.4	3,5
Number of injections per day	2	4.2	3.8	nr	4.3	nr	3	5.1	2.5	1
Dosage per day	8.6	8.9	11.6	18.6	17.9	nr	9	9.7	13.5	3,5
Relative Improvement/ Aggraviation vs. Baseline										
Time in “off” %	-56	-63	-41	-41.9	-53.2	-43	-45.2	-41	-34	nr
Time in “on” with dyskinesia %	nr	nr	nr	nr	nr	nr	nr	7.7	nr	nr
Intensity of Dyskinesia	nr	nr	nr	nr	nr	nr	nr	-5.8	nr	nr
Daily L-dopa dosage %	0	-14	nr	-6.7	0	nr	15.3	27	nr	nr

nr= nothing to report

1. Poewe et al., 1989, 2. Pollak et al., 1990, 3. Kempster et al., 1991, 4. Hughes et al., 1993, Leiguarda et al., 1995, 6. Ostergaard et al., 1995, 7. Esteban-Munoz et al., 1997, 8. Pietz et al., 1998, 9. Dewey et al., 2001, 10. Isaacson et al., 2017

Table 7: Clinical studies with apomorphine intermittent s.c. injection.(Aadapted from Hagell et al., 2014)

from 5 to 26 (mean 15.2) years and the duration of levodopa treatment ranged from 4 to 21 (mean 13) years. “On” period dyskinesias were present in 41 patients and all had severe “on-off” fluctuations with a mean duration of 7.6 (3-18) years. Seventy nine percent of patients maintained their response for 1 – 5 years of treatment. Follow-up data showed that compared with 1 year of treatment, the daily apomorphine requirements increased, whereas the daily levodopa dose had decreased slightly. The majority of patients (70%) used two to seven injections of 2-5 mg each per day. Anti-Parkinson medication other than levodopa was unchanged in 36 patients (Hughes et al., 1993).

In a study by Ostergaard et al., the effect, therapeutic dose range, and pharmacokinetics of apomorphine, given as subcutaneous injections by a single use pen, were evaluated in the treatment of “off” phenomena in 22 patients with PD. At study entry, a placebo controlled apomorphine test was performed, and apomorphine doses were then individually titrated (mean 3.4 mg, range 0.8 - 6.0 mg) and compared with placebo in a double blind cross over phase. Apomorphine reduced the mean daily duration of “off” periods by 51% as assessed by the patients and by 58% as assessed by the staff as compared with placebo. The severity of “off” periods was also significantly reduced. The effect was unchanged after a maintenance phase of eight weeks. At study termination 13 of 14 patients were able to inject themselves and 11 of 14 patients found that their feeling of freedom had increased. Pharmacokinetics were linear and did not change with repeat dosing. The t_{max} ranged from 5 to 45 minutes (16 patients). The authors concluded that pen-injected apomorphine is a valuable treatment for patients with advanced Parkinson’s disease with “on-off” phenomena (Ostergaard et al., 1995).

To investigate the therapeutic response during long-term treatment with apomorphine in advanced PD, 49 patients (30 men, 19 women; age range 42-80 years) were treated for 3 to 66 months with intermittent s.c. injections or continuous infusions of apomorphine. During the apomorphine test phase the initial dose of 0.5-1.0 mg was increased in a stepwise manner by no more than 1.0 mg/day, to a maximum of 6.0 mg/day, until an optimal effect was reached. Twenty four patients (16 men, 8 women) were treated with intermittent s.c. injections. Most of the patients experienced a long-term symptomatic improvement. The time spent in „off“ was significantly reduced from 50 to 29.5% ($p < 0.001$). The overall frequency and intensity of dyskinesias did not change. The therapeutic effects of apomorphine were stable over time and the authors concluded that s.c. apomorphine is a highly effective treatment that can substantially improve the symptomatology in patients with advanced stage Parkinson’s disease over a prolonged period of time (Pietz et al., 1998).

The efficacy of s.c. apomorphine administration for “off” periods in patients with PD with motor fluctuations under both inpatient titration and outpatient therapeutic conditions has been investigated. The study was performed in 29 patients with advanced PD with 2 hours or more “off” periods despite aggressive oral therapy. Patients randomly received titrated doses of s.c. apomorphine hydrochloride (2-10 mg, n = 20) or pH-matched vehicle as placebo (n = 9) during an inpatient and 1-month outpatient phase. A change in the United Parkinson Disease Rating Scale (UPDRS) motor score 20 minutes after inpatient dosing during a practically defined “off” period event and the percentage of injections successfully aborting off-state events were the primary outcomes. The average levodopa equivalent dose of apomorphine was 5.4±0.5 mg and the mean placebo dose was 1.0 ml. Mean inpatient UPDRS motor scores were reduced by 23.9 and 0.1 points (62% and 1%) by apomorphine treatment and placebo, respectively ($p < 0.001$). The mean percentage of outpatient injections resulting in successful abortion of “off” periods was 95% for apomorphine and 23% for placebo ($p < 0.001$). Inpatient response was significantly correlated with and predictive of outpatient efficacy ($p < 0.001$). The levodopa dose was not predictive of the apomorphine dose requirement. The authors concluded that apomorphine by intermittent s.c. injection is effective and safe for outpatient use to reverse “off” periods that occur despite optimised oral therapy (Dewey et al., 2001).

A number of studies have assessed the long-term efficacy of intermittent s.c. apomorphine injections. The following pivotal US registration study assessed the efficacy of apomorphine in the acute management of “off” periods in patients with advanced Parkinson’s disease who had previously received apomorphine for < 3 months. Patients (n = 62) were randomised to receive double-blind treatment with apomorphine at their typically effective dose (TED, APO), apomorphine at their TED+0.2 ml (2.0 mg; APO+2), placebo at volume equal to their TED (PL), or placebo at volume equal to their TED+0.2 ml (PL+2), for a single “off” episode. Significantly greater improvement in mean UPDRS motor scores was seen with pooled apomorphine versus pooled placebo 20 min after administration (24.2 vs. 7.4; $p < 0.0001$); the difference was also significant at 10 min ($p < 0.0001$). Overall adverse event incidence did not significantly differ between pooled apomorphine and pooled placebo. This study supports the long-term use of intermittent apomorphine as effective acute therapy for “off” periods in patients with advanced Parkinson’s disease (Pfeiffer et al., 2007).

In an open-label study the long-term efficacy of intermittent s.c. apomorphine for ”off” periods in patients with advanced PD was observed. A 6-month outpatient extension of an in-office dose-escalation study was conducted. Patients (n = 51) received apomorphine at a dose consi-

dered optimal based on safety and efficacy assessments during the dose-titration phase (during the first phase of the study, patients received s.c. apomorphine escalated in 2 mg increments from 2 mg to 10 mg, depending on tolerability). Outpatient evaluation visits were scheduled at 1 and 2 weeks, and 1, 4 and 6 months. Efficacy parameters included changes in UPDRS motor scores. Apomorphine significantly ($p < 0.05$) reduced UPDRS motor scores at 20, 40 and 90 minutes post-dose versus pre-dose at all evaluation visits. The efficacy of s.c. apomorphine throughout this open-label outpatient study suggest that it is suitable for the long-term acute treatment of “off” periods in patients with advanced Parkinson’s disease (Trosch et al., 2008).

For the Management of Morning Akinesia in Parkinson‘s disease time to “On” (TTO) and percent of dose failures during the L-dopa baseline period and Apomorphine treatment period (FAS; n = 88) and motor symptoms in PD patients who experienced delayed onset of their oral Levodopa medication taken upon awakening (Early Morning “Off” = EMO) were measured before and after treatment with subcutaneous Apomorpine Pen injections. 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. Almost all subjects (95.5%) showed improvement in time-to-”On” (Isaacson et al., 2017).

9.3 Clinical Trials - Continuous Therapy

Clinical utility of apomorphine s.c. infusion therapy was assessed in patients with parkinsonism and motor fluctuations and sought evidence for alterations in drug response resulting from chronic treatment.

Continuous s.c. apomorphine infusions during waking hours are recommended for all patients with refractory motor fluctuations (“on-off” effects) that cannot be managed by oral medication, or less than six intermittent s.c. injections of apomorphine (Lees et al., 2002).

The continuous s.c. infusion of apomorphine can reduce “off” time by more than 50% (up to 85%) and lessen pre-existing levodopa dyskinesias significantly. There are reports with a mean follow up of up to more than 100 months (Ceballos-Baumann, 2011).

Six out of seven patients with PD were treated with s.c. infusions of apomorphine administered during waking hours for 3 months. At the beginning and the end of the study, test doses of apomorphine (12.5 - 100 µg/kg i.v. over 10 minutes) were administered to establish a dose-response curve. Over the study, the patients reported a significant improvement in the number of “on” hours experienced per day and substantially reduced the dose and frequency of levodopa and other anti-Parkinson medications. No average change in apomorphine dose-response relationships or pharmacokinetics was observed during the study. However, two patients lowered the infusion rate during the 3-month observation and exhibited higher drug levels and longer responses following test doses of apomorphine given at the end of the study. Although pragmatic concerns with the use of infusion pumps solutions and adverse effects limited the overall benefit afforded by the treatment, this kind of drug treatment was found to be useful in selected patients with severe parkinsonism and fluctuations (Gancher et al., 1995).

Twenty parkinsonian patients with moderate to severe motor fluctuations and dyskinesia consented to participate in a randomized study to evaluate the comparative efficacy of apomorphine and lisuride. In one group of 10 patients apomorphine was administered at individually adjusted doses for 12 hours during waking hours. Efficacy was formally evaluated after 6, 12, and 24 months using the Abnormal Involuntary Movement Scale (KCRS) and self-rating evaluation forms. Mean apomorphine requirement was 3.2 mg/hr, plus 327±324 mg/day of oral levodopa. Dose requirements did not significantly change over the 2-year infusion therapy in both treatment groups. Parkinsonian symptoms improvement, as expressed by the KCRS score was about 74% with apomorphine (from 52.8± 13.8 to 15.1±9.1). Apomorphine produced a significant reduction in “off” time and a reduction in dyskinesia severity. In addition, apomorphine improved diphasic dystonia and peak-dose dyskinesia remarkably while the effect on the benefit of dose dyskinesia was minimal (Stocchi et al., 1993).
Reduced levodopa medication was confirmed in a study with the clinical data of 30 patients who received continuous s.c. apomorphine infusion for at least five years. The 30 fluctuating parkinsonian patients had been previously treated with oral levodopa preparation and other anti-parkinsonian medication. At the beginning of apomorphine infusion, the patients, 21 men and 9 women, had a mean age of 62.0 ± 8.5 years, a mean duration of disease of 14.8 ± 5.5 years, and a severity of disease of 4.2 ± 0.8 on Hoehn and Yahr stage. They were on pharmacological treatment for 14.6 ± 4.7 years, with a mean levodopa dosage of 708 ± 245 mg/day, given, on average, 4.1 ± 2.3 times daily. The treatment with apomorphine was started at the initial dosage of 2 mg/h and the rate gradually increased according to the therapeutic requirements of the patients. Apomorphine is a potent water-soluble dopamine receptor agonist that has been shown to successfully control motor fluctuation when subcutaneously infused in complicated parkinsonian patients (Stocchi et al., 2001).

In a prospective follow-up study for a period of two years the effectiveness and decrease of dyskinesias during the waking period was investigated. Following an apomorphine challenge test to assess responsiveness, 12 patients

Data Continuous s.c. Apomorphine Therapy

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Patient Characteristics [A]																		
Number of patients	7	9	14	10	22	7	25	34	11	12	12	12	13	82	12	23	53	99
Age (years)	59	52	60.2	60	60.6	61.1	64.7	nr	nr	64.3	54	61.3	59	67	58	48,4	63,6	61,6
Duration of disease (years)	17	15	12.4	11.5	19.2	17.6	16	10	13.4	14.4	10	14.5	10	14.3	9	13,9	11,8	13,6
Hoehn & Yahr stage	3-5	5	3.8	3.7	nr	4	4.5	nr	nr	4.5	3.7	4	3	nr	≥3	4,2	2-5	nr
Follow-up (months)	11	10	26	12	36	3	44	30	12	24	24	6	12	19.9	30	12	12	12
Apomorphine Therapy [A]																		
Duration (h per day)	8-12	12-24	24	12	wh	wh	24	nr	nr	12	wh	13.4	wh	10-16.5	10-16	15,1	16	14,1
Dosage (mg/h)	nr	5.4/2 [D]	6.8	3.2	nr	4.2	4	nr	nr	nr	6-8	nr	nr	5.03	nr	3,5	4,7	3,8
Bolus (mg)	nr	2.2	0	nr	nr	0	1,6	nr	nr	nr	nr	2.5	nr	nr	nr	3,0	nr	nr
Dosage (mg per day)	29.7	93	151.7	38.4	70	50.4	112.5	70	48	31.4	100	77.7	74.8	72	83,4	62,6	74,9	55,7
Change towards Time before Treatment Start [A]																		
Time in „off“ %	-85	-67	-77	-57	-59	-58	-50	-42	-40	-80	-60	-38	-51	-79.4	-49	-36	-36,92	-48,48
Time in „on“ without dyskinesia %	nr	nr	nr	nr	nr	nr	12	nr	nr	61	nr	nr	nr	nr	7	±0	36,9	39,78
Intensity of Dyskinesia	-45	-20	nr	-40	nr	nr	-14	nr	nr	nr	-48	-58	3	-31.1	-5	nr	nr	nr
Daily L-dopa dosage	-39	-53	-81	-48	15.7	-50	-50	-18	-30	-23	-52	-55	-29	-32.9	nr	-26	-22,6	-18,5

nr= nothing to report, wh= waking hours, [A]average, [D]during day/night

1. Chaudhuri et al. 1988, 2. Pollak et al. 1990, 3. Kreczy-Kleedorfer et al. 1993, 4. Stocchi et al. 1993, 5. Hughes et al. 1993, 6. Gancher et al. 1995, 7. Pietz et al. 1998, 8. Chaudhuri et al. 1999 acc. to Lees 2001, 9. Vanderheyden et al. 1999 acc.to Lees 2001, 10. Kanovsky et al. 2002, 11. Morgante et al. 2004, 12. Katzenschlager et al. 2005, 13. De Gaspari et al. 2006, 14. García Ruiz et al. 2008, 15. Antonini et al. 2011, 16. Drapier et al., 2012, 17. Katzenschlager et al., 2018, 18. Isaacson et al.2025

Table 8 (adapted): Overview of apomorphine continuous s.c. infusion studies (Hagell et al., 2014)

were treated with continuous subcutaneous apomorphine, while their daily dose of levodopa was slowly reduced. The differences in the occurrence of biphasic dyskinesia at onset and at months 6, 12 and 24 were all significant ($p \geq 0.05$) while the mean daily doses of levodopa reduced from 1650 mg to 1250 mg at month 6, 1150 mg at month 12 and 1270 mg at month 24. This significant reduction of dyskinesias has major long-term effects, and remained stable over years (Kanovský et al., 2002).

Treating patients with steady-state plasma levels of apomorphine throughout the waking day and minimising additional pulsatile stimulation either by oral dopaminergic medication or bolus parenteral injections of apomorphine has been reported. Sixty-four patients were treated with apomorphine pumps and 45 of these successfully converted to monotherapy, managing to discontinue all other forms of dopaminergic stimulation during the daytime treatment period with apomorphine. Patients were followed up for a mean of 33.8 months (range, 4 - 108 months) and clinical data analysed retrospectively. The mean maintenance dose of apomorphine was 98 mg per 24 hours (monotherapy group: 103 mg/24 hours; polytherapy group: 93 mg/24 hours), which did not significantly increase at final follow-up. There was a mean maximum dyskinesia reduction of 64% in the monotherapy group, compared to 30% in those continuing on polytherapy ($p < 0.001$), despite a maintained increase in “on” time (monotherapy group: 55%, $p < 0.005$; polytherapy group: 50%, $p = 0.05$). Fifteen patients failed to successfully convert to monotherapy but benefited nonetheless, and only 3 failed apomorphine infusional therapy altogether. Reasons for failure were mixed, including difficulty with compliance and adverse effects. There was a significantly higher success rate in patients able to manage the treatment either independently or with the help of their caregiver. The results confirm that s.c. apomorphine monotherapy can reset peak-dose dyskinesia threshold in levodopa-treated patients and further reduce “off” period disability after all available forms of oral medication, including long-acting dopamine agonists, have been tried (Manson et al., 2002).

In a prospective study the antidyskinetic effect of continuous s.c. apomorphine therapy has been assessed. Twelve patients with a diagnosis of PD and with “on-off” fluctuations and disabling dyskinesias who were scheduled to start apomorphine pump treatment underwent acute levodopa and apomorphine challenges at baseline and 6 months later. At 6 months, mean apomorphine dose was 75.2 mg per day and the mean levodopa dose had been reduced by 55%. Daily “off” time in patients‘ diaries was reduced by 38% (2.4 hours). The levodopa challenges showed a reduction of 44% in AIMS and 40% in Goetz scores (both $p < 0.01$). Apomorphine challenges showed a reduction of 39% in AIMS and 36% in Goetz scores (both $p < 0.01$). Patients‘ self-assessment scores reflected these significant changes. Dyskinesia improvement correlated with reduction in oral medication and with the final apomorphine dose ($p < 0.05$). The study confirmed marked dyskinesia reduction on continuous s.c. apomorphine therapy, paralleled by reduced dyskinesias during dopaminergic challenge tests. These results also support the concept that replacement of short-acting oral antiparkinsonian medication with continuous dopamine receptor stimulation may reverse, at least partially, the sensitisation process believed to mediate the development of drug-induced dyskinesias in PD (Katzenschlager et al., 2005).

Clinical and neuropsychological 12-month outcome following s.c. apomorphine infusion and chronic deep brain stimulation of the subthalamic nucleus (STN-DBS) were compared in patients with advanced PD and medically untreatable fluctuations. They underwent either apomorphine (13 patients) or STN-DBS (12 patients). All patients were clinically (UPDRS-III, AIMS, 12h “on-off” daily) and neuropsychologically (MMSE, Hamilton-17 depression, NPI) evaluated at baseline and at 12 months. Apomorphine was discontinued at night. Apomorphine treatment (74.78±24.42 mg/day) resulted in significant reduction in “off” time (-51%) and no change in AIMS at 12 months evaluation. Levodopa equivalent medication doses were reduced from 665.98±215 mg/day at baseline to 470±229 mg/day. MMSE, NPI, and Hamilton depression scores were unchanged. At 12 months STN-DBS resulted in significant clinical improvement in terms of reduction in daily “off” time (-76%) and AIMS (-81%) as well as levodopa equivalent medication doses (980±835 to 374±284 mg/day). Four out of 12 patients had stopped oral medications. MMSE was unchanged (from 28.6±0.3 to 28.4±0.6). Hamilton depression was also unchanged, but NPI showed significant worsening (from 6.58±9.8 to 18.16±10.2; $p < 0.02$). Category fluency also declined. Both apomorphine and STN-DBS resulted in significant clinical improvement. STN-DBS resulted in greater reduction in dopaminergic medications and provided 24 h motor benefit. However, STN-DBS, unlike apomorphine, appears to be associated with significant worsening on NPI resulting from long term behavioural problems in some patients (De Gaspari et al., 2006).

The evolution of patients with PD and severe motor fluctuations treated long-term with continuous s.c. apomorphine infusion was evaluated in 82 patients (mean age, 67±11.07; disease duration, 14.39±5.7 years). These patients were treated long-term (for at least 3 months) with continuous s.c. apomorphine infusion and tolerated the procedure without serious side effects. The baseline data of these 82 patients (before continuous s.c. apomorphine infusion) were compared with those obtained from the last follow-up visit of each patient. The mean follow-up of continuous s.c. apomorphine infusion was 19.93±16.3 months. Mean daily dose was 72.00±21.38 mg infused over 14.05±1.81 hours. The authors found a statistically significant reduction in “off” hours, according to self-scoring diaries (6.64±3.09 vs. 1.36±1.42 hours/day, $p < 0.0001$), total and motor UPDRS scores ($p < 0.0001$), dyskinesia severity ($p < 0.0006$), and equivalent dose of antiparkinsonian therapy (1,405±536.7 vs. 800.1±472.9 mg of levodopa equivalent units $p < 0.0001$). They concluded that continuous s.c. apomorphine infusion was an effective option for patients with Parkinson’s disease and severe fluctuations, poorly controlled by conventional oral drug treatment (García Ruiz et al., 2008).

25 PD patients treated with either STN-DBS (n = 13) or CSAI (n = 12) were prospectively assessed in a 5-year follow-up. Cohorts were matched for disease duration and severity of motor complications. Baseline clinical and neuropsychological status did not differ among cohorts. Patients were assessed with the UPDRS, MMSE, HAMD-17 and Neuropsychiatric Inventory (NPI). The average apomorphine dose at last visit was 83.4 ± 19.2 mg/day and average treatment duration was 30 months. At 1-year as well as at last follow-up (intention-to-treat analysis), both therapies decreased daily off-time but only STN-DBS reduced dyskinesia duration and severity. Decrement of medications was greater with STN-DBS. There was a significant worsening of NPI after STN-DBS, primarily because four subjects developed apathy (Antonini et al., 2011).

23 advanced parkinsonian patients (mean age: 62.3 years; mean disease duration: 13.9 years) whose dopa-resistant axial motor symptoms and/or cognitive decline constituted contraindications for STN-DBS were assessed. Daily OFF time, recorded in a 24-h diary, was reduced by 36% and ON time improved by 48%. There was a significant reduction (26%) in mean oral levodopa equivalent dose. Dopa-resistant axial symptoms and neuropsychological performance remained stable. No adverse event was noted and none of the patients needed to take clozapine at any time. APO is both safe and effective in advanced parkinsonian patients with untreatable motor fluctuations, for whom STN-DBS is contraindicated due to dopa-resistant axial motor symptoms and/or cognitive decline. As such, it should be regarded as a viable alternative for these patients (Drapier et al., 2012).

Subcutaneous apomorphine infusion is a clinically established therapy for patients with Parkinson’s disease with motor fluctuations not optimally controlled by oral medication. In a randomised, placebo-controlled, double-blind, multicentre trial, we enrolled patients at 23 European hospitals who had been diagnosed with Parkinson’s disease more than 3 years previously and had motor fluctuations not adequately controlled by medical treatment. Patients received 3–8 mg/h apomorphine or placebo saline infusion during waking hours (16 h a day [range 14–18 was acceptable]) for 12 weeks. 128 patients were screened for eligibility and 107 were randomly assigned, of whom 106 were included in the full analysis set (n=53 in both groups). Apomorphine infusion (mean final dose 4·68 mg/h [SD 1·50]) significantly reduced off time compared with placebo (–2·47 h per day [SD 3·70] in the apo-

morphine group vs –0·58 h per day [2·80] in the placebo group; difference –1·89 h per day, 95% CI –3·16 to –0·62; p=0·0025). Apomorphine was well tolerated without any unexpected safety signals. Apomorphine infusion results in a clinically meaningful reduction in off time in patients with Parkinson's disease with persistent motor fluctuations despite optimised oral or transdermal therapy (Katzenschlager et al., 2018).

9.4 Toxicology

9.4.1 Repeated Dose/Subacute Toxicity

Repeat dose subcutaneous toxicity studies reveal no special hazard for humans, beyond the information included in other sections of the SmPC (SmPC, 2023).

Gancher et al. (1989) studied the renal effects of a two-week subcutaneous infusion of apomorphine in rats. Drug-treated rats did not exhibit any change in creatinine clearance, or fractional excretion of sodium and potassium. Renal histology showed no specific changes related to the application of the drug. A small increase in urinary N-acetylglucosaminidase, was measured but a second tubular enzyme showed no change. Parenteral administered apomorphine was not associated with renal toxicity (Studies of renal function in animals chronically treated with apomorphine, 1989).

In addition, Gancher, Woodward, Boucher & Nutt 1989 studied the effect of apomorphine administration by subcutaneous injection, subcutaneous infusion and intravenous infusion on 15 volunteers with parkinsonism. Initial doses were 20-30 µg/kg administered either once, or up to 3 times daily on each study day. There was no evidence of nephrotoxicity; blood urea, nitrogen, creatinine, lactic dehydrogenase isoenzymes, urinalyses and urinary N-acetyl-beta-D-glucosaminidase did not change over the study period. The drug absorption, volume of distribution, plasma clearance and half-lives were similar for each method of administration (Gancher et al., 1989).

Acute and subacute testing of apomorphine HCL has been reported in studies with daily doses ranging up to 300 mg/kg in low vertebrates (amphibian and birds) and to up to 10 mg/kg in higher mammalians. In mammalans, doses of apomorphine HCL are tolerated up to 13 mg/kg in a single bolus s.c. injection. Doses at or above this amount have been reported lethal in mouse, although, the LD50 is considerably higher (>50 mg/kg) in these species. Continuous infusion of apomorphine has been tolerated in mammalians and reported to doses of 420µg/kg/h for 14 days. In primates, multiple doses of apomorphine HCL have been administered for up to four days at 100-400µg/kg without major adverse effects (Argiolas et al., 2001); (El-Rashidy et al., 2001).

9.4.2 Cytotoxicity

Gassen et al. (1996) demonstrated that apomorphine acts as a potent antioxidative and protects lipids and proteins from radical damage. These data suggest that apomorphine, similar to levodopa and dopamine, displays scavenger properties at low doses, whereas at high concentrations it causes cell death. They compared dopamine with apomorphine, indicating that apomorphine is more potent by a factor of 20 (Gassen et al., 1996).

Many catechol derivatives are currently used as drugs, even if they produce reactive oxygen species that may be related to tissue damage. Among them, apomorphine, a potent dopamine agonist, displays efficient anti-parkinsonian properties, but the sequel of its oxidant and toxic properties have been poorly investigated in vitro. El-Bácha et al. studied the effect of apomorphine cytotoxicity by incubating cultures of rat glioma C6 cells and primary cultures of neurons with different concentrations of the drug. Apomorphine showed a dose and time dependent effect on cell death. The ED50 of apomorphine after 48h was about 200mM in vitro. The cytotoxic effects induced by apomorphine were correlated to its autoxidation, leading to the formation of reactive oxygen species, semi-quinones, quinones, and melanin-like pigments. Rat glioma C6 cells that underwent treatment with 400mM apomorphine displayed features of necrosis, including loss of membrane integrity, degeneration of mitochondria, and DNA fragmentation after six hours. Thiols, such as cysteine, N-acetyl-L-cysteine, and glutathione, significantly protected cultured neurons and C6 cells against apomorphine-induced cytotoxicity. Thiols also inhibited apomorphine autoxidation. These data strongly suggest that apomorphine cytotoxicity towards neurons and rat glioma C6 cells results from an intracellular oxidative stress. In conclusion, the present study shows that apomorphine induces cytotoxicity in both rat glioma C6 cells and rat cultured neurons in vitro. However, there is no obvious evidence of in vivo apomorphine neurotoxicity or evidence that it is altering the natural progression of the disease (El-Bachá, et al., 2001).

Pardini et al. (2003) observed that apomorphine has an anti-proliferative effect on the CHO-K1 (cell line from the ovary of an adult Chinese hamster) cell line. This study showed how R-APO (R-apomorphine), in a manner similar to dopamine, induces in vitro a dose-dependent cytotoxic effect on CHO-K1 cells. CHO-K1 cells were exposed to 10, 25 and 50µM of R-APO for 24, 48 and 72h. After 3 days of incubation with different doses of R-APO the CHO-K1 cell line showed specific markers of apoptotic cell death, such as the intra-nucleosomal DNA fragmentation (Pardini, et al., 2003). The authors confirmed a dose-dependent toxicity of R-APO on the CHO-K1 cell line, as previously described (Maggio et al., 2000).

9.4.3 Genotoxicity

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 (SmPC, 2023).

Genotoxicity of apomorphine was evaluated using Ames tests, DNA repair-deficient as well as DNA repair-proficient Bacillus subtilis strains. In the absence of an S9 liver homogenate, apomorphine induced frameshift mutations in Salmonella typhimurium, mainly in strain TA 1537. No indication of DNA-damaging effects was observed in Bacillus subtilis. The mode of action of apomorphine and the relevance of the positive Ames test data were investigated. Glutathione in physiological concentrations reduced the mutagenic effect of apomorphine in a dose-dependent way in both the presence and absence of an S9 liver homogenate. The S9 liver homogenate also reduced the mutagenicity of apomorphine. By comparing the effects of a complete S9 liver homogenate mix with those of a preparation without glucose-6-phosphate and nicotinamide adenine dinucleotide phosphate (NADP), it was evident that the S9 liver homogenate also had an activating effect, potentially underscored using standard conditions. Apomorphine was not mutagenic under anaerobic conditions. Superoxide dismutase and catalase reduced the mutagenic effect of apomorphine. All test conditions that reduced the mutagenic effect also inhibited the dark discolouration of test plates, indicating a prolongation of apomorphine oxidation. Based on results it could be concluded that oxidation of apomorphine leads to mutagenic products that induce frameshift mutations in Salmonella typhimurium. This oxidation was prevented both by glutathione in concentration well below physiological levels or by catalases and superoxide dismutases. Under these conditions, apomorphine was non-mutagenic in therapeutic concentrations as well as at higher dose levels (Suter et al., 1984).

The genotoxic activity of apomorphine in bacteria might be related to its ability to intercalate into DNA, or to its pro-oxidant effects, or generation of superoxide radicals during autoxidation, hence promoting frameshift mutations without inducing oxidative mutagenesis. This idea is supported by the higher mutagenic frameshift induced by 8-oxo-apomorphine-semiquinone (8-OASQ) a more aromatic structural compound which favours intercalation into DNA. The neurotoxic effects of apomorphine have been correlated with its auto oxidation products such as superoxide radical, H2O2 and quinone and semiquinone compounds. It is possible that 8-OASQ is one of these cytotoxic products, since it induced oxidative mutagenesis in bacteria, adaptive response in Salmonella cerevisiae as well as DNA damage and alterations of oxidative parameters in the brain (Picada et al., 2005).

9.4.4 Carcinogenicity

No carcinogenicity studies have been performed (SmPC, 2023).

9.4.5 Reproductive and Developmental Toxicity
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 (SmPC, 2023).
The potential for reproductive toxicity in males was assessed based on a rat study (a fertility study in male rats) and a 6-month study in dogs after subcutaneous administration. Dosages of apomorphine were: placebo (ascorbic acid, sodium metabisulfate in saline solution), 0.8, 2, and 8 mg/kg/day in the 13-week study in rats, with 8 mg/kg/day used for only 9 weeks. No adverse effect was observed in any of the reproductive parameters in the study. Based on this study in two species (rodent and non-rodent) it was demonstrated the absence of any potential reproductive toxicity for apomorphine in males. These studies also demonstrated a safety margin of at least 100-fold, based on comparison to maximum plasma levels of the clinical dose used to treat erectile dysfunction (Youssef et al., 1999).

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 (SmPC, 2023).

9.4.6 Other Toxicity Studies
Montastruc et al. studied tolerance to the pharmacological effects of apomorphine in anaesthetised dogs. Changes in blood pressure, heart rate, plasma noradrenaline level, rectal temperature, respiratory rate and retching plus vomiting were compared after administration of apomorphine or saline in dose 200 µg/kg i.v. as a bolus at different time intervals; 30, 120 and 720 min. The first administration of apomorphine induced a significant decrease in blood pressure and rectal temperature, a marked increase in heart rate with no change in noradrenaline plasma levels or respiratory rate. Vomiting occurred in 71% of animals. A second administration of apomorphine 30 min later did not alter blood pressure or heart rate. In contrast, the magnitude of apomorphine-induced changes in blood pressure and heart rate was similar to that observed after the first administration when apomorphine was given 120 and 720 min later. The apomorphine-induced decrease in rectal temperature evoked by a second dose of apomorphine was less marked given 30 and 120 min after the first dose and unchanged when given 720 min later. The number of animals exhibiting retching and vomiting was lower when apomorphine was reinjected after 30 min-than when the time between two successive injections of apomorphine was 120 or 720 min. These results show that tolerance to apomorphine involves its cardiovascular, hypothermic and emetic effects. The time course of tolerance to repeated injections of apomorphine is longer for its hypothermic than for its hypotensive or emetic effect. This suggests a tissue-specific regulation of D2 dopamine receptors to repeated injections of apomorphine (Montastruc, et al., 1996).

Nakayama et al. investigated electrophysiological and haemodynamic effects of apomorphine in dogs. The study was conducted to monitor cardiovascular functions in dogs given the standard emetic dose of apomorphine, 0.05mg/kg or 10 times that. There were no changes produced by the 0.05 mg/kg dose of apomorphine except for a decrease in mean systemic arterial pressure (AP) at 1 through 15 min recordings. For the 0.5 mg/kg dose, there were reductions in systemic vascular resistance at the 1 and 5 min recordings and in AP at 1 through 60 min recordings. At the usual emetic dose of 0.05 mg/kg apomorphine resulted in no signs of cardiovascular toxicity and at 0.5 mg/kg cardiovascular changes were minimal (Nakayama et al., 2001).

10. COMPARISON WITH OTHER PARKINSON´S DRUGS

In terms of on demand treatments intermittent injection with subcutaneous Apomorphine is the speediest to take effect. It has the longest clinical experience. The decision to adopt the use of an on-demand therapy might have to do with a patient's personalized view of the experience in living with motor fluctuations (Martinez-Nunez et al., 2023).
L-Dopa misdistribution to non-dopaminergic cells is a significant hurdle, regardless of continuous administration. Even the subcutaneous route of levodopa can not overcome challenges (Demailly et al., 2024).
While all continuous device-assisted therapies (DATs) including deep brain stimlation, duodenal and subcutaneous infusions are approved for the treatment of motor fluctuations, patient profiles vary significantly, necessitating an individualized pproach for differential indication (Koeglsperger et al., 2025).
Therapy selection should be personalized based on effectiveness, tolerability, and patient preference, considering factors like disease duration, symptoms, cognitive function, and caregiver support (Reese et al. 2025).
Although several open-label studies compared pump therapies and deep brain stimulation (Alegret et al. 2004; Gaspari et al. 2006; Antonini et al. 2011; Merola et al. 2011; Elia et al. 2012; Dafsari et al. 2019; Liu et al. 2019), there are no head-to-head comparisons between these therapies and these studies did not include subcutaneous levodopa infusions. Similar to deep brain stimulation non-levodopa-responsive symptoms may not benefit from pump therapies including subcutaneous levodopa infusions (Koeglsperger et al., 2025).

11. CONCLUSIONS/SUMMARY

The administration of apomorphine by s.c. injection or infusion has been shown to significantly reduce "off" time in those patients with refractory, levodopa-induced "on-off" fluctuations in advanced PD.
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 (Trenkwalder et al., 2015).

Continuous subcutaneous apomorphine infusions reduce motor fluctuations and dyskinesia, and improve motor scores while in "on" periods.
Intermittent pulsatile stimulation with apomorphine appears to show less favourable results than the continuous mode of administration, which may reduce erratic and intermittent striatal dopamine receptor activation, hence improving motor fluctuations and dyskinesias. The latter mode of administration is likely to be more physiological to stimulate dopaminergic receptors. The reduction in dyskinesias may reflect striatal dopamine receptor desensitization (Deleu et al., 2002).

The improvement in dyskinesias suggests that their pathophysiological mechanism is based on the reversal of the imbalance in neuropeptide expression and receptor activity in the direct and indirect striato-pallidal pathways and interconnecting circuitry of the basal ganglia (Piccini et al., 1997); (Brotchie, 1998).
A significant improvement is observed in the UPDRS motor scores after long-term therapy with subcutaneous apomorphine. In addition, the data from long-term studies do not indicate that there is any significant tolerance to the antiparkinsonian effect of apomorphine.
With regard to the adverse effect profile, apomorphine continuous infusion treatment results in a higher incidence of neuropsychiatric adverse effects that restrict the therapy predominantly to parkinsonian patients with normal cognitive function.

Apomorphine is effective on non-motor symptoms (NMS) including mood and apathy, perceptual problems, memory, gastro-intestinal and urinary domains (Martinez-Martin et al., 2011).

When "off"periods are associated with intractable pain, apomorphine should be considered as an important option to relieve the patients' discomfort (Torti et al., 2019).

Subcutaneous infusion of apomorphine mitigates pharmacodynamic issues by lessening the dependence on oral levodopa administration (Demailly et al., 2024).

12. LITERATURE

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Dacepton® 10 mg/ml Solution for injection or infusionin in 5 ml ampoule. QUALITATIVE AND QUANTITATIVE COMPOSITION, 1 ml solution contains 10 mg apomorphine hydrochloride hemihydrate. 5 ml solution contains 50 mg apomorphine hydrochloride hemihydrate. Excipient: Sodium metabisulphite (E223) 1 mg per ml. PHARMACEUTICAL FORM: Solution for injection/infusion. The solution is clear and colourless or almost colourless to slightly yellow, practically free from visible particles. pH of 3.0 – 4.0. CLINICAL PARTICULARS: 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 injections: Patients selected for treatment with Dacepton® 10 mg/ml 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. Adults: Administration: Dacepton® 10 mg/ml is for subcutaneous use by intermittent bolus injection. Dacepton® 10 mg/ml may also be administered as a continuous subcutaneous infusion by minipump and/or syringe-driver. 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 (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 (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 varies between individuals but, once established, remains relatively constant for each patient. Precautions on continuing treatment: The daily dose of Dacepton® 10 mg/ml varies widely between patients, typically within the range of 3 to 30 mg, given as 1 to 10 injections and sometimes as many as 12 separate injections per day. It is recommended that the total daily dose of apomorphine hydrochloride should not exceed 100 mg and that individual bolus injections should not exceed 10 mg per hour. 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. Continuous infusion: 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 as follows: Continuous infusion is started at a rate of 1 mg apomorphine hydrochloride (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. Unless the patient is experiencing severe night-time problems, 24 hour infusions are not advised. Tolerance to the therapy does not seem to occur as long as there is an overnight period without treatment of at least 4 hours. In any event, the infusion site should be changed every 12 hours. Patients may need to supplement their continuous infusion with intermittent bolus boosts, as necessary, and as directed by their physician. A reduction in dosage of other dopamine agonists may be considered during continuous infusion. Paediatric population: Dacepton®10 mg/ml 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 Dacepton® 10 mg/ml. The management of elderly patients treated with Dacepton® 10 mg/ml 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: In patients with respiratory depression, dementia, psychotic diseases or hepatic insufficiency. Apomorphine hydrochloride must not be administered to

patients who have an “on” response to levodopa which is marred by severe dyskinesia or dystonia. Dacepton® 10 mg/ml should not be administered to patients who have a known hypersensitivity to apomorphine or any excipients of the medicinal product. Dacepton® 10 mg/ml is contraindicated for children and adolescents under 18 years of age. Special warnings and precautions for use: Apomorphine hydrochloride 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 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 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 other dopamine agonists can be associated with sudden sleep onset episodes, 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 must refrain from driving or operating machines. Furthermore, a reduction of dosage 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 contains sodium metabisulphite which may rarely cause severe allergic 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 are almost certain to be taking concomitant medications for their Parkinson‘s disease. In the initial stages of apomorphine hydrochloride 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. If neuroleptic medicinal products have to be used in patients with Parkinson‘s disease treated by dopamine agonists, a gradual reduction in apomorphine dose may be considered when administration is by minipump and or syringe-driver (symptoms suggestive of neuroleptic malignant syndrome have been reported rarely with abrupt withdrawal of dopaminergic therapy). 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. Based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron, the concomitant use of apomorphine with ondansetron is contraindicated. Pregnancy: 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 should not be used during pregnancy unless clearly necessary. Breast-feeding: 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 should be made taking into account the benefit of breast-feeding to the child and the benefit of Dacepton® 10 mg/ml to the woman. Effects on ability to drive and use machines: Apomorphine hydrochloride 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. 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 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 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: pomorphine 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 domperidone. 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 of suspected adverse reactions: 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: 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. PHARMACOLOGICAL PROPERTIES: 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. PHARMACEUTICAL PARTICULARS: List of excipients: Sodium metabisulphite (E223). Hydrochloric acid (for pH-adjustment). Sodium hydroxide (for pH-adjustment). Water for injections. Incompatibilities: This medicinal product must not be mixed with other medicinal products. Shelf life: Unopened: 30 months. Once opened, use immediately. Discard any unused contents. Shelf-life after dilution (if applicable): Chemical and physical in-use stability has been demonstrated for up to 24 hours at 15°C - 25°C when the product is diluted with sodium chloride 0.9%. From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 15°C to 25°C, unless opening and dilution has taken place in controlled and validated aseptic conditions. Special precautions for storage: Keep the ampoules in the outer carton in order to protect from light. Do not refrigerate or freeze. Nature and contents of container: Clear, colourless type I glass ampoules containing 5 ml solution for injection, in packs of 1, 5 or 10 ampoules. Bundle packs: 5 x 1, 10 x 1, 2 x 5, 5 x 5, 10 x 5, 3 x 10 and 10 x 10. Not all pack sizes may be marketed. Special precautions for disposal: 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. For single use only. Any unused product should be disposed of in compliance with local requirements. Continuous infusion and the use of a minipump and or syringe-driver. The choice of which minipump and or syringe-driver to use, and the dosage settings required, will be determined by the physician in accordance with the particular needs of the patient. Dacepton® 10 mg/ml is compatible with sodium chloride solution 0.9 % (9 mg/ml). MARKETING AUTHORISATION HOLDER: EVER Neuro Pharma GmbH, A-4866 Unterach, Austria. MARKETING AUTHORISATION NUMBER: AT/H/0364/001/DC. Legal Category: POM. Last revision: October 2023.

Dacepton 5 mg/ml solution for infusion in 20 ml vial. QUALITATIVE AND QUANTITATIVE COMPOSITION: 1 ml contains 5 mg apomorphine hydrochloride hemihydrate, 20 ml contain 100 mg apomorphine hydrochloride hemihydrate. Excipient with known effect: Sodium metabisulphite (E223) 1 mg per ml, Sodium chloride 8 mg per ml. PHARMACEUTICAL FORM: Solution for infusion. Clear and colourless to slightly yellow solution, free from visible particles, pH of 3.3 – 4.0. Osmolality: 290 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® 5 mg/ml solution for infusion: Patients selected for treatment with Dacepton® 5 mg/ml solution for infusion 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. It is essential that the patient is established on domperidone, usually 20 mg three times daily, for at least two days prior to initiation of therapy. 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® 5 mg/ml solution for infusion. Adults: METHOD OF ADMINISTRATION: Dacepton 5 mg/ml solution for infusion is a pre-diluted vial intended for use without dilution for subcutaneous use and to be administered as a continuous subcutaneous infusion by minipump and/or syringe-driver. It is not intended to be used for intermittent injection. 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 to slightly yellow and particle free solution should be used. POSOLOGY: Continuous Infusion 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 as follows: The choice, of which minipump and / or syringe-driver to use, and the dosage settings required, will be determined by the physician in accordance with the particular needs of the patient. DETERMINATION OF THRESHOLD DOSE: The threshold dose for continuous infusion should be determined as follows: Continuous infusion is started at a rate of 1 mg apomorphine hydrochloride hemihydrate (0.2 ml) per hour then increased according to the individual response each day. Increases in the infusion rate should not exceed 0.5 mg at intervals of not less than 4 hours. Hourly infusion rates may range between 1 mg and 4 mg (0.2 ml and 0.8 ml), equivalent to 0.014-0.06 mg/kg/hour. Infusions should run for waking hours only. Unless the patient is experiencing severe night-time problems, 24 hour infusions are not advised. Tolerance to the therapy does not seem to occur as long as there is an overnight period without treatment of at least 4 hours. In any event, the infusion site should be changed every 12 hours. Patients may need to supplement their continuous infusion with intermittent bolus boosts, as necessary, and as directed by their physician. A reduction in dosage of other dopamine agonists may be considered during continuous infusion. ESTABLISHMENT OF 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® 5 mg/ml solution for infusion varies widely between patients, typically within the range of 3-30 mg. It is recommended that the total daily dose of apomorphine hydrochloride hemihydrate should not exceed 100 mg. 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® 5 mg/ml solution for infusion 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. In patients with respiratory depression, dementia, psychotic diseases or hepatic insufficiency. Apomorphine hydrochloride hemihydrate treatment must not be administered to patients who have an “on” response to levodopa which is marred by severe dyskinesia or dystonia. Dacepton® 5 mg/ml solution for infusion 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. 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 dosage 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® 5 mg/ml solution for infusion contains sodium metabisulphite which may rarely cause severe hypersensitivity reactions and bronchospasm. Dacepton® 5 mg/ml contains 3.4 mg sodium per ml. To be taken into consideration by patients on a controlled sodium diet. 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. If neuroleptic medicinal products have to be used in patients with Parkinson‘s disease treated by dopamine agonists, a gradual reduction in apomorphine dose may be considered when administrati-

on is by minipump and or syringe-driver (symptoms suggestive of neuroleptic malignant syndrome have been reported rarely with abrupt withdrawal of dopaminergic therapy). 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. 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® 5 mg/ml solution for infusion 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 breastfeeding or to continue/discontinue therapy with Dacepton® 5 mg/ml solution for infusion should be made taking into account the benefit of breast-feeding to the child and the benefit of Dacepton® 5 mg/ml solution for infusion 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: Common: Neuropsychiatric disturbances are common in parkinsonian patients. Dacepton® 5 mg/ml solution for infusion should be used with special caution in these patients. 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 / lightheadedness 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 domperidone. Skin and subcutaneous tissue disorders: Uncommon: Local and generalised rashes have been reported. eneral 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 of suspected adverse reactions 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: 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, 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 nigrostriatal 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), Sodium chloride, Hydrochloric acid (for pH-adjustment), water for injections: Incompatibilities: In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. SHELF LIFE: Unopened: 30 months. After opening and filling the drug product in syringes attached with infusion sets: chemical and physical in-use stability has been demonstrated for 7 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. Single use only. Discard any unused contents. Special precautions for storage: Keep the vials in the outer carton in order to protect from light. Do not refrigerate or freeze. NATURE AND CONTENTS OF CONTAINER: Clear glass vials, type I with bromobutyl rubber stopper and a flip-off cap, containing 20 ml solution for infusion, in packs of 1 or 5 vials. Bundle packs: 5 x 1, 10 x 1, 30 x 1, 2 x 5 and 6 x 5. 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. For single use only. Any unused medicinal product or waste material should be disposed in accordance with local requirements. Continuous infusion and the use of a minipump and or syringe-driver The choice of which minipump and or syringe-driver to use, and the dosage settings required, will be determined by the physician in accordance with the particular needs of the patient. MARKETING AUTHORISATION HOLDER: EVER Neuro Pharma GmbH, Oberburgau 3, 4866 Unterach, Österreich. MARKETING AUTHORISATION NUMBER: AT/H/0364/002/DC. Legal Category: POM. Date of last revision: October 2023.

Dacepton 10 mg/ml solution for injection in 3 ml 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. Based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron, the concomitant use of apomorphine with ondansetron is contraindicated. 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 breastfeeding 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: 18 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.

The Dacepton® Drug Profile was first discussed and proofed with friendly support by Jürgen Winkler, M.D., Professor of Neurology and Head Division of Molecular Neurology, University Hospital Erlangen, Germany, August 2011.

Last revision by Dr. Branislav Adamik, April 2025.

EVER PHARMA

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