5.3 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium metabisulphite (E223)
Hydrochloric acid for pH-adjustment
Sodium hydroxide for pH-adjustment
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened: 30 months
Shelf-life after first opening: immediate use

Shelf-life after dilution (if applicable):

Chemical and physical in-use stability has been demonstrated for up to 24 hours at 15 - 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 2°C to 8°C, unless opening and dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

Keep the ampoules in the outer carton in order to protect from light.

Do not refrigerate or freeze.

6.5 Nature and contents of container

Clear, colourless type I glass ampoules containing 5ml solution for injection, in packs of 1, 5 or 10 ampoules.

6.6 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 product should be disposed of in compliance with local requirements.

For 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® 10mg/ml is compatible with sodium chloride solution 0.9% (9mg/ml).

EVER PHARMA

ABBREVIATED PRESCRIBING INFORMATION. Consult Summary of Product Characteristics before prescribing. Dacepton® 10 mg/ml Solution for injection or infusion. Indication: The treatment of disabling motor fluctuations ("on-off" phenomena) in patients with Parkinson's disease which persist despite individually titrated treatment with levodopa (with a peripheral decarboxylase inhibitor) and/or other dopamine agonists. Dosage and Administration: Dacepton® is for subcutaneous use by intermittent bolus injection. Dacepton® may also be administered as a continuous subcutaneous infusion by minipump and/or syringe-driver. Apomorphine must not be used via the intravenous route. Patients selected for treatment with Dacepton® 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. Dacepton® 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®. The daily dose of Dacepton® 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. Contraindications: Dacepton® is contraindicated in patients with respiratory depression, dementia, psychotic diseases or hepatic insufficiency. Intermittent treatment with Dacepton® is not suitable for patients who have an "on" response to levodopa which is marred by severe dyskinesia or dystonia. Dacepton® should not be administered to patients who have a known hypersensitivity to apomorphine or any excipients of the medicinal product. Dacepton® is contraindicated for children and adolescents under 18 years of age. Pregnancy and lactation: Dacepton® should not be given to pregnant women unless clearly necessary. Interactions: 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. It is recommended to avoid the administration of apomorphine with other drugs known to prolong the QT interval. Concomitant use of apomorphine with ondansetron may lead to severe hypotension and loss of consciousness and is therefore contraindicated (see section 4.3). Such effects might also occur with other 5-HT3 antagonists. Precautions: Dacepton® 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) to areas of nodularity and induration. Dacepton® contains sodium metabisulphite which may rarely cause severe allergic reactions and bronchospasm. 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. Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including apomorphine. Side effects: 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. Common: Neuropsychiatric disturbances are common in parkinsonian patients. Apomorphine should be used with special caution in these patients. Neuropsychiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine hydrochloride therapy. 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 and headache. Dizziness / light-headedness and Yawning have been reported during apomorphine therapy. Nausea and vomiting, particularly when apomorphine treatment is first initiated, usually as a result of the omission of domperidone. Uncommon: Haemolytic anaemia and thrombocytopenia have been reported in patients treated with apomorphine. 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. Postural hypotension is seen infrequently and is usually transient. Breathing difficulties, local and generalised rashes, injection site necrosis and ulceration have been reported. Positive Coombs' tests have been reported for patients receiving apomorphine and levodopa. Rare: Eosinophilia has rarely occurred during treatment with apomorphine hydrochloride. Due to the presence of sodium metabisulphite, allergic reactions (including anaphylaxis and bronchospasm) may occur. Very rare: There have been case reports of patients who developed atrial fibrillation (transient or recurrent) after s.c. apomorphine administration. Apomorphine may produce heart conduction abnormalities such as QT/QTc prolongation. Not known: Patients treated with dopamine agonists for treatment of Parkinson's disease, including apomorphine, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation. Peripheral oedema has been reported. Presentations: 1 ml of Dacepton® contains 10 mg apomorphine hydrochloride. Each 5 ml ampoule Dacepton® contains 50 mg apomorphine hydrochloride. Each pack of Dacepton® contains 1, 5 or 10 clear glass ampoules of 5 ml. Marketing Authorisation Number: Dacepton® 10 mg/ml Solution for injection or infusion: AT/H0364/001/DC. Legal Category: POM. Date of last revision: October 2023. For further information please contact: EVER Neuro Pharma GmbH, A-4866 Unterach, Austria.

DAC/INT/04-2024/17

EVER PHARMA

Parkinson´s disease in the advanced stage:
It´s a dire existence. It´s odd. Really. Caught in a cage of stiffness and unability. **Dacepton® gets them back to life.**
As the strongest non selective dopamine agonist, Dacepton® shortens the "off"-phases[1] and reduces the intensity of dyskinesias[2].
Dacepton® is the therapy with continuous dopaminergic stimulation for advanced Parkinson´s disease via subcutaneous infusion.

1) Gunzler, 2009, 2) Kanovsky et al., 2002

SUBCUTANEOUS USE

Dacepton®
Apomorphine Hydrochloride

1. NAME OF THE MEDICINAL PRODUCT

Dacepton® 10mg/ml Solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1ml solution for injection or infusion contains 10mg apomorphine hydrochloride hemihydrate.

5ml solution for injection or infusion contain 50mg apomorphine hydrochloride hemihydrate.

Excipient: Sodium metabisulphite (1mg per ml)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

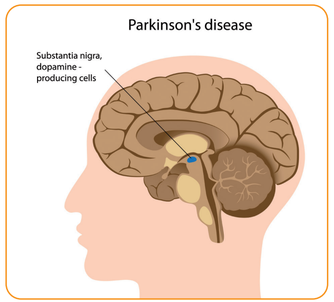
Solution for injection or infusion

The solution is clear and colourless to slightly yellow with a pH of 3.0 – 4.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The treatment of disabling motor fluctuations ("on-off" phenomena) in patients with Parkinson´s disease which persist despite individually titrated treatment with levodopa (with a peripheral decarboxylase inhibitor) and/or other dopamine agonists.



4.2 Posology and method of administration

Dacepton® 10mg/ml is for subcutaneous use by intermittent bolus injection.
Dacepton® 10mg/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.

Selection of Patients suitable for Dacepton® 10mg/ml injections:
Patients selected for treatment with Dacepton® 10mg/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.

It is essential that the patient is established on domperidone, usually 20mg three times daily for at least two days prior to initiation of therapy.

Dacepton® 10mg/ml 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® 10mg/ml.

Determination of the threshold dose
The appropriate dose for each patient is established by incremental dosing schedules. The following schedule is suggested:

1mg of apomorphine hydrochloride (0.1ml), 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 2mg of apomorphine hydrochloride (0.2ml) 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 40 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® 10mg/ml varies widely between patients, typically within the range of 3 to 30mg, 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 100mg and that individual bolus injections should not exceed 10mg 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, 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 1mg apomorphine hydrochloride (0.1ml) per hour then increased according to the individual response. Increases in the infusion rate should not exceed 0.5mg per hour at intervals of not less than 4 hours. Hourly infusion rates may range between 1mg and 4mg (0.1ml and 0.4ml), equivalent to 0.015 - 0.06mg/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 via the pump system as necessary, and as directed by their physician.

A reduction in dosage of other dopamine agonists may be considered during continuous infusion.

4.3 Contraindications

Dacepton® 10mg/ml is contraindicated in patients with respiratory depression, dementia, psychotic diseases or hepatic insufficiency.

Intermittent treatment with Dacepton® 10mg/ml is not suitable for patients who have an "on" response to levodopa which is marred by severe dyskinesia or dystonia.

Dacepton® 10mg/ml should not be administered to patients who have a known hypersensitivity to apomorphine or any excipients of the medicinal product.

Dacepton® 10mg/ml is contraindicated for children and adolescents under 18 years of age.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-Parkinson drugs, dopamine agonists

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.

5.2 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.

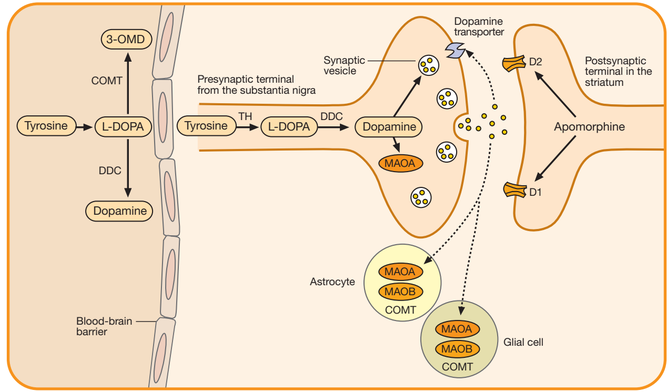


Figure 1: EVER Neuro Pharma, 2012