EVER PHARMA

Continuous Dopaminergic Stimulation

Apomorphine therapy for advanced Parkinson‘s Disease

Dacepton®

Apomorphine Hydrochloride

PARKINSON´S DISEASE (PD) IN THE ADVANCED STAGE

Parkinson´s disease affects the central nervous system. Parkinson's disease is a degenerative disease and with progression the beneficial effects of oral medication become increasingly unpredictable.
In the advanced stage the disease affects motor function. Patients may experience the loss of control in movements or frequent motor fluctuations. In addition further difficulties might occur:

- Cognitive decline and behavioral problems
- Communication
- Difficulty with urination
- Falls
- Impaired performance of activities of daily living
- Sexual dysfunction
- Swallowing
- Walking and balance problems
- Weight loss

WHAT IS DACEPTON®?

Dacepton® is a medication for PD patients in the advanced stage of the disease. The active ingredient of Dacepton® is apomorphine hydrochloride. Dacepton® is a strong and direct-acting dopamine-receptor agonist. Given subcutaneously, it has a rapid onset of antiparkinsonian effect qualitatively faster compared to levodopa.

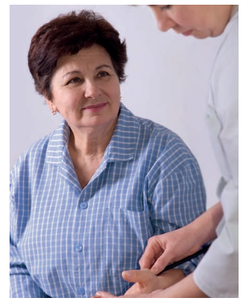
Some patients have taken dopamine agonists as oral medication before. The onset of the efficacy of Dacepton® is faster due to subcutaneous administration.

Under consultation with the PD specialist, patients may have tried to optimize or adjust oral medication. Many patients have experienced that this achieves very little improvement, or the problems they have had remained unchanged.

WHAT DOES DACEPTON® CONTINUOUS INFUSION THERAPY MEAN?

Parkinson's disease is a degenerative disease and with progression the beneficial effects of oral medication become increasingly unpredictable. The side effects such as "wearing off" or "peak of dose" dyskinesias (involuntary movements) and "off-periods" become more prevalent and patients may find that they:

- Become progressively less mobile
- Experience increasing or longer "off" periods
- Have dyskinesias – which may include:
  - involuntary movements
  - Slow, writing motions
  - Increased muscle tone
  - Delayed initiation of movements
  - Uncontrollable movements of arms or legs
- Are suffering from "on" and "off" periods



Such symptoms may cause to put off some activities, leaving patients feel increasingly dependent on others. Maybe patients do not want to leave their home any more because they feel unable to cope with symptoms. Doing simple things of daily activities by oneself become challenging and affect patients and their family. All of this may have a strong impact on quality of life.

The PD specialist will talk with patients about options to improve their situation. Continuous dopaminergic stimulation (CDS) as infusion therapy is an experienced therapy and might be suitable for some patients. Even if patients haven't responded to oral dopamine agonists in the past, they could benefit from Dacepton®.

WHY DO SYMPTOMS INCREASE?

Risk factors for motor complications include disease severity, longer disease duration and higher levodopa dosage. Motoric problems are often addressed with levodopa adjustments and the addition of other oral medication. As disease progresses the number of dopamine cells in the brain deteriorates and the formation of dopamine in the brain is limited. The ability of the body to absorb oral medication decreases with progression of age and the disease. Especially the gut might be unable to absorb oral medication. This phase is characterized by the need to diminish the interval between intake of oral medication. As a result plasma levels may fluctuate erratically and cause side effects such as involuntary movements.

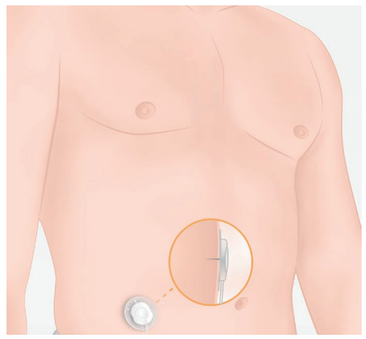
WHY MIGHT DACEPTON® CONTINUOUS INFUSION WORK?

Dacepton® offers improved disease management when oral medication is failing to control motor fluctuations. Dacepton® continuous infusion therapy works well in patients who:

- Have had a positive response to levodopa in the past
- Have clear „on“ and „off“ periods
- Are well motivated
- Have good social network for assistance

WHAT DOES SUBCUTANEOUS ADMINISTRATION MEAN?

Dacepton® is administered via a catheter over a small portable pump system.
A short and extremely fine needle is positioned into the subcutaneous fatty tissue of the belly just under the skin.
By continuous drug administration into the subcutaneous tissue, almost 100% of the drug is absorbed into the blood stream. Because of the high absorption of apomorphine, the therapy can help to have maximum control of Parkinson's disease.



WHY IS THE CONTINUOUS INFUSION MORE BENEFICIAL?

The primary treatment goal is to reduce the frequency and duration of "off" periods. Continuous and constant dopaminergic stimulation with subcutaneous infusion mimics best the effect of dopamine in the brain. The therapy may:

- reduce motor complications and dyskinesias and
- improve overall quality of life.

Dacepton® infusion can reduce „off“ periods and improves motor complications which consequently enables a better control of PD.
Dacepton® continuous infusion therapy can also reduce the intake of oral PD medication – enabling patients to enjoy life more independently.

As the disease progresses additional treatment options are available. The therapy with apomorphine is the least invasive form of continuous infusion. Patients can be on Dacepton® continuous infusion therapy for many years.

HOW DOES THE CONTINUOUS INFUSION PUMP LOOK LIKE?

The portable and discreet pump for the application of continuous infusion of Dacepton® has been especially designed for PD patients.

- Small pump dimensions
- Leight weight
- Comfortable waistband or neck/shoulderstrap under clothing

WHAT ARE THE POSSIBLE SIDE EFFECTS OF DACEPTON® CONTINUOUS INFUSION THERAPY?

In the beginnig of the therapy Dacepton® continuous infusion can cause nausea and vomiting. Nausea doesn't affect everyone, is very temporary and usually only occurs in the beginning when the Dacepton® therapy is initiated. An antiemetic medication has to be given just in the beginning of the therapy.
Although apomorphine is rapidly absorbed from subcutaneous tissue, it can pool in the skin causing nodules. Nodule formation is usually not a significant problem and can be improved with strict rotation of the injection site used and skin hygiene.
In general symptoms like low blood pressure, vivid dreams, hallucinations, confusion and sedation may occur under dopaminergic therapy.

Please refer to the complete summary of product characteristics or patient information leaflet for furher information.

HOW COMPLICATED IS THE HANDLING WITH A PUMP SYSTEM?

The pump system is intuitive and easy to operate. For most patients, a full day's treatment can be set up. This enables patients to set the pump up in the morning (or have it set up by a carer) just once a day. Patients may get on with their daily activities without living after strict timetables.

HOW WILL BE EVALUATED IF DACEPTON® CONTINUOUS INFUSION THERAPY IS SUITABLE?

In advance the patients will have to do a response test with the PD specialist. If the patient is suitable for Dacepton® continuous infusion therapy, the PD specialist will discuss the options with him/her and an extended support team (GP, carer, district nurse etc).

APOMORPHINE RESPONSE TEST

The response test confirms that the patient responds to apomorphine. The appropriate dose for each patient is established by incremental dosing schedules. The test involves a series of subcutaneous injections and movement assessments. Each injection will be a slightly higher dose than the previous one to establish the individual and right dose for the patient.

- BEFORE THE TEST

  Three days prior to the test and as directed by ther PD specialist, the patient will be asked to take an anti-emetic (anti-sickness medication). This is very important as Dacepton® (like levodopa), may make patients feel sick, although this is very temporary and does not affect everyone.

- THE TEST

  The test will be done with small injection needles. They are short and extremely fine and are injected into the subcutaneous tissue (just under the skin). Some patients report that they do not notice they are being injected. At each dose level the patient will be asked to attempt a number of motor assessments, including standing, walking or finger tapping. On rare occasions, Dacepton® can cause a drop in blood pressure. The PD nurse/ specialist will monitor the blood pressure, throughout the test using a blood pressure cuff. The patients will be asked about condition an wellbeing during the testing period.

WHY MIGHT DACEPTON® CONTINUOUS INFUSION THERAPY NOT WORK?

The response to PD therapies varies. Optimal effect from Dacepton® therapy is seen in patients with idiopathic Parkinson's disease. Some patients with syndromes very similar to PD do not respond well to anti-parkinsonian medications, including Dacepton®. If patients have had no response to levodopa in the past they might be not suitable for the Dacepton® therapy. In some cases patients are suffering from additional diseases which might prevent their PD specialist from recommending the Dacepton® therapy (like kidney, lung or cardiovascular diseases).

FREQUENTLY ASKED QUESTIONS

DOESN'T APOMORPHINE MAKE DEPENDENT?

Apomorphine is not morphine and has no narcotic effect which could make dependent. Apomorphine is specifically used to treat Parkinson's disease.

WHY IS A NEEDLE REQUIRED FOR APPLICATION?

Continuous infusion of medication is the most rapid and efficient way of delivering a drug and ensures constant and consistent control. Absorption issues seen with oral medication are avoided. When Dacepton® is applied a very small, fine needle is used that only goes into the subcutaneous fatty layer of the skin. Dacepton® application does not need long needles like those for intravenous treatment. „Set and forget" aspect of subcutaneous Dacepton® with a pump system ensures optimal treatment.

DO PATIENTS HAVE TO WEAR THE PUMP SYSTEM THE WHOLE DAY LONG?

Usually the pump system works during waking hours.

MAY PATIENTS WEAR THE PUMP SYSTEM WHILST BATHING OR SHOWERING?

The pump system is splash water resistant but may not be worn during showering or bathing.

IS IT POSSIBLE TO TRAVEL AROUND?

Patients travelling will need to take a doctors letter detailing that it is necessary for Parkinson's disease patients to carry supplies of apomorphine hydrochloride, needles and injectable pens/ syringes with them at all times, together with their infusion pump. The letter should also note that this Parkinson´s medication must be stored at room temperature (25 degrees centigrade). Dacepton® should be taken onboard as hand luggage.

ANY OTHER QUESTIONS?

- For medical information, please contact a PD specialist or PD Nurse.
- For any further questions concerning disposables, please call your local distributor.

Our Vision is to improve the quality of your life. Each and every day, step by step.

ABBREVIATED PRESCRIBING INFORMATION: Dacepton 5 mg/ml Solution for infusion. 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 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. 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 / 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, syncope and 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 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), 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: July 2020.

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