1. NAME OF THE MEDICINAL PRODUCT

Produodopa™

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 240 mg foslevodopa and 12 mg foscarbidopa.
10 ml contain 2400 mg foslevodopa and 120 mg foscarbidopa.

Foslevodopa and foscarbidopa are prodrugs equivalent to approximately 170 mg levodopa and 9 mg carbidopa per 1 ml.

Excipient with known effect

Produodopa contains approximately 1.84 mmol (42.4 mg) sodium per ml.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion (infusion).

Produodopa is a clear to slightly opalescent solution in a glass vial. The solution should be free from particulates. Produodopa may vary from colourless to yellow to brown and may have a purple or red tint. Variations in colour are expected and have no impact on product quality. The solution may become darker in colour after piercing of the vial stopper or while in the syringe.

The pH is approximately 7.4. Osmolality is approximately 2200 to 2500 mOsmol/kg but may range up to 2700 mOsmol/kg.

Patient safety information card

The marketing of Produodopa is subject to a risk management plan (RMP) including a 'Patient safety information card'. The 'Patient safety information card', emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card before starting treatment.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of advanced levodopa-responsive Parkinson's disease with severe motor fluctuations and hyperkinesia or dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results.

4.2 Posology and method of administration

Posology

Produodopa is administered as a continuous subcutaneous infusion, 24 hours per day.

The recommended starting infusion rate of Produodopa is determined by converting the daytime levodopa intake to levodopa equivalents (LE) and then increasing it to account for a 24-hour administration (see Initiation of treatment). The dose may be adjusted to reach a clinical response that maximises the functional "On" time and minimises the number and duration of "Off" episodes and "On" episodes with troublesome dyskinesia. The maximum recommended daily dose of foslevodopa is 6000 mg (or 25 ml of Produodopa per day equivalent to approximately 4260 mg levodopa per day).

Produodopa replaces levodopa-containing medications and catechol-O-methyl transferase (COMT)-inhibitors. If required, other classes of medicinal products for Parkinson's disease can be taken concurrently.

Initiation of treatment
Patients selected for treatment with Produodopa should be capable of understanding and using the delivery system themselves or with assistance from a caregiver.

Patients should be trained on the proper use of Produodopa and the delivery system (see Method of administration) prior to initiating treatment with Produodopa and, as necessary, thereafter.

Three steps are required to initiate treatment with Produodopa.

- Step 1: Calculate the LE based on the levodopa-containing medications used during the patient's awake time.
- Step 2: Determine the hourly infusion rate of Produodopa.
- Step 3: Determine the volume of the loading dose.

Step 1: Calculate the LE based on the levodopa-containing medications used during the patient's awake time.

The levodopa amount from all levodopa-containing formulations used during the awake time of the day (typically 16-hour/day) should be converted to LE using the appropriate dose multiplication factor from Table 1 and then summed. For this calculation, only consider levodopa and COMT inhibitors. Do not include rescue levodopa or any other anti-Parkinsonian medication or therapy, including medications taken outside of awake time (e.g., night-time dosing) in this calculation. If any COMT inhibitors are taken within a 24-hour period, regardless of the COMT inhibitor dose, a correction factor should be applied to the sum of LE as presented in Table 1.

Table 1. Calculating the Levodopa Equivalents (LE)

Levodopa formulation	**Dose multiplication factor**
Immediate-release, including enteral suspension	**1**
Sustained-release, controlled-release or prolonged-release[a]	**0.75**
If any COMT inhibitor is used, multiply sum of calculated LE from above by **1.33**[a]	
[a] The levodopa contained in combined LD/CD/COMT-inhibitor formulations count as immediate-release and needs to be added to the LE from all other sources of levodopa before the sum is multiplied for the COMT-inhibitors correction factor (i.e., do not apply COMT correction factor to single LE). CD = carbidopa; LD = levodopa; COMT = catechol-O-methyl transferase; LE = levodopa equivalents.	

Step 2: Determine the hourly infusion rate of Produodopa.

Refer to Table 2 for suggested Produodopa starting infusion rates based on the LE calculated in Step 1.

The hourly infusion rate for Produodopa in Table 2 is based on a patient's LE intake during a typical 16-hour awake time (LE_{16}).

If the LE determined in Step 1 were based on an awake time either longer or shorter than 16 hours, the LE should be adjusted to a 16-hour period. To adjust to a 16-hour period, take the LE calculated in Step 1, divide by the number of hours the patient is typically awake, and then multiply by 16. Then refer to Table 2 for Produodopa suggested starting infusion rates. An alternative is to calculate the starting hourly infusion rate according to the formula given under Table 2, where X is the number of patient's awake hours/day.

The hourly infusion rate determined in this step should be entered as the Base infusion rate when programming the pump (refer to the pump instructions for use for details).

Table 2. Suggested Produodopa starting hourly infusion rate

LE_{16} (LE from all oral LD-containing medications taken over 16-hour awake time (mg))	**Suggested Produodopa starting hourly infusion rate (ml/hr)[a] administered over 24 hours**
< 400	0.15
400-499	0.15-0.17
500-599	0.17-0.20
600-699	0.20-0.24
700-799	0.24-0.27
800-899	0.27-0.30
900-999	0.30-0.34
1000-1099	0.34-0.37
1100-1199	0.37-0.40
1200-1299	0.40-0.44
1300-1399	0.44-0.47
1400-1499	0.47-0.51
1500-1599	0.51-0.54
1600-1699	0.54-0.57
1700-1799	0.57-0.61
1800-1899	0.61-0.64
1900-1999	0.64-0.68
2000-2099	0.68-0.71
2100-2199	0.71-0.74
2200-2299	0.74-0.78
2300-2399	0.78-0.81
2400-2499	0.81-0.84
2500-2599	0.84-0.88
2600-2699	0.88-0.91
2700-2799	0.91-0.94
2800-2899	0.94-0.98
2900-2999	0.98-1.01
3000-3099	1.01-1.04

>3100	1.04

[a] The hourly infusion rate can be calculated using the following formula, where X is the number of patient's awake hours used to determine the LE (e.g., X=16, in the table above).

Hourly infusion rate (ml/hr) = [(LE · 0.92 · 1.41)⁄240]⁄X

Assumptions used to generate the "Suggested Produodopa starting hourly infusion rate":

- Total daily LE over 16 hours are increased by 50% to account for 24-hour dosing
- Subcutaneous foslevodopa is 8% more bioavailable than enterally absorbed levodopa
- The molecular weight ratio between foslevodopa and levodopa is 1.41:1
- One millilitre of Produodopa contains 240 mg of foslevodopa and 12 mg of foscarbidopa
- Most patients with PD are treated with oral PD medications during their waking time (typically 16-hour/day treatment period); once the amount of foslevodopa needed over the 16-hour period has been calculated, it is divided by 240 mg to determine the number of millilitres needed over the 16-hour period, and then divided over 16 hours to establish the hourly infusion rate

LE = levodopa equivalents; LD = levodopa.

Step 3: Determine the volume of the loading dose.

A loading dose can be administered immediately prior to commencing the hourly infusion to quickly achieve symptomatic control when starting Produodopa therapy in an "Off" state (or if the pump has been off for more than 3 hours). Loading doses can be administered either via the pump or using oral immediate-release carbidopa-levodopa tablets.

Table 3 provides the recommended loading dose volume (ml) of Produodopa to be programmed into the pump (refer to the pump instructions for use for details) and the corresponding amount of immediate-release levodopa (mg), regardless of the peripheral inhibitor of the DOPA decarboxylase (e.g., carbidopa, benserazide) co-administered.

Table 3. Determination of Produodopa volume recommended for the loading dose

Recommended loading dose volume (ml) to be programmed into the pump	**Approximate corresponding levodopa amount (mg)**
0.6	100
0.9-1.2	150-200
1.5-1.8	250-300
2.0	350
0.1 ml of Produodopa contains 24 mg foslevodopa (equivalent to approximately 17 mg of levodopa). The pump is capable of delivering a loading dose ranging from 0.1 ml to a maximum of 3.0 ml, in increments of 0.1 ml.	

Optimisation and maintenance

The healthcare professional may adjust the starting hourly infusion rate to achieve the optimal clinical response for the patient. The hourly infusion rate should be delivered continuously over the 24-hour daily infusion period. If desired, the healthcare professional can program and enable 2 alternative hourly infusion rates (Low/High). All infusion rates may be adjusted in increments of 0.01 ml/hr (which is equivalent to approximately 1.7 mg of levodopa/hour) and should not exceed 1.04 ml/hr (or approximately 4260 mg levodopa per day [6000 mg of foslevodopa per day]). The pump incorporates

secure access to dose configuration to prevent patients from making changes to their pre-programmed flow rates or Extra Dose functionality.

Produodopa can be taken alone or, if necessary, with other concurrent medicinal products for Parkinson's disease, based on the judgement of the healthcare professional. A reduction in other concomitant medications for Parkinson's disease, followed by an adjustment in Produodopa dosage, may be considered during Produodopa infusion. The concomitant use of Produodopa with other levodopa-containing medications or with medicinal products that significantly regulate synaptic dopamine levels (such as COMT inhibitors) has not been studied.

Alternative flow rate

The pump also allows for 2 alternative infusion rate options to be programmed for patient use (Low/High). The alternative infusion rates must be enabled and pre-programmed by the healthcare professional and may be selected by patients to account for changes in functional demand, e.g., lowering the dosage at night-time or increasing the dose for prolonged intense activity (refer to the pump instructions for use for details).

Extra doses

If enabled by their healthcare professional, patients may self-administer an Extra Dose to manage acute "Off" symptoms experienced during continuous infusion. The Extra Dose volume can be chosen from 5 options (see Table 4). The Extra Dose feature is limited to no more than 1 extra dose per hour. If 5 or more extra doses are used by the patient during the 24-hour/day treatment period, a revision of the Base Infusion Rate should be considered. The ability to enable this function, as well as the minimum time required between extra doses, is determined by the healthcare professional and cannot be modified by the patient (refer to the pump instructions for use for details on programming the Extra Dose feature).

Table 4. Extra dose option for Produodopa

Produodopa volume (ml)	**Levodopa equivalents (mg)**
0.10	17
0.15	25.5
0.20	34
0.25	42.5
0.30	51

Method of administration

Produodopa is administered subcutaneously, preferably in the abdomen, avoiding a 5-cm radius area from the navel. Use aseptic technique when preparing and administering this product. The infusion set (cannula) can remain in place for up to 3 days when the medication is infused continuously. Rotate the infusion site and use a new infusion set at least every 3 days. It is recommended that new infusion sites be at least 2.5 cm from sites used within the previous 12 days. Produodopa should not be infused into areas where the site is tender, bruised, red, or hard to the touch. For administration of Produodopa only the Vyafuser pump should be used (refer to the pump instructions for use for details) using sterile, single-use infusion components (syringe, infusion set, and vial adapter) qualified for use. Patients should be trained on the proper use of Produodopa and the delivery system (pump, solution vial, vial adapter, syringe, infusion set, carrying accessory, rechargeable battery, and charger) prior to initiating treatment with Produodopa and, as necessary, thereafter.

In a Pharmacokinetic crossover study, administration of Produodopa via the arm and thigh resulted in nearly equivalent exposure to the abdomen (see section 5.2 Absorption). Long-term safety and efficacy of administration to the arm and thigh have not been evaluated.

The medication should be stored and handled as described in section 6.4, Special precautions for storage. The medication vials are for single use only. Once the content of a vial is transferred into the syringe, the contents of the syringe should be administered within 24 hours. Used medication vials and syringes should be discarded according to local regulations. Syringes must be discarded, even if residual product remains, as instructed by the healthcare professional (see section 6.6 Special precautions for disposal).

Interruption of therapy

Sudden discontinuation or rapid dose reduction of Produodopa, without administration of alternative dopaminergic therapy, should be generally avoided (see section 4.4).

Produodopa can be interrupted without further actions for brief periods of time, such as when the patient is taking a shower. For interruptions longer than 1 hour, a new infusion set (tubing and cannula) should be used and rotated to a different infusion site. If the infusion has been interrupted for longer than 3 hours, the patient may also self-administer a loading dose, if enabled by their healthcare professional, to quickly re-establish symptom control.

If treatment with Produodopa is interrupted for a prolonged time (>24 hours) or permanently discontinued, the healthcare professional should determine appropriate alternative dopaminergic treatment (e.g., oral levodopa/carbidopa). Treatment with Produodopa may be resumed at any time following instructions as for initiation of Produodopa (see section 4.2 Initiation of treatment).

Special populations

The pharmacokinetics of Produodopa has not been evaluated in any special population. Produodopa is intended for use in Parkinson's disease patients who are already on a stable dose of oral levodopa. Differences in exposure are not considered clinically significant because Produodopa is optimised once patients begin therapy. Therefore, covariate effects are not expected to impact clinical efficacy or safety. See section 5.2 for more information on the pharmacokinetics of levodopa and carbidopa in special populations.

4.3 Contraindications

Produodopa is contraindicated in patients with:

- hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- narrow-angle glaucoma
- severe heart failure
- acute stroke
- severe cardiac arrhythmia
- non-selective MAO inhibitors and selective MAO type A inhibitors are contraindicated for use with Produodopa. These inhibitors must be discontinued at least two weeks prior to initiating therapy with Produodopa. Produodopa may be administered concomitantly with the manufacturer's recommended dose of a MAO inhibitor with selectivity for MAO type B (e.g., selegiline HCl) (see section 4.5).
- conditions in which medication with adrenergic activity are contraindicated, e.g., pheochromocytoma, hyperthyroidism and Cushing's syndrome.

Because levodopa may activate malignant melanoma, Produodopa should not be used in patients with suspicious undiagnosed skin lesions or a history of melanoma.

4.4 Special warnings and precautions for use

Special warnings and precautions for Produodopa
Several warnings and precautions below are generic for levodopa and, therefore, also for Produodopa.

- Produodopa is not recommended for the treatment of drug-induced extrapyramidal reactions.
- Produodopa therapy should be administered with caution to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic, or endocrine disease, or history of peptic ulcer disease or of convulsions.
- In patients with a history of myocardial infarction who have residual atrial nodal or ventricular arrhythmias, cardiac function should be monitored with particular care during the period of initial dosage adjustments.
- All patients treated with Produodopa should be monitored carefully for the development of mental changes, depression with suicidal tendencies, and other serious mental changes. Patients with past or current psychosis should be treated with caution. Higher frequency of hallucinations can occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa including Produodopa. Review of treatment is recommended if such symptoms develop.
- Concomitant administration of antipsychotics with dopamine receptor-blocking properties, particularly D2 receptor antagonists, should be carried out with caution, and the patient should be carefully observed for loss of antiparkinsonian effect or worsening of parkinsonian symptoms (see section 4.5).
- Patients with chronic wide-angle glaucoma may be treated with Produodopa with caution, provided the intra-ocular pressure is well controlled and the patient is monitored carefully for changes in intra-ocular pressure during therapy.
- Produodopa may induce orthostatic hypotension. Therefore, Produodopa should be given cautiously to patients who are taking other medicinal products which may cause orthostatic hypotension (see section 4.5).
- Levodopa has been associated with somnolence and episodes of sudden sleep onset in patients with Parkinson's disease, and caution should, therefore, be exercised when driving and operating machines (see section 4.7).
- A symptom complex resembling Neuroleptic Malignant Syndrome (NMS), including muscular rigidity, increased body temperature, mental changes (e.g., agitation, confusion, coma) and increased serum creatine phosphokinase, has been reported when anti-Parkinsonian medicinal products were withdrawn abruptly. Rhabdomyolysis secondary to NMS or severe dyskinesias have been observed rarely in patients with Parkinson's disease. Therefore, patients should be carefully observed when the dose of levodopa/carbidopa combinations are abruptly reduced or discontinued, especially if the patient is receiving antipsychotics. Neither NMS nor rhabdomyolysis has been reported in association with Produodopa.
- 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 pathologic gambling, increased libido and hypersexuality, compulsive spending or buying, binge-eating and compulsive-eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa including Produodopa. Review of treatment is recommended if such symptoms develop.
- Epidemiological studies have shown that patients with Parkinson's disease have a higher risk of developing melanoma than the general population. It is unclear whether the increased risk observed was due to Parkinson's disease or other factors, such as medicines used to treat Parkinson's disease. Therefore, patients and providers are advised to monitor for melanomas on a regular basis when using Produodopa for any indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

- Dopamine Dysregulation Syndrome (DDS) is an addictive disorder resulting in excessive use of the product seen in some patients treated with levodopa/carbidopa. Before initiation of treatment, patients and caregivers should be warned of the potential risk of developing DDS.
- The dose of Produodopa may need to be adjusted downwards in order to avoid levodopa induced dyskinesias.
- Periodic evaluation of hepatic, haematopoietic, cardiovascular and renal function is recommended during extended therapy with Produodopa.
- Produodopa contains hydrazine, a degradation product of foscarbidopa, that can be genotoxic and probably carcinogenic. The median daily dose of Produodopa is approximately 2541 mg/day of foslevodopa and 127 mg/day of foscarbidopa. The maximum recommended daily dose is 6000 mg foslevodopa and 300 mg foscarbidopa. This includes hydrazine at up to a median exposure of 0.2 mg/day, with a maximum of 0.5 mg/day. The clinical significance of this hydrazine exposure is not known.
- Reduced ability to handle the delivery system can lead to complications. In such patients a caregiver (e.g., nurse, or close relative) should assist the patient.
- A sudden or gradual worsening of bradykinesia may indicate an obstruction in the device for whatever reason and needs to be explored.
- Polyneuropathy has been reported in patients treated with levodopa/carbidopa-containing products. Before starting therapy evaluate patients for history or signs of polyneuropathy and known risk factors, and periodically thereafter.
- Infusion site events (see section 4.8) have been reported in patients receiving Produodopa. Following aseptic techniques while using this medication and frequent rotation of the infusion site are recommended to reduce the risk. In clinical studies, few patients who reported infusion site reactions also experienced infusion site infections. Therefore, careful monitoring of serious infusion site reactions and infusion site infections is recommended.

Produodopa contains sodium

Produodopa contains 42.4 mg (approximately 1.84 mmol) of sodium per ml, equivalent to 2.1% of the WHO recommended maximum daily dietary intake of sodium. The maximum daily dose of this medicine contains 54% of the WHO recommended maximum daily intake of sodium.

Produodopa is high in sodium. This should be considered especially in patients on a low salt diet.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with Produodopa. The following interactions are known from the generic combination of levodopa/carbidopa.

Caution is needed in concomitant administration of Produodopa with the following medicinal products:

Antihypertensives

Symptomatic postural hypotension has occurred when combinations of levodopa and a decarboxylase inhibitor are added to the treatment of patients already receiving anti-hypertensives. Dosage adjustment of the antihypertensive agent may be required.

Antidepressants

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant administration of tricyclic antidepressants (e.g., amoxapine and trimipramine) and carbidopa/levodopa preparations.

COMT inhibitors (e.g., tolcapone, entacapone, opicapone)

Concomitant use of COMT (catechol-O-methyl transferase) inhibitors and Produodopa can increase the bioavailability of levodopa. The dose of Produodopa may need to be adjusted.

Other medicinal products

Dopamine receptor antagonists (some antipsychotics, e.g., phenothiazines, butyrophenones and risperidone and antiemetics, e.g., metoclopramide), benzodiazepines, isoniazid, phenytoin and papaverine can reduce the therapeutic effect of levodopa. Patients taking these medicinal products together with Produodopa should be observed carefully for loss of therapeutic response.

MAO inhibitors are contraindicated in patients taking Produodopa, with the exception of MAO-B selective inhibitors (for instance selegiline HCl). The dose of Produodopa may need to be reduced when a MAO inhibitor selective for type B is added.

Concomitant use of selegiline and levodopa/carbidopa has been associated with serious orthostatic hypotension.

Amantadine has synergistic effect with levodopa and may increase levodopa related adverse events. An adjustment of the dose of Produodopa may be needed.

Sympathomimetics (e.g., adrenergic drugs not limited to - salbutamol, phenylephrine, isoproterenol, dobutamine) may increase cardiovascular adverse events related to levodopa.

Foscarbidopa has been identified as a potential inducer of CYP1A2 in vitro. Care should be taken when prescribing Produodopa in combination with sensitive CYP1A2 substrates (e.g., fluvoxamine, clozapine, caffeine, theophylline, duloxetine and melatonin). No clinical DDI studies have been conducted to assess the clinical relevance of this finding.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of Produodopa in pregnant women. Studies of levodopa and carbidopa in animals have shown reproduction toxicity (see section 5.3). Produodopa is not recommended during pregnancy and in women of childbearing potential not using contraception unless the benefits for the mother outweigh the possible risks to the foetus.

Breastfeeding

Levodopa and possibly levodopa metabolites are excreted in human milk. There is evidence that lactation is suppressed during treatment with levodopa.

It is unknown whether carbidopa or its metabolites are excreted in human milk. Animal studies have shown excretion of carbidopa in breast milk.

There is insufficient information on the effects of Produodopa or their metabolites in newborns/infants. Breast-feeding should be discontinued during treatment with Produodopa.

Fertility

In reproduction studies, no effects on fertility were observed in rats receiving levodopa/carbidopa.

4.7 Effects on ability to drive and use machines

Produodopa can have a major influence on the ability to drive and use machines. Levodopa and carbidopa may cause dizziness and orthostatic hypotension. Therefore, caution should be exercised when driving or using machines. Patients being treated with Produodopa and presenting with somnolence and/or sudden sleep episodes must be advised to refrain from driving or engaging in activities where impaired alertness may put them, or others, at risk of serious injury or death (e.g., operating machines) until such recurrent episodes and somnolence have resolved (see also section 4.4).

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions (≥10%) reported in all Phase 3 studies in patients exposed to Produodopa were infusion site events (infusion site erythema, infusion site cellulitis, infusion site nodule, infusion site pain, infusion site oedema, infusion site reaction, and infusion site infection), hallucination, fall, and anxiety.

Tabulated list of adverse reactions

Adverse reactions reported in all Phase 3 studies in patients exposed to Produodopa (379 patients with total exposure of 414.3 person-years, 230 subjects exposed for ≥ 6 months, 204 subjects exposed for ≥ 12 months) or data from Duodopa Intestinal Gel based on treatment emergent frequencies, regardless of causality assigned are presented in Table 5, listed by MedDRA system organ class. Adverse reaction frequencies are based on the following convention: 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); and very rare (<1/10 000).

Table 5. List of adverse reactions

System organ class	Frequency	Adverse reactions
Infections and infestations	Very common	Infusion site cellulitis Infusion site infection Urinary tract infection[b]
	Common[a]	Infusion site abscess
Blood and lymphatic system disorders	Common	Anaemia[b]
	Uncommon	Leukopenia[b] Thrombocytopenia[b]
Immune system disorders	Not known	Anaphylactic reaction[b,e]
Metabolism and nutrition disorders	Common	Decreased appetite
Psychiatric disorders	Very common	Anxiety Depression Hallucination[c]
	Common	Abnormal dreams[b] Agitation[b] Confusional state Delusion Impulse control disorder Insomnia Paranoia Psychotic disorder Sleep attacks[b] Sleep disorder[b] Suicidal ideation
	Uncommon	Completed suicide[b] Dementia[b] Disorientation[b] Dopamine dysregulation syndrome Euphoric mood[b] Fear[b] Libido increased[b] Nightmare[b] Suicide attempt[b]
	Rare	Abnormal thinking[b]
Nervous system disorders	Common	Cognitive disorder Dizziness Dizziness postural Dyskinesia Dystonia Headache Hypoaesthesia On and off phenomenon Paraesthesia Polyneuropathy[d] Somnolence Syncope Tremor[b]
	Uncommon	Ataxia[b] Convulsion[b] Gait disturbance[b]

Eye disorders	Uncommon	Angle closure glaucoma[b] Blepharospasm[b] Diplopia[b] Optic ischaemic neuropathy[b] Vision blurred[b]
Cardiac disorders	Common	Heart rate irregular[b]
	Uncommon	Palpitations
Vascular disorders	Common	Hypertension Hypotension Orthostatic hypotension
	Uncommon	Phlebitis[b]
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea Oropharyngeal pain[b]
	Uncommon	Dysphonia[b]
	Rare	Respiration abnormal[b]
Gastrointestinal disorders	Common	Abdominal distension[b] Abdominal pain Constipation Diarrhoea Dry mouth Dysgeusia[b] Dyspepsia[b] Dysphagia[b] Flatulence[b] Nausea Vomiting
	Uncommon	Salivary hypersecretion[b]
	Rare	Bruxism[b] Saliva discolouration[b] Glossodynia[b] Hiccups[b]
Skin and subcutaneous tissue disorders	Common	Dermatitis contact[b] Hyperhidrosis[b] Pruritus Rash
	Uncommon	Alopecia[b] Erythema[b] Urticaria[b]
	Rare	Sweat discolouration[b] Malignant melanoma[b]
Musculoskeletal and connective tissue disorders	Common	Muscle spasms Neck pain[b]
Renal and urinary disorders	Common	Urinary incontinence Urinary retention
	Uncommon	Chromaturia[b]
	Rare	Priapism[b]
General disorders and administration site conditions	Very common	Infusion site erythema Infusion site reaction Infusion site nodule Infusion site oedema Infusion site pain

	Common[a]	Asthenia Fatigue Infusion site bruising Infusion site exfoliation Infusion site extravasation Infusion site haematoma Infusion site haemorrhage Infusion site induration Infusion site inflammation Infusion site irritation Infusion site mass Infusion site papule Infusion site pruritus Infusion site rash Infusion site swelling Malaise Oedema peripheral Pain[b]
	Uncommon	Chest pain[b]
Investigations	Common	Amino acid level increased (Methylmalonic acid increased)[b] Blood homocysteine level increased[b] Vitamin B6 decreased Vitamin B12 deficiency[b] Weight decreased Weight increased[b]
Injury, poisoning and procedural complications	Very common	Fall
[a] Common adverse reactions pertaining to infusion site events included if ≥2%. [b] These adverse reactions were identified with Duodopa Intestinal Gel as drug-related events. However, these events were not considered adverse reactions for Produodopa. [c] Hallucination includes hallucination, hallucination visual, hallucination auditory, hallucination olfactory, hallucinations tactile, and hallucinations mixed. [d] Polyneuropathy includes neuropathy peripheral, polyneuropathy, decreased vibratory sense, peripheral sensory neuropathy, sensory disturbance, and sensory loss. [e] Based on post-marketing data		

Description of selected adverse reactions

Infusion site events

In the Phase 3 studies, the most common AEs related to Produodopa were infusion site reactions 77.6% (N=294) and infusion site infections 41.4% (N=157). Infusion site events including infusion site reactions and infections, commonly seen with subcutaneous infusions were observed with Produodopa in the clinical studies. The majority of the infusion site events were non-serious, were mild or moderate in severity, and resolved spontaneously or with treatment such as antibiotics and/or incision and drainage. Three subjects with infusion site infections had a complication of sepsis resulting in hospitalisation. Monitor for any skin changes at the infusion site that could indicate a potential infection, such as redness associated with warmth, swelling, pain, and discolouration when you apply pressure to it. Aseptic techniques should be followed while using this medication and consider rotating the infusion site more frequently than every 3rd day, using a new infusion set if you

see these skin changes. It is recommended that new infusion sites be at least 2.5 cm from sites used within the previous 12 days.

Laboratory values: The following laboratory abnormalities have been reported with levodopa/carbidopa treatment and should, therefore, be acknowledged when treating patients with Produodopa: elevated urea nitrogen, alkaline phosphatases, S-AST, S-ALT, LDH, bilirubin, blood sugar, creatinine, uric acid and positive Coomb's test, and lowered values of haemoglobin and haematocrit. Leucocytes, bacteria and blood in the urine have been reported. Levodopa/carbidopa, and thus Produodopa, may cause a false positive result when a dipstick is used to test for urinary ketone; this reaction is not altered by boiling the urine sample. The use of glucose oxidase methods may give false negative results for glucosuria.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il

4.9 Overdose

In the event of an overdosage with Produodopa, the infusion should be stopped immediately. The treatment of an acute overdose of Produodopa is the same as that of an acute overdose of levodopa; however, pyridoxine has no effect on the reversal of the action of Produodopa. Electrocardiographic monitoring should be used, and the patient observed carefully for the development of cardiac arrhythmias; if necessary, an appropriate antiarrhythmic therapy should be given. Patients must also be monitored for hypotension. The possibility that the patient took other medicinal products together with Produodopa should be taken into consideration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-Parkinson drugs, foslevodopa and decarboxylase inhibitor ATC code: N04BA07

Mechanism of action

Produodopa (foslevodopa/foscarbidopa) 240 mg/12 mg per ml solution for infusion is a prodrug combination of levodopa monophosphate and carbidopa monophosphate (ratio 20:1) in a solution for 24 hour/day continuous subcutaneous infusion in advanced Parkinson's disease patients who are not adequately controlled with current medical therapy. Foslevodopa and foscarbidopa are converted *in-vivo* to levodopa and carbidopa. Levodopa relieves symptoms of Parkinson's disease following decarboxylation to dopamine in the brain. Carbidopa, which does not cross the blood-brain barrier, inhibits the extracerebral decarboxylation of levodopa to dopamine, which means that a larger amount of levodopa becomes available for transportation to the brain and transformation into dopamine.

Pharmacodynamic effects

Produodopa subcutaneous administration and Duodopa intestinal administration were shown to have comparable levodopa $C_{max,}$ AUC, and degree of fluctuation, which supports a comparable efficacy

profile. By achieving same concentrations of levodopa as Duodopa, Produodopa reduces the motor fluctuations and increases the “On”-time in levodopa-responsive patients with advanced Parkinson’s disease. The motor fluctuations and hyperkinesia or dyskinesia are reduced because the plasma concentrations of levodopa are being kept at a steady level within the individual therapeutic window. Therapeutic effect on motor symptoms (“On” state) is achieved on the first treatment day.

Clinical efficacy and safety

Studies with Duodopa intestinal gel formulation

The efficacy of Duodopa intestinal gel was confirmed in two identically-designed Phase 3, 12-week, randomised, double-blind, double-dummy, active-controlled, parallel group, multicentre studies to evaluate the efficacy, safety, and tolerability of the Duodopa intestinal gel system against levodopa/carbidopa 100/25 mg tablets. The studies were conducted with patients with advanced Parkinson's disease who were levodopa-responsive and had persistent motor fluctuations despite optimised treatment with oral levodopa/carbidopa and other available anti-Parkinson's disease medications and enrolled a total of 71 patients. The results of the two studies were combined and a single analysis was conducted.

The primary efficacy endpoint, change in normalised "Off" time (baseline to endpoint) based on Parkinson's Disease Diary (PD Diary) data using last observation carried forward demonstrated a statistically significant least square (LS) mean difference in favour of the Duodopa treatment group (Table 6).

The primary end point results were supported by a Mixed Model Repeated Measures (MMRM) analysis which examined the change from baseline to each post-baseline study visit. This analysis of “Off” time demonstrated a statistically significant greater improvement of the Duodopa group over the Active control group at Week 4, and that improvement was shown to be statistically significant at Weeks 8, 10, and 12.

This change in “Off” time was associated with a statistically significant LS mean difference from baseline in the average daily normalised "On" time without troublesome dyskinesia between the Duodopa intestinal gel treatment group and the active control group based on PD Diary data. The baseline values were collected three days prior to randomisation and after 28 days of oral therapy standardisation.

Table 6. Change from baseline to endpoint in "off" time and in "on" time without troublesome dyskinesia

Treatment Group	N	Baseline mean (SD) (hours)	Endpoint Mean (SD) (hours)	LS mean (SE) of change (hours)	LS mean (SE) of difference (hours)	*P* value
Primary measure: “Off” time						
Active control[a]	31	6.90 (2.06)	4.95 (2.04)	-2.14 (0.66)		
Duodopa intestinal gel	35	6.32 (1.72)	3.05 (2.52)	-4.04 (0.65)	-1.91 (0.57)	0.0015
Key secondary measure: "On" time without troublesome dyskinesia						
Active control	31	8.04 (2.09)	9.92 (2.62)	2.24 (0.76)		
Duodopa intestinal gel	35	8.70 (2.01)	11.95 (2.67)	4.11 (0.75)	1.86 (0.65)	0.0059

SD = standard deviation; SE = standard error

[a.] Active control, oral levodopa/carbidopa 100/25 mg tablets (Sinemet tablets over-encapsulated)

Analyses of other secondary efficacy endpoints, in order of the hierarchical testing procedure, demonstrated statistically significant results for Duodopa intestinal gel compared to oral levodopa/carbidopa for the Parkinson's Disease Questionnaire (PDQ-39) Summary Index (*an index Parkinson's disease-related quality of life*), Clinical Global Impression-Improvement (CGI-I) score, and Unified Parkinson's Disease Rating Scale (UPDRS) Part II score (Activities of Daily Living). The PDQ-39 Summary Index showed a decrease from baseline of 10.9 points at week 12 for Duodopa intestinal gel group. Other secondary endpoints UPDRS Part III score, EuroQol 5-dimensions Questionnaire (EQ-5D) Summary Index, and Zarit Burden Interview (ZBI) total score, did not meet statistical significance based on the hierarchical testing procedure.

A Phase 3, open-label, single-arm, multicentre study was conducted to assess the long-term safety and tolerability of Duodopa over 12 months in 354 patients. The study population was levodopa-responsive patients with advanced Parkinson's disease and motor fluctuations despite optimised treatment with available Parkinson's disease medications. The average daily normalised "Off" time changed by – 4.44 hours from Baseline to Endpoint (6.77 hours at Baseline and 2.32 hours at Endpoint) with a corresponding 4.8-hour increase in "On" time without troublesome dyskinesia.

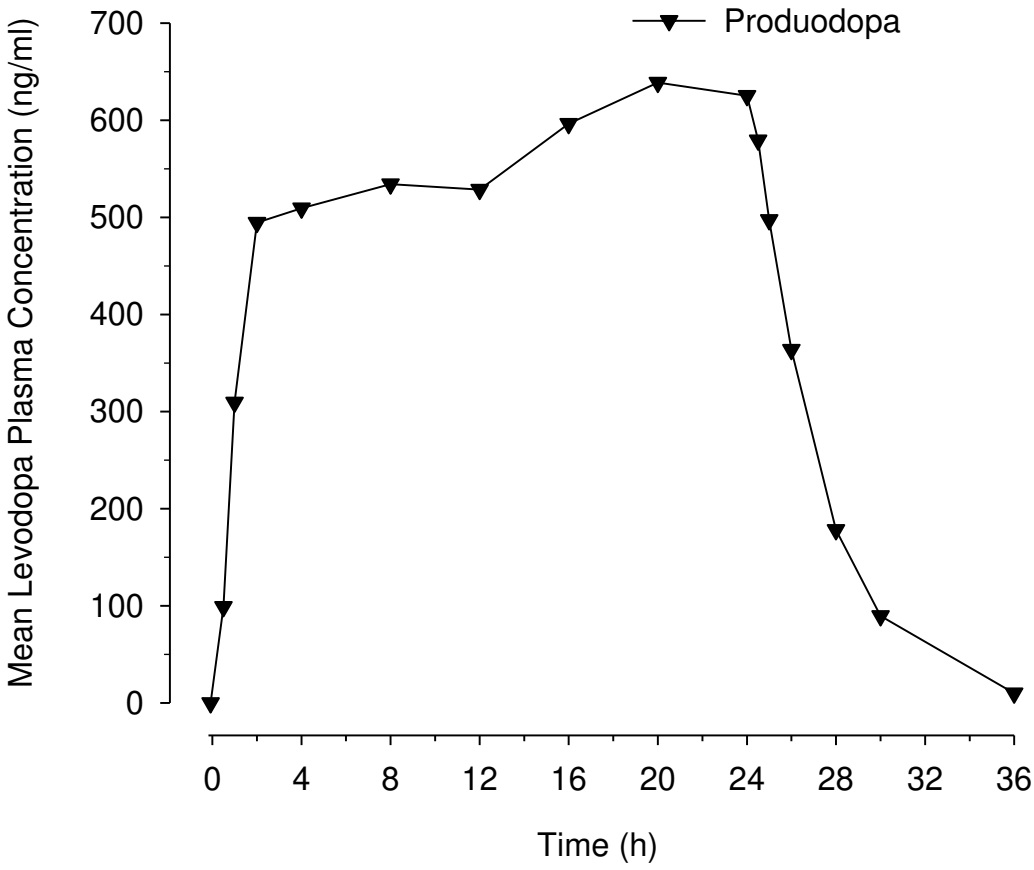
A Phase 3, open-label, randomised, multicentre study was conducted to assess the effect of Duodopa intestinal gel on dyskinesia compared with optimised medical treatment (OMT) over 12 weeks in 61 patients. The study population was levodopa-responsive patients with advanced PD and motor fluctuations inadequately controlled with OMT and with a baseline Unified Dyskinesia Rating Scale (UDysRS) Total Score ≥30. The change from baseline to Week 12 in UDysRS total score (primary efficacy endpoint) demonstrated a statistically significant LS Mean difference (-15.05; $P < 0.0001$) in favour of the Duodopa treatment group compared with OMT group. Analysis of secondary efficacy endpoints using a fixed sequence testing procedure, demonstrated statistically significant results in favour of Duodopa compared with OMT for "On" time without troublesome dyskinesia as measured by PD Diary, for Parkinson's Disease Questionnaire-8 (PDQ-8) summary index, Clinical Global Impression Change (CGI-C) score, UPDRS Part II score, and for "Off" time as measured by PD Diary. The UPDRS Part III score did not meet statistical significance.

Studies with Produodopa

Produodopa is a prodrug combination of levodopa monophosphate and carbidopa monophosphate (ratio 20:1) in a solution intended for 24-hour/day continuous subcutaneous infusion. Subcutaneous Produodopa administration and Duodopa intestinal administration were shown to have comparable levodopa C_{max} and AUC parameters, which supports a comparable efficacy profile. The study showed stable levodopa exposure with fluctuation values of 0.262 and 0.404 for Produodopa and Duodopa, respectively.

Following Produodopa administration in healthy volunteers, levodopa steady state is achieved rapidly, generally within 2 hours and maintained during the infusion period. Figure 1 below shows levodopa exposure following 24-hour Produodopa administration.

Figure 1. Mean Levodopa exposure following 24-hour Produodopa infusion



Results from an additional PK comparability study demonstrated that levodopa exposure was comparable between Produodopa and Duodopa when both were delivered over a 24-hour period.

A Phase 3, double-blind, double-dummy, randomised, active-controlled, multicentre study was conducted to assess the effect of Produodopa in patients with advanced PD over 12 weeks. A total of 145 patients were randomised in 1:1 ratio and 141 patients received either 24-hour/day continuous subcutaneous administration of Produodopa plus oral placebo capsules (N=74) or 24-hour/day continuous subcutaneous administration of placebo solution plus oral encapsulated carbidopa-levodopa IR tablets (N=67).

The study population was patients with levodopa-responsive PD whose motor fluctuations were inadequately controlled by their current medications and who experienced a minimum of 2.5 hours of “Off” time/day as assessed by PD diaries.

Produodopa demonstrated statistically significant improvements from baseline to Week 12 in "On" time without troublesome dyskinesia and “Off” time compared with the oral IR carbidopa-levodopa group (Table 7). Other secondary endpoints, motor experiences of daily living, morning akinesia, sleep, and quality of life indicators did not meet statistical significance based on the hierarchical testing procedure.

Table 7. Change from Baseline to Endpoint in Primary and Key Secondary Measures

Treatment Group	N	Baseline Mean (SD)	Change from Baseline to Endpoint Mean (SD)	LS Mean of Change	LS Mean of Difference	*P* value (95% Confidence Interval)
Primary Measure						
"On" time without troublesome dyskinesia (hours)[a]						
Oral IR carbidopa-levodopa[b]	67	9.49 (2.62)	0.85 (3.46)	0.97		
Produodopa	73	9.20 (2.42)	3.36 (3.62)	2.72	1.75	0.0083 (0.46, 3.05)
Secondary Measure						
"Off" time (hours)[a]						
Oral IR carbidopa-levodopa[b]	67	5.91 (1.88)	-0.93 (3.31)	-0.96		
"Produodopa	73	6.34 (2.27)	-3.41 (3.76)	-2.75	-1.79	0.0054 (-3.03, -0.54)

SD = standard deviation;.
[a] Derived from Parkinson's Disease (PD) diary.
[b] Oral immediate release carbidopa-levodopa tablets.

A total of 110 patients completed the study. During the double-blind treatment period, 7.5 % (N=5) of patients in the oral IR carbidopa-levodopa group and 35.1% (N=26) in the Produodopa group prematurely discontinued. The most common reason for discontinuation in the Produodopa group was adverse events 18.9% (N=14). One of the 74 patients in the Produodopa group was excluded from the analysis because the subject did not have valid baseline data for the efficacy model (N=73 in table 7) A J2R sensitivity analysis was also performed to evaluate the analysis results under a more conservative assumption. The results of the J2R sensitivity analysis were consistent with the results of the primary analysis.

A Phase 3, open-label, single-arm study was conducted to evaluate the safety and tolerability of 24-hour daily exposure of continuous subcutaneous infusion of Produodopa over 52 weeks in 244 patients. The study population was levodopa-responsive patients with Parkinson's disease whose motor symptoms that were inadequately controlled with current treatment who experienced a minimum of 2.5 hours of "Off" time per day as assessed by Parkinson's disease (PD) diaries.

A total of 137 patients completed the study. The most common reasons for discontinuation were adverse events (26%) and withdrawal of consent (16%). Adverse events reported for ≥ 10% of subjects were infusion site events, hallucination, fall, anxiety and dizziness. The most common adverse events related to Produodopa were infusion site events, which were nonserious, mild or moderate in severity and resolved. The summary of the safety profile of Produodopa from this study are provided in section 4.8 (see section 4.8 Undesirable effects).

Paediatric

The safety of Produodopa in patients under 18 years of age has not been established and its use in patients below the age of 18 is not recommended.

5.2 Pharmacokinetic properties

Absorption

Produodopa is administered directly into the subcutaneous space and is quickly absorbed and converted to levodopa and carbidopa. In a phase 1 study in healthy volunteers, levodopa and carbidopa were detectable in plasma within 30 minutes at the first pharmacokinetic collection point. In most subjects the steady state was achieved within 2 hours when Produodopa dosing was delivered as loading dose followed by continuous infusion.

In order to determine absorption of Produodopa at different subcutaneous sites, healthy volunteers were administered Produodopa to the abdomen, arm and thigh using a 3-way crossover design. Pharmacokinetic analysis from this study showed that the 3 sites have nearly identical levodopa and carbidopa exposure suggesting Produodopa absorption is similar at the different subcutaneous sites.

Produodopa bypasses the gut, so food does not change absorption or exposure of levodopa/carbidopa.

Distribution

The volume of distribution of levodopa is moderately small. The partitioning ratio for levodopa between erythrocytes and plasma is approximately 1. Levodopa has negligible binding to plasma proteins (< 10%). Levodopa is transported into the brain by the carrier mechanism for large neutral amino acids.

Carbidopa is approximately 36% bound to plasma protein. Carbidopa does not cross the blood-brain barrier.

Both foslevodopa and foscarbidopa have low binding to plasma proteins (24%-26%).

Biotransformation and elimination

Foslevodopa and foscarbidopa prodrugs are rapidly converted by alkaline phosphatases into levodopa and carbidopa. Levodopa is mainly metabolised by the aromatic amino acid decarboxylase (AAAD) and the COMT enzymes. Other routes of metabolism are transamination and oxidation. The decarboxylation of levodopa to dopamine by AAAD is the major enzymatic pathway when no enzyme inhibitor is co-administered. O-methylation of levodopa by COMT forms 3-O-methyldopa. When administered with carbidopa, the elimination half-life of levodopa is approximately 1.5 hours.

Carbidopa is metabolised to two main metabolites (α-methyl-3-methoxy-4-hydroxyphenylpropionic acid and α-methyl-3,4-dihydroxyphenylpropionic acid). These 2 metabolites are primarily eliminated in the urine unchanged or as glucuronide conjugates. Unchanged carbidopa accounts for 30% of the total urinary excretion. The elimination half-life of carbidopa is approximately 2 hours.

Special Populations

Produodopa is intended for use in Parkinson's disease patients who are already on a stable dose of oral levodopa and Produodopa dose is optimised once patients begin therapy.

Elderly

The impact of age on the levodopa pharmacokinetics following Produodopa infusion was not specifically evaluated. Studies with levodopa suggest a modest reduction of levodopa clearance with increasing age.

Renal or hepatic impairment

The pharmacokinetics of Produodopa in subjects with renal and/or hepatic impairment has not been established.

The anticipated daily phosphorus load from the highest proposed clinical dose of foslevodopa/foscarbidopa (6000/300 mg/day of foslevodopa/foscarbidopa) is approximately 700 mg, which is considerably less than the United States National Academy of Sciences dietary reference intake upper limit of 3000 mg/day; however, there are no pharmacokinetic or safety data with Produodopa in patients with End Stage Renal Disease requiring dialysis. Therefore, caution should be exercised in patients with End Stage Renal Disease on dialysis requiring treatment with Produodopa because of diminished ability of the kidneys to eliminate phosphate.

Body weight

The impact of body weight on the levodopa pharmacokinetics following Produodopa infusion was not specifically evaluated. Previous studies of levodopa have shown that weight increases volume of distribution and can lower levodopa exposure.

Gender or race

Following Produodopa administration, carbidopa and levodopa exposures in both Japanese subjects and Han Chinese subjects were comparable to those in Caucasian subjects.

The impact of gender on the pharmacokinetics following Produodopa infusion was not specifically evaluated. The effect of gender on the pharmacokinetics of levodopa has been evaluated and studies suggested there is no clinically meaningful gender related difference in levodopa exposure. Following Produodopa dosing, levodopa exposure was higher in females once weight was considered by approximately 18% based on AUC.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. In reproductive toxicity studies, both levodopa and the combination of levodopa/carbidopa have caused visceral and skeletal malformations in rabbits.

Hydrazine is a degradation product of foscarbidopa. In animal studies, hydrazine showed notable systemic toxicity, particularly by inhalation exposure. These studies reported that hydrazine is hepatotoxic, has CNS toxicities (although not described after oral treatment), and is genotoxic as well as carcinogenic (see also section 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections
Sodium hydroxide 10N (for pH adjustment)
Hydrochloric acid, concentrated / hydrochloric acid (for pH adjustment)
Nitrogen

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened: The expiry date of the product is indicated on the packaging materials.

Once opened: Use immediately. The product is to be used within 24 hours once it is transferred from the vial to the syringe.

6.4 Special precautions for storage

Store and transport refrigerated (2°C-8°C). Do not freeze.

Keep the vials in the outer carton to protect the vials from breaking.

May be stored at room temperature up to a maximum of 30°C for a single period of up to 28 days. Once a vial has been stored at room temperature, do not return the product to the refrigerator. Record the date when Produodopa is first removed from the refrigerator in the space provided on the carton.

For storage conditions after first opening of the medicinal product, see section 6.3.

The medicine should be at room temperature prior to infusion. If refrigerated prior to use, the vial should be removed from the refrigerator and allowed to sit at room temperature out of direct sunlight for 30 minutes. If refrigerated the medicine must not be warmed (in the vial or syringe) in any way other than letting it warm at room temperature. For example, it must not be warmed in a microwave or in hot water.

6.5 Nature and contents of container

Total amount of 10 ml in type I clear, colourless glass vial fitted with a grey rubber stopper, aluminium crimp cap, and turquoise plastic flip-off cap, carton with 7 vials.

Sterile, single-use infusion components (syringe, infusion set, and vial adapter) qualified for use are provided separately.

The Vyafuser pump is provided separately.

6.6 Special precautions for disposal

Vials are for single use only. The entire contents of a vial should be transferred into a syringe for administration. Do not dilute the solution or fill the syringe with any other solution. Discard the vial after transfer of the medicinal product to the syringe.

Do not re-use an opened vial.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Discard the vial if not used within the 28-day room temperature period.

Discard the syringe and any unused product in the syringe after the medicinal product has been in the syringe for 24 hours. Do not use the product from the same vial or same syringe for more than 24 hours.

An overview of the instructions for use is provided in the package leaflet.

7. MARKETING AUTHORISATION HOLDER

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Israel

9. MANUFACTURER

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10. REGISTRATION NUMBER

173-60-37468-99

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