SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Veltassa 8.4 g powder for oral suspension
Veltassa 16.8 g powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Veltassa 8.4 g powder for oral suspension
Each sachet contains 8.4 g patiromer (as patiromer sorbitex calcium)
Veltassa 16.8 g powder for oral suspension
Each sachet contains 16.8 g patiromer (as patiromer sorbitex calcium)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension.
Off-white to light-brown powder, with occasional white particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Veltassa is indicated for the treatment of hyperkalaemia in adults.

4.2 Posology and method of administration

Posology

The recommended starting dose is 8.4 g patiromer once daily.

The daily dose may be adjusted in intervals of one week or longer, based on the serum potassium level and the desired target range. The daily dose may be increased or decreased by 8.4 g as necessary to reach the desired target range, up to a maximum dose of 25.2 g daily. If serum potassium falls below the desired range, the dose should be reduced or discontinued.

If a dose is missed, the missed dose should be taken as soon as possible on the same day. The missed dose should not be taken with the next dose.

Administration of Veltassa should be separated by 3 hours from other oral medicinal products (see section 4.5).

The onset of action of Veltassa occurs 4-7 hours after administration. It should not replace emergency treatment for life-threatening hyperkalaemia.

Special population

Elderly population (≥65 years of age)
No special dose and administration guidelines are recommended for this population.

Patients on dialysis

There is limited data on the use of Veltassa in patients on dialysis. No special dose and administration guidelines were applied to these patients in clinical studies.

Paediatric population

The safety and efficacy of Veltassa in children aged under 18 years have not yet been established. No data are available.

Method of administration

Oral use.
Veltassa should be mixed with water and stirred to a suspension of uniform consistency, according to the following steps:

The complete dose should be poured into a glass containing approximately 40 ml of water, then stirred. Another approximately 40 ml of water should be added, and the suspension stirred again thoroughly. The powder will not dissolve. More water may be added to the mixture as needed for desired consistency.

The mixture should be taken within 1 hour of initial suspension. If powder remains in the glass after drinking, more water should be added and the suspension stirred and taken immediately. This may be repeated as needed to ensure the entire dose is administered.

The following liquids or soft foods can be used instead of water to prepare the mixture by following the same steps as described above: apple juice, cranberry juice, pineapple juice, orange juice, grape juice, pear juice, apricot nectar, peach nectar, yoghurt, milk, thickener (for example: cornstarch), apple sauce, vanilla and chocolate pudding.

The potassium content of liquids or soft foods used to prepare the mixture should be considered as part of the dietary recommendations on potassium intake for each individual patient.

In general, cranberry juice intake should be limited to moderate amounts (for example less than 400 ml per day) due to its potential interaction with other medicinal products.

Veltassa can be taken with or without food. It should not be heated (e.g. microwaved) or added to heated foods or liquids. It should not be taken in its dry form.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Low Magnesium

In clinical studies, serum magnesium values <1.4 mg/dL (0.58 mmol/L) occurred in 9% of patients treated with patiromer. Mean decreases in serum magnesium were 0.17 mg/dL (0.070 mmol/L) or less.

Hypomagnesemia may occur during treatment. Monitoring of serum magnesium should be performed at the beginning of treatment, at appropriate intervals at least 1 month after initiating treatment, and at any clinical need.

Gastrointestinal Disorders

Patients with a history of bowel obstruction or major gastrointestinal surgery, severe gastrointestinal disorders, or swallowing disorders were not included in the clinical studies. Gastrointestinal ischaemia, necrosis and/or intestinal perforation have been reported with other potassium binders. The benefits and risks of administering patiromer should be carefully evaluated in patients with current or history of severe gastrointestinal disorders, before and during treatment.

Discontinuing patiromer

When discontinuing patiromer, serum potassium levels may rise, especially if renin angiotensin aldosterone system (RAAS) inhibitor treatment is continued. Patients should be instructed not to discontinue therapy without consulting their physicians. Increases in serum potassium may occur as early as 2 days after the last patiromer dose.

Serum potassium levels

Serum potassium should be monitored when clinically indicated, including after changes are made to medicinal products that affect the serum potassium concentration (e.g. RAAS inhibitors or diuretics) and after the patiromer dose is titrated.

Limitations of the clinical data

Patients with end-stage renal disease (ESRD)

Patiromer has been studied only in a limited number of patients with estimated glomerular filtration rate (eGFR) <15 ml/min/1.73 m^2 and patients receiving dialysis treatment.

Data regarding efficacy and safety in end stage renal disease CKD-5 and patients on dialysis is limited.

Severe hyperkalaemia

There is limited experience in patients with serum potassium concentrations greater than 6.5 mmol/L.

Long term exposure

Clinical trials with patiromer have not included exposure longer than one year.

Information about sorbitol

Veltassa contains sorbitol as part of the counterion complex. The sorbitol content is approximately 4 g (10.4 kcal) per 8.4 g of patiromer.
Patients with hereditary fructose intolerance (HFI) should not take this medicinal product .

Information about calcium

Veltassa contains calcium as part of the counterion complex. Calcium is partially released some of which may be absorbed (see section 5.1). The benefits and risks of administering this medicinal product should be carefully evaluated in patients at risk of hypercalcaemia.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of patiromer on other medicinal products

Patiromer has the potential to bind some oral co-administered medicinal products, which could decrease their gastrointestinal absorption. Increased bioavailability of co administrated drugs was not observed in the conducted drug drug interaction studies. As patiromer is not absorbed or metabolised by the body, there are limited effects on the function of other medicinal products.

As precautionary measure, and based on the data summarised below, administration of patiromer should therefore be separated by at least 3 hours from other oral medicinal products.

In vivo studies:

Concomitant administration of patiromer did not affect the bioavailability as measured by the area under the curve (AUC) of amlodipine, cinacalcet, clopidogrel, furosemide, lithium, metoprolol, trimethoprim, verapamil and warfarin. For these medicinal products no separation is needed. Concomitant administration of patiromer showed reduced bioavailability of ciprofloxacin, levothyroxine and metformin. However, there was no interaction when patiromer and these medicinal products were taken 3 hours apart.

In vitro studies:

In vitro studies have shown no potential interaction of patiromer with the following active substances: allopurinol, amoxicillin, apixaban, acetylsalicylic acid, atorvastatin, azilsartan, benazepril, bumetanide, canagliflozin, candesartan, captopril, cephalexin, dapagliflozin, digoxin, empagliflozin, enalapril, eplerenone, finerenone, fosinopril, glipizide, irbesartan, lisinopril, losartan, olmesartan, perindopril, phenytoin, quinapril, ramipril, riboflavin, rivaroxaban, sacubitril, sevelamer, spironolactone tacrolimus, torasemide, trandolapril, and valsartan.

In vitro studies have shown potential interaction of patiromer with bisoprolol, carvedilol, mycophenolate mofetil, nebivolol, quinidine, and telmisartan.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of patiromer in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of patiromer during pregnancy.

Breast-feeding

No effects on the breast-fed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to patiromer is negligible. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from patiromer therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effect of patiromer on fertility in humans. Animal studies showed no effects on reproductive function or fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Patiromer has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The majority of the adverse reactions (ARs) reported from trials were gastrointestinal disorders, with the most frequently reported ARs being constipation (6.2%), diarrhoea (3%), abdominal pain (2.9%), flatulence (1.8%) and hypomagnesaemia (5.3%). Gastrointestinal disorder reactions were generally mild to moderate in nature, did not appear to be dose related, generally resolved spontaneously or with treatment, and none were reported as serious. Hypomagnesaemia was mild to moderate, with no patient developing a serum magnesium level <1 mg/dL (0.4 mmol/L).

Tabulated list of adverse reactions

Adverse reactions are listed below by system organ class and by frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10) and 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). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

MedDRA System Organ Class	**Common**	**Uncommon**
Metabolism and nutrition disorders	Hypomagnesaemia	
Gastrointestinal disorders	Constipation Diarrhoea Abdominal pain Flatulence	Nausea Vomiting

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

Since excessive doses of Veltassa may result in hypokalaemia, serum potassium levels should be monitored. Patiromer is excreted after approximately 24 to 48 hours, based on average gastrointestinal transit time. If it is determined that medical intervention is required, appropriate measures to restore serum potassium may be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for treatment of hyperkalaemia and hyperphosphataemia. ATC code: V03AE09

Mechanism of action

Patiromer is a non-absorbed, cation exchange polymer that contains a calcium-sorbitol complex as a counterion.

Patiromer increases faecal potassium excretion through binding of potassium in the lumen of the gastrointestinal tract. Binding of potassium reduces the concentration of free potassium in the gastrointestinal lumen, resulting in a reduction of serum potassium levels.

Pharmacodynamic effects

In healthy adult subjects, patiromer caused a dose-dependent increase in faecal potassium excretion, and a corresponding decrease in urinary potassium excretion with no change in serum potassium. 25.2 g of patiromer, administered once daily for 6 days, resulted in a mean increase in faecal potassium excretion of 1283 mg/day, and a mean decrease in urinary potassium excretion of 1438 mg/day. Daily urinary calcium excretion increased from baseline by 53 mg/day.

In an open-label study to assess the time to onset of action, a statistically significant reduction in serum potassium in hyperkalaemic patients was observed at 7 hours after the first dose. Following discontinuation of patiromer, potassium levels remained stable for 24 hours after the last dose, then rose again during a 4-day observation period.

Clinical efficacy and safety

The safety and efficacy of patiromer were demonstrated in a two-part, single-blind randomised withdrawal study that evaluated this treatment in hyperkalaemic patients with chronic kidney disease (CKD) on stable doses of at least one RAAS inhibitor (i.e. angiotensin-converting enzyme inhibitor [ACEI], angiotensin II receptor blocker [ARB] or aldosterone antagonist [AA]).

In Part A, 243 patients were treated with patiromer for 4 weeks. Patients with a baseline serum potassium of 5.1 mEq/L to <5.5 mEq/L (mmol/L) received a starting dose of 8.4 g patiromer per day (as a divided dose) and patients with a baseline serum potassium of 5.5 mEq/L to <6.5 mEq/L received a starting dose of 16.8 g patiromer per day (as a divided dose). The dose was titrated, as needed, based on the serum potassium level, assessed starting on Day 3 and then at weekly visits to the end of the 4-week treatment period, with the aim of maintaining serum potassium in the target range (3.8 mEq/L to <5.1 mEq/L). The mean daily doses of patiromer were 13 g and 21 g in patients with serum potassium of 5.1 to <5.5 mEq/L and 5.5 to <6.5 mEq/L, respectively.

The mean age of patients was 64 years (54% aged 65 and over, 17% aged 75 and over), 58% of patients were men, and 98% were Caucasian. Approximately 97% of patients had hypertension, 57% had type 2 diabetes, and 42% had heart failure.

Mean serum potassium levels and change in serum potassium from Part A Baseline to Part A Week 4 is shown in Table 1. For the Part A secondary outcome, 76% (95% CI: 70%, 81%) of patients had a serum potassium in the target range of 3.8 mEq/L to <5.1 mEq/L at Part A Week 4.

Table 1: Patiromer treatment phase (Part A): Primary endpoint

	Baseline Potassium		Overall Population (n=237)
	5.1 to < 5.5 mEq/L (n=90)	5.5 to <6.5 mEq/L (n=147)	
	Serum Potassium (mEq/L)		
Baseline, mean (SD)	5.31 (0.57)	5.74 (0.40)	5.58 (0.51)

Week 4 Change from Baseline, Mean ± SE (95% CI)	-0.65 ± 0.05 (-0.74, -0.55)	-1.23 ± 0.04 (-1.31, -1.16)	-1.01 ± 0.03 (-1.07, -0.95)
p-value			<0.001

In Part B, 107 patients with a Part A baseline serum potassium of 5.5 mEq/L to <6.5 mEq/L and whose serum potassium was in the target range (3.8 mEq/L to <5.1 mEq/L) at Part A Week 4 and still receiving RAAS inhibitor treatment were randomised to continue patiromer or to receive placebo for 8 weeks to evaluate the effect of withdrawing patiromer on serum potassium. In patients randomised to patiromer, the mean daily dose was 21 g at the start of Part B and during Part B.

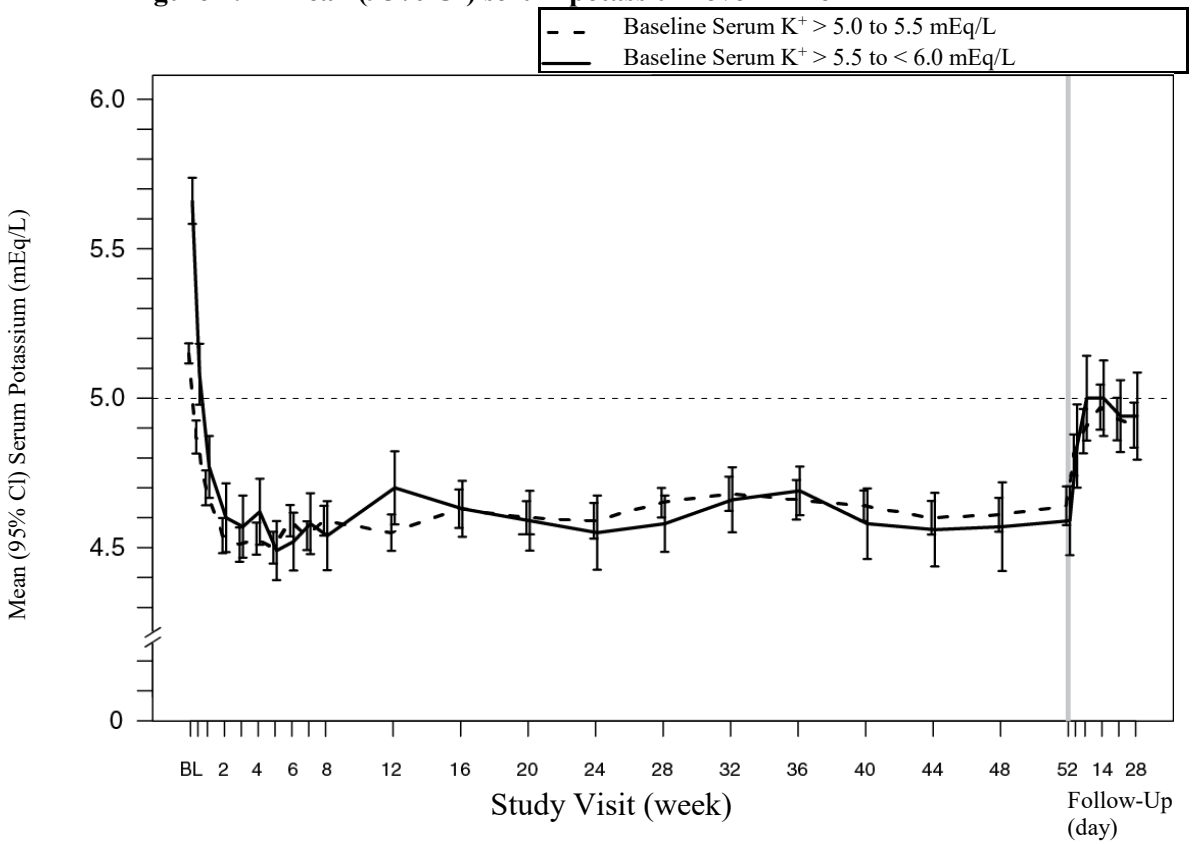
The Part B primary endpoint was the change in serum potassium from Part B baseline to the earliest visit at which the patient's serum potassium was first outside of the range of 3.8 to <5.5 mEq/L or to Part B Week 4 if the patient's serum potassium remained in the range. In Part B, serum potassium in patients on placebo increased significantly relative to patients who remained on patiromer (p<0.001).

More placebo patients (91% [95% CI: 83%, 99%]) developed a serum potassium ≥5.1 mEq/L at any time during Part B than patiromer patients (43% [95% CI: 30%, 56%]), p<0.001. More placebo patients (60% [95% CI: 47%, 74%]) developed a serum potassium ≥5.5 mEq/L at any time during Part B than patiromer patients (15% [95% CI: 6%, 24%]), p<0.001.

The potential of patiromer to enable concomitant RAAS inhibitor treatment was also assessed in part B. Fifty-two percent (52%) of subjects receiving placebo discontinued RAAS inhibitor treatment because of recurrent hyperkalaemia compared with 5% of subjects treated with patiromer.

The effect of treatment with patiromer for up to 52 weeks was evaluated in an open-label study of 304 hyperkalaemic patients with CKD and type 2 diabetes mellitus on stable doses of a RAAS inhibitor. The mean age of patients was 66 years (59.9% aged 65 and over, 19.7% aged 75 and over), 63% of patients were men, and all were Caucasian. Decreases in serum potassium with patiromer treatment were maintained over 1 year of chronic treatment as shown in Figure 1, with a low incidence of hypokalaemia (2.3%) and the majority of subjects reaching (97.7%) and maintaining target serum potassium levels (overall during maintenance period, serum potassium was within the target range for approximately 80% of the time). In patients with a baseline serum potassium of >5.0 to 5.5 mEq/L who received an initial dose of 8.4 g patiromer per day, the mean daily dose was 14 g; in those with a baseline serum potassium of >5.5 to <6.0 mEq/L who received an initial dose of 16.8 g patiromer per day, the mean daily dose was 20 g during the entire study.

Figure 1: Mean (95% CI) serum potassium over Time



Number of Subjects:																
Lower K^+ Stratum:	218	199	192	175	168	161	161	163	158	156	151	148	149	145	131	126
Higher K^+ Stratum:	83	73	70	65	62	62	62	61	53	53	53	52	49	49	48	47

The ability of patiromer to enable concomitant spironolactone treatment was investigated in a randomised, double-blind, placebo-controlled study in heart failure patients who were clinically indicated to receive AA. Patients initiated spironolactone at 25 mg/day at the same time as their randomised treatment (patiromer 12.6 g BID or placebo), and were up-titrated to 50 mg/day after Day 14 if serum potassium was >3.5 and ≤5.1 mEq/L. Of the 105 patients who were randomised and received study treatment (patiromer 56; placebo 49), mean age was 68.3 years, 60.6% were men, 97.1% were Caucasian, and mean eGFR was 81.3 mL/min. Mean baseline serum potassium values were 4.71 mEq/L for patiromer and 4.68 mEq/L for placebo.
The primary efficacy endpoint, change from baseline in serum potassium to the end of the 28-day treatment period, was significantly lower ($p<0.001$) in the patiromer group (LS mean [SEM]: -0. 21 [0.07] mEq/L) as compared to the placebo group (LS mean [SEM]: +0.23 [0.07] mEq/L). There were also fewer patients in the patiromer group with serum potassium values >5.5 mEq/L (7.3% vs. 24.5%; p=0.027) and more patients on spironolactone 50 mg/day (90.9% versus 73.5%, p=0.022).

The ability of patiromer to enable concomitant spironolactone treatment in patients with resistant hypertension and CKD was further investigated in a randomised, double-blind, placebo-controlled study over 12 weeks. Normokalaemic patients initiated spironolactone at 25 mg QD together with their randomised treatment (patiromer 8.4 g QD or placebo). Patiromer/placebo was titrated weekly (up to 25.2 g QD) to maintain serum potassium ≥4.0 mEq/L and ≤5.1 mEq/L. At week 3 or after, spironolactone dose was increased to 50 mg QD for subjects with systolic blood pressure ≥120 mmHg and serum potassium ≤5.1 mEq/L.
Of the 295 randomized patients receiving study treatment (patiromer 147; placebo 148), mean age was 68.1 years, 51.9% were men, 98.3% were Caucasian, and mean eGFR was 35.73 mL/min/1.73m2. At randomization, mean baseline serum potassium values were 4.74 mEq/L for patiromer and 4.69 mEq/L for placebo. The primary efficacy endpoint, the proportion of subjects remaining on spironolactone at Week 12, was significantly higher ($p<0.0001$) in the patiromer group (85.7%)

compared to the placebo group (66.2%). Significantly more patients received spironolactone 50 mg/day (69.4% versus 51.4%).
Overall, patients in the patiromer group remained on spironolactone 7.1 days longer (95% CI 2.2–12.0; *p*=0.0045) compared to the placebo group and received significantly higher cumulative doses of spironolactone (2942.3 (SE 80.1) mg vs 2580.7 (SE 95.8) mg, *p*=0.0021).
There were also significantly fewer patients in the patiromer group with serum potassium values ≥5.5 mEq/L (35.4% vs. 64.2%, *p*<0.001).
At Week 12, the mean systolic blood pressure had decreased by 11.0 mmHg (SD 15.34) in the spironolactone + placebo group and by 11.3 mmHg (SD 14.11) in the spironolactone + patiromer group. These decreases from baseline were statistically significant within each treatment group (*p*<0.0001), but not statistically significant between the groups.

Overall, in the phase 2 and 3 clinical studies, 99.5% of patients were receiving RAAS inhibitor therapy at baseline, 87% had CKD with eGFR <60 mL/min/1.73 m^2, 65.6% had diabetes mellitus and 47.5% had heart failure.

Effect of Food
In an open-label study, 114 patients with hyperkalaemia were randomized to patiromer once daily with food or without food. Serum potassium at the end of treatment, the change from baseline in serum potassium, and the mean dose of patiromer were similar between groups.

5.2 Pharmacokinetic properties

Patiromer works by binding potassium in the gastrointestinal tract and thus the serum concentration is not relevant for its efficacy. Due to the insolubility and nonabsorptive characteristics of this medicinal product, many classical pharmacokinetic studies cannot be carried out.

Patiromer is excreted approximately 24 to 48 hours after intake, based on average gastrointestinal transit time.

5.3 Preclinical safety data

In radiolabeled studies in rats and dogs, patiromer was not systemically absorbed and was excreted in the faeces. Quantitative whole-body autoradiography analysis in rats demonstrated that radioactivity was limited to the gastrointestinal tract, with no detectable level of radioactivity in any other tissues or organs.

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, toxicity to reproduction and development.

Patiromer was not genotoxic in the reverse mutation test (Ames assay), chromosome aberration or rat micronucleus assays.

Carcinogenicity studies have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Xanthan gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

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

6.4 Special precautions for storage

Store and transport refrigerated (2°C – 8°C).
Patients may store Veltassa below 25°C for up to 6 months.
For either storage condition, Veltassa should not be used after the expiry date printed on the sachet.
The mixture should be taken within 1 hour of initial suspension.

6.5 Nature and contents of container

8.4 g or 16.8 g of patiromer, as powder in sachets made of five layers: polyethylene, aluminium, polyethylene, polyester and paper.

Pack sizes: boxes of 30 sachets.

6.6 Special precautions for disposal and other handling

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

7. MANUFACTURER

Vifor Fresenius Medical Care Renal Pharma Ltd., Switzerland.
Rechenstrasse 37 CH-9017 St. Gallen, Switzerland.

8. MARKETING AUTHORISATION HOLDER

CTS Ltd.
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Hod-Hasharon
Israel

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