Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rayaldee 30 microgram prolonged-release capsules, soft

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 30 microgram Calcifediol as Calcifediol monohydrate.

Active ingredient: calcifediol.
Excipient(s) with known effect
Each capsule contains 18 mg sorbitol (E420) and 3.944 mg Ethanol.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release capsule, soft
Blue oval soft capsules, 11.7 mm by 6.4 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

RAYALDEE is indicated for the treatment of secondary hyperparathyroidism (SHPT) in adults with chronic kidney disease (CKD) Stage 3 or 4 and vitamin D insufficiency or deficiency.

4.2 Posology and method of administration

Posology

The initial dose of Rayaldee is 30 microgram, administered orally once daily at bedtime, at least 2 hours after any meals.
Prior to initiation of the treatment serum calcium should be below 2.45 mmol/L, serum phosphorus should be below 1.78 mmol/L (see section 4.4).
The dose should be increased to 60 microgram administered orally at bedtime, at least 2 hours after any meal after approximately 3 months, if intact PTH remains above the desired therapeutic range, individualised per patient. Prior to titration to the higher dose, serum calcium should be below 2.45 mmol/L, serum phosphorus should be below 1.78 mmol/L and serum 25-hydroxyvitamin D should be below 162 nmol/L.
The maintenance dose of Rayaldee should target serum 25-hydroxyvitamin D levels between 75 and 250 nmol/L, intact parathyroid hormone (PTH) levels within the desired therapeutic range, serum calcium within the normal range and serum phosphorus below 1.78 mmol/L.
Serum calcium, serum phosphorus, serum 25-hydroxyvitamin D and intact PTH levels should be monitored at a minimum of 3 months after initiation of therapy or dose adjustment, and subsequently at least every 6 to 12 months.
Dosing should be suspended if intact PTH is persistently abnormally low to reduce the risk of adynamic bone disease (see section 4.4), if serum calcium is consistently above the normal range to reduce the risks associated with hypercalcemia (see section 4.4), or if serum 25-hydroxyvitamin D is consistently above 250 nmol/L. Treatment should be restarted at a reduced dose after these laboratory values have normalized.

Paediatric population

The safety and efficacy of Rayaldee in children and adolescents below the age of 18 years have not been established
No data are available.

Elderly
No dose adjustment is required in elderly patients. Of the total number of subjects in phase 3 placebo-controlled clinical studies of Rayaldee, 63% were ≥65 years of age and 22% were ≥75 years of age. No overall differences in the safety or efficacy of Rayaldee were observed between subjects older than 65 years and younger subjects.

Renal impairment
The safety and efficacy of Rayaldee in the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on dialysis have not been established (see section 4.4).

Hepatic impairment
No data is available

Method of administration
Rayaldee is for oral use.
The capsules should be swallowed whole.
The prolonged-release capsule should be taken once a day at bedtime, at least 2 hours after any meal.

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

Hypercalcemia and hyperphosphatemia
Hypercalcemia may occur during Rayaldee treatment (see section 4.2). Acute hypercalcemia may increase the risk of cardiac arrhythmias and seizures. Chronic hypercalcemia can lead to vascular calcification and other soft-tissue calcification. Severe hypercalcemia may require emergency attention.
Hypercalcemia may be exacerbated by concomitant administration of high doses of calcium containing preparations, thiazide diuretics, or other vitamin D compounds. In these clinical situations, more frequent serum calcium monitoring and Rayaldee dose adjustments may be required. Patients with a history of hypercalcemia prior to initiating therapy with Rayaldee should be monitored more frequently for possible hypercalcemia during therapy. In CKD, high intake of calcium concomitantly with vitamin D compounds may lead to hypercalciuria.
Patients should be informed about the symptoms of elevated serum calcium. Increased phosphate intake concomitantly with vitamin D compounds may lead to hyperphosphatemia.
Patients with a history of hyperphosphatemia prior to initiating therapy with Rayaldee should be monitored more frequently for possible hyperphosphatemia during therapy.

Digitalis toxicity
Hypercalcemia of any cause, including hypercalcemia associated with Rayaldee use, increases the risk of digitalis toxicity (see section 4.5). Patients using Rayaldee concomitantly with digitalis compounds should be monitored for increases in serum calcium, and for signs and symptoms of digitalis toxicity. The frequency of monitoring should be increased when initiating or adjusting the dose of Rayaldee (see section 4.5).

Adynamic bone disease
Adynamic bone disease with subsequent increased risk of fractures may develop if intact PTH levels are over-suppressed for extended periods of time. Intact PTH levels should be monitored and Rayaldee dose adjusted, if needed (see section 4.2).

Renal impairment
The dosing recommendations are provided for adult patients with chronic kidney disease not on dialysis. No difference in efficacy was observed between patients with stage 3 chronic kidney disease or those with stage 4 disease in subgroup analysis. Safety outcomes were similar in these subgroups. The safety and efficacy of Rayaldee in the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on dialysis have not been established.

Paediatric population
No data is available.

Geriatric Use
No dose adjustment is required in elderly patients. Of the total number of subjects in phase 3 placebo-controlled clinical studies of Rayaldee, 63% were ≥65 years of age and 22% were ≥75 years of age. No overall differences in the safety or efficacy of Rayaldee were observed between subjects older than 65 years and younger subjects.

Hepatic Impairment
No data is available.

Drug Abuse and Dependence
Not applicable

Laboratory Tests
No data is available.

Laboratory Abnormalities
No data is available.

Warning on excipients:
This medicine contains 18 mg sorbitol (E420) per capsule which corresponds to 0.1 mg/mg
This medicine contains 3.9 mg of ethanol (alcohol) which corresponds to less than 100mg per dose.
This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No drug-drug interaction studies have been performed.
CYP3A Inhibitors: Cytochrome P450 inhibitors, such as ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin or voriconazole, may inhibit enzymes involved in vitamin D metabolism (CYP24A1 and CYP27B1), and may alter serum levels of calcifediol. Dose adjustment of Rayaldee may be required, and serum 25-hydroxyvitamin D, intact PTH and serum calcium concentrations should be closely monitored if a patient initiates or discontinues therapy with a strong CYP3A4 inhibitor.

Thiazides: Thiazides decrease urine calcium excretion and can increase the risk for hypercalcemia.. Concomitant administration of thiazides with Rayaldee may cause hypercalcemia. Patients may require more frequent serum calcium monitoring in this setting (see section 4.4).

Digitalis: Hypercalcemia may occur during Rayaldee treatment, which increases the risk of digitalis toxicity (risk of arrhythmias). Patients who receive cardiac glycosides must be monitored (ECG, serum calcium levels, see section 4.4).

Cholestyramine: Cholestyramine has been reported to reduce intestinal absorption of fat-soluble vitamins and may impair the absorption of calcifediol, the active ingredient in Rayaldee. Dose adjustment of Rayaldee may be required, and serum 25-hydroxyvitamin D, intact PTH and serum calcium concentrations should be closely monitored if a patient initiates or discontinues therapy with cholestyramine.

Other Agents: Phenobarbital or other anticonvulsants or other compounds that stimulate microsomal hydroxylation reduce the half-life of calcifediol, the active ingredient in Rayaldee. Dose adjustment of Rayaldee may be required, and serum 25-hydroxyvitamin D, intact PTH and serum calcium concentrations should be closely monitored if a patient initiates or discontinues therapy with phenobarbital or other anticonvulsants.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is no or limited amount of data from the use of calcifediol in pregnant women. Rayaldee should not be used during pregnancy unless the clinical condition of the woman requires treatment with calcifediol and the potential benefits to the mother outweigh the potential risks to the fetus. Studies in animals have shown reproductive toxicity (see section 5.3). There is no indication that vitamin D is teratogenic in humans at therapeutic doses The recommended daily intake level for vitamin D during pregnancy and lactation follows national guidelines and is around 600 I.U. (corr 15 microgram cholecalciferol) and should not exceed 4000 I.U.(100 microgram cholecalciferol).
Since an overdose of vitamin D has to be avoided during pregnancy, as prolonged hypercalcaemia can lead to physical and mental retardation, supravalvular aortic stenosis and retinopathy of the child.

Breast-feeding
There is insufficient information on the excretion of calcifediol/metabolites in human milk. This should be considered when giving additional vitamin D to the breastfed child.
A decision must be made whether to discontinue breast-feeding or to discontinue from Rayaldee therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

It is unknown whether calcifediol has an effect on human fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the Safety Profile
The current safety profile of Rayaldee is based on a total of 435 patients with chronic kidney disease (CKD) not on dialysis suffering from SHPT who received Rayaldee for up to 52 weeks.
The majority of adverse drug reactions (ADRs) reported from trials were blood phosphorus increased, hypercalcemia and gastrointestinal disorders.

Tabulated List of Adverse Reactions

System Organ Class	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**
Metabolism and nutrition disorders	blood phosphorus increased Hypercalcemia	Decreased appetite
Gastrointestinal disorders	Constipation Nausea Diarrhea	Abdominal discomfort Dry mouth Vomiting
General disorders and administration site conditions		Asthenia
Nervous system disorders		Dizziness Headache

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:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

No case of overdose has been reported.

However, overdosage of calcifediol may lead to hypercalcaemia, hypercalciuria, hyperphosphatemia, and over-suppression of PTH (see section 4.4).

In the event of an overdose, signs and symptoms of hypercalcemia (serum calcium levels) should be monitored and reported to a physician. Treatment should be initiated as appropriate.

Common symptoms of vitamin D overdosage may include constipation, decreased appetite, dehydration, fatigue, irritability, muscle weakness, or vomiting.
Treatment of acute accidental overdosage with Rayaldee should consist of general supportive measures. If the overdosage is discovered within a short time, emesis should be induced or gastric lavage should be performed to prevent further absorption. Serial serum calcium measurements should be obtained, and any electrocardiographic abnormalities due to hypercalcemia should be assessed. Supplemental calcium should be discontinued. Standard medical care is advised if persistent and markedly elevated serum calcium levels occur.
Calcifediol is not significantly removed by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other anti-parathyroid agents, ATC code: H05BX05

Calcifediol (25-hydroxyvitamin D3) is a prohormone of the active form of vitamin D3, calcitriol (1,25 dihydroxyvitamin D3). RAYALDEE is an oral prolonged release formulation of calcifediol which gradually raises serum 25-hydroxyvitamin D. This increase results in increases in progressive serum 1,25-dihydroxyvitamin D levels allowing for effective and sustained reductions of elevated blood PTH levels. Unlike nutritional vitamin D, calcifediol does not require further metabolism in the liver. Circulating calcitriol is derived from calcifediol after conversion by cytochrome P450 27B1 (CYP27B1), including in the kidneys. Circulating calcitriol binds to the vitamin D receptor in target tissues and activates vitamin D responsive pathways leading to reduced parathyroid hormone synthesis within the parathyroid glands and increasing intestinal tract absorption of calcium and phosphorus. Within the kidney the conversion of calcifediol to calcitriol is tightly regulated by elements of the bone mineral axis including serum PTH, FGF-23 (Fibroblast Growth Factor), calcium, and phosphate.

Data from the repeat-dose studies with RAYALDEE show that gradual elevation of serum 25-hydroxyvitamin D reduces circulating iPTH by suppression of iPTH production within the parathyroid gland. The increased serum calcifediol concentrations also gradually increases serum total calcitriol (the most active form of vitamin D).

Clinical Efficacy and Safety

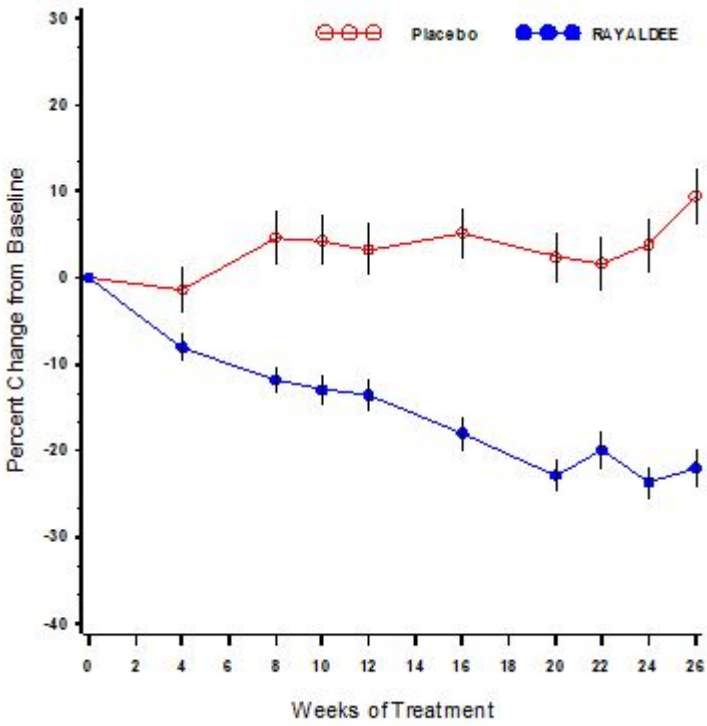
The efficacy and safety of Rayaldee were evaluated in two identical multicenter, randomized, placebo-controlled, double-blind trials in patients with secondary hyperparathyroidism, stage 3 or 4 chronic kidney disease and serum 25-hydroxyvitamin D levels between 25 and 75 nmol/L. Patients were stratified by chronic kidney disease stage and randomized in a 2:1 ratio to receive Rayaldee or a matching placebo at bedtime over 26 weeks. The dose of Rayaldee was 30 microgram once daily for the first 12 weeks and either 30 or 60 microgram once daily for the last 14 weeks. The dose was increased to 60 microgram at the start of week 13 if the plasma intact PTH level was greater than 7.4 pmol/L, the serum 25-hydroxyvitamin D level was less than 162 nmol/L and the serum calcium level was less than 2.4 mmol/L.

A total of 213 patients were randomized in one trial (72 received placebo and 141 received Rayaldee), and 216 patients were randomized in the second trial (72 received placebo and 144 received Rayaldee). The subjects' mean age was 66 years (range 25-85), 50% were male, 65% White, 32% African-American or Black and 3% Other. At baseline, patients had secondary hyperparathyroidism, and stage 3 (52%) or stage 4 (48%) chronic kidney disease without macroalbuminuria. The most common causes of chronic kidney disease were diabetes and hypertension and the mean estimated glomerular filtration rate (GFR) was 31 mL/min/1.73m2. Mean baseline intact PTH was 13.7 pmol/L for patients with stage 3 disease (n=222) and 17.6 pmol/L for patients with stage 4 disease (n=207). Mean serum calcium was 2.3 mmol/L, mean serum phosphorus was 1.2 mmol/L and mean serum 25-hydroxyvitamin D was 50 nmol/L. Of the 429 patients randomized, a total of 354 subjects (83%) completed these 26-week studies, comprised of 182 subjects (82%) with stage 3 CKD and 172 subjects (83%) with stage 4 CKD, and 298 (69%) enrolled in the subsequent extension study.

The primary analysis compared the proportion of individuals who experienced at least a 30% reduction in plasma intact PTH from baseline to end of trial (average of weeks 20, 22, 24 and 26). A larger proportion of patients randomized to Rayaldee experienced at least a 30% reduction in plasma intact PTH from baseline compared to placebo in both trials [33% versus 8% in the first trial ($P<0.001$) and 34% versus 7% in the second trial ($P<0.001$)].

A description of mean (SE) percent change in plasma intact PTH from baseline across study visits in the two trials combined is shown in Figure 1. Serum 25-hydroxyvitamin D levels increased to at least 75 nmol/L in 80% and 83% of patients treated with Rayaldee vs. 3% and 7% of patients treated with placebo ($P<0.001$) in the two studies, respectively. Average steady-state 25-hydroxyvitamin D levels were 125 and 140 nmol/L for subjects receiving 30 microgram daily, and 167 and 172 nmol/L for subjects receiving 60 microgram daily, in the first and second studies, respectively.

Figure 1. Mean (±SE) Percent Change from Baseline in Plasma Intact PTH in the Per Protocol Populations (Pooled Data from Two Phase 3 Studies)



The Per Protocol (PP) population consisted of all patients with at least 2 intact PTH values in the calculated baseline and EAP (Efficacy Assessment Period) values and who did not have a major protocol deviation during the treatment period of the study. The PP population comprised 83% of randomized subjects.

Increase in Serum Calcium

Patients randomized to Rayaldee experienced a greater mean (SE) increase in serum calcium (P<0.001) than patients randomized to placebo [i.e., 0.05 (0.05) mmol/L on Rayaldee versus 0.025 (0.0075) mmol/L on placebo from baseline to trial end]. Six subjects (2%) in the Rayaldee treatment group and no subjects (0%) in the placebo group required dose reductions for protocol-defined hypercalcemia (two consecutive serum calcium values greater than 2.57 mmol/L). A total of 4.2% of Rayaldee treated subjects and 2.1% of placebo treated subjects experienced at least 1 elevation in serum calcium above the upper limit of normal (2.62 mmol/L).

Increase in Serum Phosphorus

Patients randomized to Rayaldee experienced a greater mean (SE) increase in serum phosphorus than patients randomized to placebo [i.e., 0.065 (0.001) mmol/L on Rayaldee versus 0.032 (0.013) mmol/L on placebo from baseline to trial end]. One subject (0.4%) in the Rayaldee treatment group met protocol-defined hyperphosphatemia (two consecutive serum phosphorus values>1.78 mmol/L deemed to be study drug related) compared to no subjects in the placebo group. A total of 45% of Rayaldee treated subjects and 44% of placebo treated subjects experienced at least one elevation in serum phosphorus above the upper limit of normal (1.45 mmol/L).

Paediatric Population

No data is available.

5.2 Pharmacokinetic properties

Pharmacokinetic Properties

Absorption

Calcifediol is readily absorbed in the intestine. Its bioavailability from Rayaldee's formulation is approximately 25%, and the maximum plasma concentrations is reached after approximately 11 to 32 hours depending on whether administration occurs with a high fat, high calorie meal or in the fasting state.

No food effect study was conducted with 30 microgram and 60 microgram doses of Rayaldee. However, a food effect study with a supratherapeutic dose of 450 microgram in healthy subjects showed an approximately 5-fold increase in maximum serum calcifediol concentration (Cmax) and a 3.5-fold increase in AUC0-t when Rayaldee was administered with a high fat, high calorie meal compared to fasting.

Steady-state levels of serum 25-hydroxyvitamin D are reached after approximately 3 months (see section 5.1).

Distribution
Calcifediol is extensively bound to plasma proteins (>98%). The mean apparent volume of distribution is 8.8 L in healthy subjects following a single oral dose of Rayaldee, and 30.1 L in patients with stage 3 or 4 chronic kidney disease following repeated dosing.

Biotransformation
Production of calcitriol from calcifediol is catalysed by the 1-alpha-hydroxylase enzyme, CYP27B1, located in the kidney and all vitamin D-responsive tissues. CYP24A1, located in these tissues, catabolises both calcifediol and calcitriol to inactive metabolites.

Elimination
The mean elimination half-life of calcifediol is approximately 11 days in healthy individuals following a single dose of Rayaldee, and approximately 25 days in patients with stage 3 or stage 4 chronic kidney disease following repeated once daily dosing. Excretion of calcifediol occurs primarily through the biliary faecal route.

Linearity / non-linearity
Exposure to calcifediol increases proportionally over the dose range of 30 to 90 microgram following repeated daily administration of Rayaldee at bedtime to subjects with secondary hyperparathyroidism, chronic kidney disease and vitamin D insufficiency.

Pharmacokinetic/pharmacodynamic relationship(s)
The effectiveness of RAYALDEE in controlling elevated iPTH is based on the prolonged-release formulation which results in a sustained release of calcifediol that has been shown to minimize upregulation of CYP24A1.
One single-dose pharmacology study evaluated the impact of the rate of calcifediol administration on iPTH lowering. In this study, calcifediol was delivered either rapidly, via an IV bolus or gradually, via the prolonged-release formulation, to subjects with secondary hyperparathyroidism, stage 3 or 4 chronic kidney disease and vitamin D insufficiency. The findings indicated that rate of delivery is an important determinant of calcitriol production and that gradual delivery allows more effective treatment of both secondary hyperparathyroidism and the underlying vitamin D insufficiency.

Furthermore, single-dose of 900 microgram of prolonged-release calcifediol was compared with a single oral high dose of immediate release calcifediol 798 microgram in healthy adults. The prolonged-release formulation produced a gradual increase in calcifediol concentrations with subsequent increases in 1,25-dihydroxyvitamin D and only modest increases in the inactive metabolic 24,25-dihydroxyvitamin D. The orally administered immediate release formulation produced a rapid increase in calcifediol concentrations with a Tmax 3 times greater and a time to Tmax shorter than the prolonged-release formulation. The immediate release formulation produced an acute spike in 1,25-dihydroxyvitamin D concentrations with resultant large increases in the inactive metabolite 24,25-dihydroxyvitamin D.

Age, gender and race
Based on a population pharmacokinetic analysis, age, gender and race had no meaningful impact on steady-state concentrations of calcifediol following Rayaldee administration.

Renal Impairment
Based on the population pharmacokinetics analysis, there was no meaningful difference in calcifediol steady-state concentrations following repeated Rayaldee administration in patients with stage 3 or stage 4 chronic kidney disease.

Hepatic Impairment
The pharmacokinetics of Rayaldee have not been investigated in patients with hepatic impairment.

Elderly
No data is available.

Paediatric Population
No data is available.

Other Special Populations
No data is available

5.3 Preclinical safety data

Effects in non-clinical repeat-dose toxicity studies were observed only at exposures considered sufficiently in excess of the maximum human exposure, indicating such toxicity is only likely to occur in chronic overdosage where hypercalcaemia could result.
No neoplastic changes attributable to calcifediol were observed at subcutaneous doses of 3, 10 and 33 microgram/kg/day in a 26-week rasH2 transgenic mouse study.
No data on fertility is available for calcifediol. No effects were observed in reproductive fertility studies with cholecalciferol. Normal endogenous levels of vitamin D are not expected to have any adverse effects on fertility.
The active metabolite of calcifediol, calcitriol, was shown to be teratogenic in rabbits when given in doses corresponding to more than 9-fold of recommended human calcitriol dose. Calcitriol was not teratogenic in rats.
Normal endogenous levels of cholecalciferol, a precursor of calcifediol, has no potential mutagenic or carcinogenic activity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The capsule fill contains:
Paraffin, hard
Paraffin, liquid
hypromellose
Glycerol monostearate
Lauroyl macrogolglycerides
Ethanol, anhydrous
Butylated hydroxytoluene

The capsule shell contains:
Modified starch (hydroxypropylstarch)
Carrageenan
Disodium phosphate, anhydrous
Sorbitol, liquid, partially dehydrated (E420)
Brilliant Blue FCF (E 133)
Titanium dioxide
purified water.
Medium chain triglyceride (fractionated coconut) oil is used as a lubricant during manufacture, and trace amounts may be present in the final formulation.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

18 months
Once opened, Rayaldee can be stored for up to 60 days

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

Round, white high density polyethylene (HD-PE) bottle with push and turn plastic closure and inner heat-seal liner and thread.
Pack size of 30 capsules or multipack of 90 capsules (3 packs of 30 capsules).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Vifor Fresenius Medical Care Renal Pharma France
100 - 101 Terrasse Boieldieu, Tour Franklin
Defense 8
92042
France

8 MARKETING AUTHORISATION NUMBER

PA22774/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th September 2020

10 DATE OF REVISION OF THE TEXT

January 2023