SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Rextol 5 mcg/ml

Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for injection contains 5 micrograms of paricalcitol.
Each 1 ml ampoule contains 5 micrograms of paricalcitol.
Each 2 ml ampoule contains 10 micrograms of paricalcitol.

Excipients: Ethanol anhydrous (11% v/v) and propylene glycol (39% v/v)

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection
A clear and colourless aqueous solution that is free from visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Rextol 5 mcg/ml is indicated for the prevention and treatment of secondary hyperparathyrodism in patients with chronic renal failure who are undergoing haemodialysis.

4.2 Posology and method of administration

Posology

Adults

1) Initial Dose should be calculated based on baseline parathyroid hormone (PTH) levels:

The initial dose of paricalcitol is based on the following formula:

$$\text{Initial dose (micrograms)} = \frac{\text{baseline intact PTH level in pmol/l}}{8}$$

OR

$$= \frac{\text{baseline intact PTH level in pg/mL}}{80}$$

and administered as an intravenous (IV) bolus dose no more frequently then every other day at any time during dialysis.

The maximum dose safely administered in clinical studies was as high as 40 micrograms.

2) Titration Dose:

The currently accepted target range for PTH levels in end-stage renal failure subjects undergoing dialysis is no more than 1.5 to 3 times the non-uremic upper limit of normal, 15.9 to 31.8 pmol/l (150-300 pg/ml), for intact PTH. Close monitoring and individual dose titration are necessary to reach appropriate physiological endpoints.
If hypercalcaemia or a persistently elevated corrected Ca x P product greater than 5.2 $mmol^2/l^2$ (65 mg^2/dl^2) is noted, the dosage should be reduced or interrupted until these parameters are normalised. Then, paricalcitol administration should be reinitiated at a lower dose. Doses may need to be decreased as the PTH levels decrease in response to therapy.

The following table is a suggested approach for dose titration:

Suggested Dosing Guidelines (Dose adjustments at 2 to 4 week intervals)	
iPTH Level Relative to Baseline	**Paricalcitol Dose Adjustment**
Same or increased	Increase by 2 to 4 micrograms
Decreased by < 30%	
Decreased by ≥ 30%, ≤ 60%	Maintain
Decreased > 60%	Decrease by 2 to 4 micrograms
iPTH < 15.9 pmol/l (150 pg/mL)	

Once dosage has been established, serum calcium and phosphate should be measured at least monthly. Serum intact PTH measurements are recommended every three months. During dose adjustment with paricalcitol, laboratory tests may be required more frequently.

Hepatic impairment
Unbound concentrations of paricalcitol in patients with mild to moderate hepatic impairment are similar to healthy subjects and dose adjustment is not necessary in this patient population. There is no experience in patients with severe hepatic impairment.

Paediatric population (0-18 years)
The safety and efficacy of Rextol 5 mcg/ml in children have not been established.

Elderly (>65years)
There is a limited amount of experience with patients 65 years of age or over receiving paricalcitol in the phase III studies. In these studies, no overall differences in efficacy or safety were observed between patients 65 years or older and younger patients.

Method of administration
Rextol 5mcg/ml Solution for Injection is administered via haemodialysis access.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Vitamin D toxicity

- Hypercalcemia

4.4 Special warnings and precautions for use

Over suppression of parathyroid hormone may result in elevations of serum calcium levels and may lead to metabolic bone disease. Patient monitoring and individualized dose titration is required to reach appropriate physiological endpoints.

If clinically significant hypercalcaemia develops, and the patient is receiving a calcium-based phosphate binder, the dose of the calcium-based phosphate binder should be reduced or interrupted.

Chronic hypercalcaemia may be associated with generalized vascular calcification and other soft-tissue calcification.

Phosphate or vitamin D-related medicinal products should not be taken concomitantly with paricalcitol due to an increased risk of hypercalcaemia and Ca x P product elevation (see section 4.5).

Digitalis toxicity is potentiated by hypercalcaemia of any cause, so caution should be applied when digitalis is prescribed concomitantly with paricalcitol (see section 4.5).

Caution should be exercised if co-administering paricalcitol with ketoconazole (see section 4.5).

Warning for excipients
This medicinal product contains 11% v/v of ethanol (alcohol). Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, and high-risk groups such as patients with liver disease or epilepsy.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with paricalcitol injection. However, an interaction study between ketoconzole and paricalcitol has been performed with the capsule formulation.

Ketoconazole: Ketoconazole is known to be a non-specific inhibitor of several cytochrome P450 enzymes. The available *in vivo* and *in vitro* data suggest that ketoconazole may interact with enzymes that are responsible for the metabolism of paricalcitol and other vitamin D analogs. Caution should be taken while dosing paricalcitol with ketoconazole (see Section 4.4). The effect of multiple doses of ketoconazole administered as 200 mg, twice daily (BID) for 5 days on the pharmacokinetics of paricalcitol capsule has been studied in healthy subjects. The Cmax of paricalcitol was minimally affected, but AUC0-∞ approximately doubled in the presence of ketoconazole. The mean half-life of paricalcitol was 17.0 hours in the presence of ketoconazole as compared to 9.8 hours, when paricalcitol was administered alone.
The results of this study indicate that following oral administration of paricalcitol the maximum amplification of the paricalcitol AUC ∞ from a drug interaction with ketoconazole is not likely to be greater than about two-fold.

Specific interaction studies were not performed with paricalcitol injection. Digitalis toxicity is potentiated by hypercalcaemia of any cause, so caution should be applied when digitalis is prescribed concomitantly with paricalcitol (see Section 4.4).

Phosphate or vitamin D-related medicinal products should not be taken concomitantly with paricalcitol, due to an increased risk of hypercalcaemia and Ca x P product elevation (see section 4.4).

High doses of calcium-containing preparations or thiazide diuretics may increase the risk of hypercalcaemia.

Magnesium-containing preparations (e.g. antacids) should not be taken concomitantly with vitamin D preparations, because hypermagnesemia may occur.

Aluminium-containing preparations (e.g., antacids, phosphate-binders) should not be administered chronically with Vitamin D medicinal products, as increased blood levels of aluminum and aluminum bone toxicity may occur.

4.6 Fertility, pregnancy and lactation

Pregnancy:

There are no or limited amount of data from the use of paricalcitol in pregnant women.
Studies in animals have shown reproductive toxicity (see section 5.3).
Rextol 5 mcg/ml is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding:

It is unknown whether paricalcitol/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of paricalcitol/metabolites in milk (for details see 5.3).
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A risk to the newborns/infants cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Rextol 5 mcg/ml therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
Animal studies have shown no effect of paricalcitol on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Dizziness may occur following administration of paricalcitol, which may have a minor influence on the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
Approximately 600 patients were treated with paricalcitol in Phase II/III/IV clinical trials. Overall, 6% of the paricalcitol treated patients reported adverse reactions.

The most common adverse reaction associated with paricalcitol therapy was hypercalcaemia, occurring in 4.7% of patients. Hypercalcaemia is dependent on the level of PTH oversuppression and can be minimised by proper dose titration.

Tabulated List of adverse reactions:
Adverse events at least possibly related to paricalcitol, both clinical and laboratory are displayed by MedDRA System Organ Class, Adverse reaction and frequency**.** The following frequency groupings are used: Very common (≥ 1/10); common (≥ 1/100, <1/10); uncommon (≥ 1/1000, <1/100); rare (≥ 1/10,000, <1/1000); very rare (<1/10000), not known (cannot be estimated from the available data).

System Organ Class	**Preferred Term**	**Frequency**
Infections and infestations	Sepsis, pneumonia, infection pharyngitis, vaginal infection, influenza	Uncommon
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Breast cancer	Uncommon
Blood and lymphatic system disorders	Anaemia, leukopenia, lymphadenopathy	Uncommon
Immune system disorders	Hypersensitivity	Uncommon
	Laryngeal oedema, angioedema, urticaria	Not Known*
Endocrine Disorders	Hypoparathyrodism	Common
	Hyperparathyrodism	Uncommon
Metabolism and nutrition disorders	Hypercalcaemia, Hyperphosphataemia	Common
	Hyperkalaemia, hypocalcemia, anorexia	Uncommon
Psychiatric disorders	Confusional state, delirium, depersonalization, agitation, insomnia, nervousness	Uncommon
Nervous system disorders	Headache, dysgeusia	Common
	Coma, cerebrovascular accident, transient ischemic attack, syncope, myoclonus, hypoaesthesia, paraesthesia, dizziness	Uncommon
Eye disorders	Glaucoma, conjunctivitis	Uncommon
Ear and labyrinth disorders	Ear disorder	Uncommon
Cardiac disorders	Cardiac arrest, arrhythmia, atrial flutter	Uncommon
Vascular disorders	Hypertension, hypotension	Uncommon
Respiratory, thoracic and mediastinal disorders	Pulmonary oedema, asthma, dyspnoea, epistaxis, cough	Uncommon
Gastrointestinal disorders	Rectal haemhorrhage, colitis, diarrhoea, gastritis, dyspepsia, dysphagia, abdominal pain,	Uncommon

	constipation, nausea, vomiting, dry mouth, gastrointestinal disorder	
	Gastrointestinal haemorrhage	Not known
Skin and subcutaneous tissue disorders	Pruritus	Common
	Bullous dermatitis, alopecia, hirsutism, rash, hyperhidrosis	Uncommon
Musculoskeletal and connective tissue disorders	Arthralgia, joint stiffness, back pain, muscle twitching, myalgia	Uncommon
Reproductive system and breast disorders	Breast pain, erectile dysfunction	Uncommon
General disorders and administration site conditions	Gait disturbance, oedema, peripheral oedema, pain, injection site pain, pyrexia, chest pain, condition aggravated, asthenia, malaise, thirst	Uncommon
Investigations	Bleeding time prolonged, aspartate aminotransferase increased, laboratory test abnormal, weight decreased	Uncommon

*Frequencies for adverse reactions from postmarketing experience cannot be estimated and have been reported as "Not known."

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

No case of overdose has been reported.

Overdosage of paricalcitol may lead to hypercalcemia, 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.

Paricalcitol is not significantly removed by dialysis. Treatment of patients with clinically significant hypercalcaemia consists of immediate dose reduction or interruption of paricalcitol therapy and includes a low calcium diet, withdrawal of calcium supplements, patient mobilisation, attention to fluid and electrolyte imbalances, assessment of electrocardiographic abnormalities (critical in patients receiving digitalis), and haemodialysis or peritoneal dialysis against a calcium-free dialysate, as warranted.

When serum calcium levels have returned to within normal limits, paricalcitol may be reinitiated at a lower dose. If persistent and markedly elevated serum calcium levels occur, there are a variety of therapeutic alternatives that may be considered. These include the use of drugs such as phosphates and corticosteroids as well as measures to induce diuresis.

Rextol solution for injection contains 39% v/v of propylene glycol as an excipient. Isolated cases of Central Nervous System depression, haemolysis and lactic acidosis have been reported as toxic effect associated with propyleneglycol administration at high doses. Although they are not expected to be found with Rextol 5mcg/ml administration as propyleneglycol is eliminated during the dialysis process, the risk of toxic effect in overdosing situations has to be taken into account.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Anti-parathyroid agents, ATC code: H05BX02

Mechanism of action:

Paricalcitol is a synthetic, biologically active vitamin D analog of calcitriol with modifications to the side chain (D2) and the A (19-nor) ring Unlike calcitriol, paricalcitol is a selective vitamin D receptor (VDR) activator. Paricalcitol selectively upregulates the VDR in the parathyroid glands without increasing VDR in the intestine and is less active on bone resorption. Paricalcitol also upregulates the calcium sensing receptor (CaSR) in the parathyroid glands. As a result, paricalcitol reduces parathyroid hormone (PTH) levels by inhibiting parathyroid proliferation and decreasing PTH synthesis and secretion, with minimal impact on calcium and phosphorus levels, and can act directly on bone cells to maintain bone volume and improve mineralization surfaces. Correcting abnormal PTH levels, with normalization of calcium and phosphorus homeostasis, may prevent or treat the metabolic bone disease associated with chronic kidney disease.

5.2 Pharmacokinetic properties

Distribution

The pharmacokinetics of paricalcitol have been studied in patients with chronic renal failure (CRF) requiring haemodialysis. Paricalcitol is administered as an intravenous bolus injection. Within two hours after administering doses ranging from 0.04 to 0.24 microgram/kg, concentrations of paricalcitol decreased rapidly; thereafter, concentrations of paricalcitol declined log-linearly with a mean half-life of about 15 hours. No accumulation of paricalcitol was observed with multiple dosing. *In vitro* plasma protein binding of paricalcitol was extensive (>99.9%) and nonsaturable over the concentration range of 1 to 100 ng/mL.

Biotransformation

Several unknown metabolites were detected in both the urine and faeces, with no detectable paricalcitol in the urine. These metabolites have not been characterized and have not been identified. Together, these metabolites contributed 51% of the urinary radioactivity and 59% of the faecal radioactivity.

Paricalcitol Pharmacokinetic Characteristics in CRF Patients (0.24 μg/kg dose)		
Parameter	**N**	**Values (Mean ± SD)**
Cmax (5 minutes after bolus)	6	1850 ± 664 (pg/mL)
AUCo-∞	5	27382 ± 8230 (pg•hr/mL)
CL	5	0.72 ± 0.24 (L/hr)
Vss	5	6 ± 2 (L)

Elimination

In healthy subjects, a study was conducted with a single 0.16 microgram/kg intravenous bolus dose of 3H-paricalcitol (n=4), plasma radioactivity was attributed to parent substance. Paricalcitol was eliminated primarily by hepatobiliary excretion, as 74% of the radioactive dose was recovered in faeces and only 16% was found in urine.

Special Populations

Gender, Race and Age: No age or gender related pharmacokinetic differences have been observed in adult patients studied. Pharmacokinetic differences due to race have not been identified.

Hepatic impairment: Unbound concentrations of paricalcitol in patients with mild to moderate hepatic impairment is similar to healthy subjects and dose adjustment is not necessary in this patient population. There is no experience in patients with severe hepatic impairment.

5.3 Preclinical safety data

Salient findings in the repeat dose toxicology studies in rodents and dogs were generally attributed to paricalcitol's calcaemic activity. Effects not clearly related to hypercalcaemia included decreased white blood cell counts and thymic atrophy in dogs, and altered APTT values (increased in dogs, decreased in rats). WBC changes were not observed in clinical trials of paricalcitol.

Paricalcitol did not affect fertility in rats and there was no evidence of teratogenic activity in rats or rabbits. High doses of other vitamin D preparations applied during pregnancy in animals lead to teratogenesis. Paricalcitol was shown to affect foetal viability, as well as to promote a significant increase of peri-natal and post-natal mortality of newborn rats, when administered at maternally toxic doses.

Paricalcitol did not exhibit genotoxic potential in a set of *in-vitro* and *in-vivo* genotoxicity assays.

Carcinogenicity studies in rodents did not indicate any special risks for human use.

Doses administered and/or systemic exposures to paricalcitol were slightly higher than therapeutic doses/systemic exposures.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol
Ethanol anhydrous (11 % v/v)
Water for Injections

6.2 Incompatibilities

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

Propylene glycol interacts with heparin and neutralises its effect. Rextol solution for injection contains propylene glycol as an excipient and should be administered through a different injection port than heparin.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
After opening, use immediately.

6.4 Special precautions for storage

Store below 25°C in the original package.

6.5 Nature and contents of container

Each Type 1 glass ampoule contains 1mL or 2mL of solution for injection.
The presentations of Rextol 5mcg/ml are:
Pack containing 5 ampoules of 1mL of solution for injection
Pack containing 5 ampoules of 2mL of solution for injection
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration. The solution is clear and colourless.
For single use only.
Any unused medicinal product or waste should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Lapidot Medical Import and Marketing Ltd.
8 Hashita st., Caesarea Industrial Park 3088900, Israel

8 MANUFACTURER

Rafarm S.A., Attiki, Greece.

9 MARKETING AUTHORISATION NUMBER

160-03-34789-00

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