Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paricalcitol 2 microgram/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect: Ethanol anhydrous (11% v/v, 0.110ml/1ml)
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

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

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Paricalcitol is indicated for the prevention and treatment of secondary hyperparathyroidism in patients with chronic renal failure undergoing haemodialysis.

4.2 Posology and method of administration

Method of administration
Paricalcitol solution for injection is administered via haemodialysis access.

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:

$$\text{Initial dose (micrograms)} = \frac{\text{baseline intact PTH level in pmol/1}}{8}$$

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 μg.

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/1 (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/1 (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 insufficiency
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.

Pediatric Population
The safety and efficacy of Paricalcitol in children have not been established. The experience in children is limited and no data for children under the age of 5 are available. The currently available data on paediatric patients are described in Section 5.1.

Geriatric Use
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.

4.3 Contraindications

Hypersensitivity to paricalcitol 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 hypercalcemia develops, and the patient is receiving a calcium-based phosphate binder, the dose of the calcium-based phosphate binder should be reduced or interrupted.

Digitalis toxicity is potentiated by hypercalcemia 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).

This medicinal product contains 11% v/v of ethanol (alcohol), i.e. up to 87mg per 1ml. Harmful for those suffering from alcoholism.
To be taken into account in pregnant or breast-feeding women, children 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.

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.

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

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

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

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 $AUC_{0-\infty}$ 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 $AUC_{0-\infty}$ from a drug interaction with ketoconazole is not likely to be greater than about two-fold.

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).

4.6 Fertility, pregnancy and lactation

Pregnancy:
There are no adequate data from the use of paricalcitol in pregnant women. Animal studies have shown reproductive toxicity *(see section 5.3).* Potential risk in human use is not known, therefore paricalcitol should not be used unless clearly necessary.

Breastfeeding:
Animal studies have shown excretion of paricalcitol or its metabolites in breast milk, in small amounts. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with paricalcitol should be made taking into account the benefit of breast-feeding to the child and the benefit of paricalcitol therapy to the woman.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

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.

Adverse events at least possibly related to paricalcitol, both clinical and laboratory are displayed by MedDRA System Organ Class, Preferred Term and frequency. The following frequency groupings are used:
Very common (≥1/10);
Common (≥1/100 to <1/10);
Uncommon (≥1/1,000 to <1/100);
Rare (≥1/10,000 to <1/1,000);
Very rare (<1/10,000),
Not known (can not 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, uritcaria	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 attach, 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, constipation, nausea, vomiting, dry mouth, gastrointestinal disorder	Uncommon
	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, 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

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: http://www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

No case of overdose has been reported.

Overdosage of paricalcitol may lead to hypercalcemia.

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.

Paricalcitol 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 Paricalcitol administration as propylene glycol 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

Pharmacotherapeutic group: Other 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 (D_2) and the A (19-nor) ring allowing for selective vitamin D receptor (VDR) activation. 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.

Paediatric population: The safety and effectiveness of paricalcitol were examined in a 12-week randomised, double-blind, placebo-controlled study of 29 pediatric patients, aged 5-19 years, with end-stage renal disease on hemodialysis. The six youngest paricalcitol-treated patients in the study were 5 - 1 2 years old. The initial dose of paricalcitol was 0.04 mcg/kg 3 times per week, based on baseline iPTH level of less than 500 pg/mL, or 0.08 mcg/kg 3 times a week based on baseline iPTH level of $\geq$ 500 pg/mL, respectively. The dose of paricalcitol was adjusted in 0.04 mcg/kg increments based on the levels of serum iPTH, calcium, and Ca x P. 67% of the paricalcitol-treated patients and 14% placebo-treated patients completed the trial. 60% of the subjects in the Paricalcitol group had 2 consecutive 30% decreases from baseline iPTH compared with 21% patients in the placebo group. 71% of the placebo patients were discontinued due to excessive elevations in iPTH levels. No subjects in either the Paricalcitol group or placebo group developed hypercalcemia. No data are available for patients under the age of 5.

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.

Elimination
In healthy subjects, a study was conducted with a single 0.16 microgram/kg intravenous bolus dose of ^{3}H-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.

Biotransformation
Several unknown metabolites were detected in both the urine and faeces, with no detectable paricalcitol in the urine. These metabolites have not been characterised and have not been identified. Together, these metabolites contributed 51% of the urinary radioactivity and 59% of the faecal radioactivity. *In vitro* plasma protein binding of paricalcitol was extensive (>99.9%) and nonsaturable over the concentration range of 1 to 100 ng/mL.

Paricalcitol Pharmacokinetic Characteristics in CRF Patients (0.24 µg/kg dose)		
Parameter	N	**Values (Mean ± SD)**
C_{max} (5 minutes after bolus)	6	1850±664 (pg/mL)
$AUC_{0-\infty}$	5	27382 ± 8230 (pg □hr/mL)
CL	5	0.72 ± 0.24 (L/hr)
V_{ss}	5	6 ± 2 (L)

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

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

6.2 Incompatibilities

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

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

6.3 Shelf life

2 years.

After opening, use immediately.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Clear glass ampoules of 2.00 ml capacity made from glass type I (Type I hydrolytic class glass).
Clear glass type I vials of 3.00 ml capacity sealed with bromobutyl flurotec-injection stoppers and secured with aluminium caps with flip-off.

The presentations of Paricalcitol are:

Pack containing 1 ampoule of 1 ml solution for injection
Pack containing 5 ampoules of 1 ml solution for injection
Pack containing 1 vial of 1 ml solution for injection
Pack containing 5 vials of 1 ml solution for injection

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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 solution should be discarded.

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

7 MARKETING AUTHORISATION HOLDER

Medice Arzneimittel Putter GmbH & Co. K.G
Kuhloweg 37
58638 Iserlohn
Germany

8 MARKETING AUTHORISATION NUMBER

PA1550/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th May 2015

10 DATE OF REVISION OF THE TEXT