Zemplar 1 microgram

Soft Capsules

Prescribing Information

1. NAME OF THE MEDICINAL PRODUCT

Zemplar 1 microgram capsules, soft

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule of Zemplar 1 microgram contains 1 microgram of paricalcitol.

Excipient with known effect:
Each capsule of Zemplar 1 microgram contains 0.71 mg of ethanol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, soft

1 microgram capsule: oval, grey soft capsule imprinted with ZA

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zemplar is indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic renal insufficiency (chronic kidney disease Stages 3 and 4) patients and chronic renal failure (chronic kidney disease Stage 5) patients on haemodialysis or peritoneal dialysis.

4.2 Posology and method of administration

Posology

Chronic Kidney Disease (CKD) Stages 3 and 4
Zemplar should be administered once a day, either daily or three times a week taken every other day.

Initial dose

The initial dose is based on baseline intact parathyroid hormone (iPTH) levels.

Table 1. Initial Dose

Baseline iPTH Level	Daily Dose	Three Times a Week Dose*
≤ 500 pg/ml (56 pmol/l)	1 microgram	2 micrograms
> 500 pg/ml (56 pmol/l)	2 micrograms	4 micrograms

* To be administered no more frequently than every other day

Dose titration

Dosing must be individualised based on serum or plasma iPTH levels, with monitoring of serum calcium and serum phosphorus. Table 2 presents a suggested approach for dose titration.

Table 2. Dose Titration

iPTH Level Relative to Baseline	Dose Adjustment at 2 to 4 Week Intervals	
	Daily Dose	**Three Times a Week Dose[1]**
The same or increased	Increase 1 microgram	Increase 2 micrograms
Decreased by < 30%		
Decreased by ≥30%, ≤60%	Maintain	Maintain
Decreased > 60%	Decrease[2] 1 microgram	Decrease[2] 2 micrograms
iPTH < 60 pg/ml (7 pmol/l)		

[1] To be administered no more frequently than every other day.
[2] If a patient is taking the lowest dose on the daily or three times a week regimen, and a dose reduction is needed, dosing frequency can be decreased.

Serum calcium levels should be closely monitored after initiation of the treatment and during dose titration periods. If hypercalcaemia or a persistently elevated calcium- phosphate product greater than 55 mg^2/dl^2 (4.4 $mmol^2/l^2$) is observed, the dose of calcium based phosphate binders should be reduced or withheld. Alternatively, the dose of Zemplar may be reduced or temporarily interrupted. If interrupted, the drug should be restarted at a lower dose, when serum calcium and calcium- phosphate product are in the target range.

Chronic Kidney Disease (CKD), Stage 5

Zemplar should be administered three times a week every other day.

Initial dose

The initial dose of Zemplar in micrograms is based on a baseline iPTH level (pg/ml)/60 [(pmol/l)/7], up to an initial maximum dose of 32 micrograms.

Dose titration

Subsequent dosing should be individualised and based on iPTH, serum calcium and phosphorus levels. A suggested dose titration of paricalcitol capsules is based on the following formula:

$$\text{Titration dose (micrograms)} = \frac{\text{most recent iPTH le}}{60}$$

OR

$$\text{Titration dose (micrograms)} = \frac{\text{most recent iPTH le}}{7}$$

Serum calcium and phosphorus levels should be closely monitored after initiation, during dose titration periods, and with co-administration of strong P450 3A inhibitors. If an elevated serum calcium or elevated Ca x P is observed and the patient is on a calcium-based phosphate binder, the binder dose may be decreased or withheld, or the patient may be switched to a non-calcium-based phosphate binder.

If serum calcium > 11.0 mg/dl (2.8 mmol/l) or Ca x P > 70 mg^2/dl^2 (5.6 $mmol^2/l^2$) or iPTH ≤ 150 pg/ml, the dose should be decreased by 2 to 4 micrograms with respect to that calculated by the most recent iPTH/60 (pg/ml) [iPTH/7 (pmol/l)]. If further adjustment is required, the dose of paricalcitol capsules should be reduced or interrupted until these parameters are normalised.

As iPTH approaches the target range (150-300 pg/ml), small, individualised dose adjustments may be necessary in order to achieve a stable iPTH. In situations where monitoring of iPTH, Ca or P occurs less frequently than once per week, a more modest initial and dose titration ratio may be warranted.

Special populations

Hepatic impairment
No dose adjustment is required in patients with mild to moderate hepatic impairment.
There is no experience in patients with severe hepatic impairment (see section 5.2).

Renal transplant
Post-renal transplant patients with CKD Stages 3 and 4 and secondary hyperparathyroidism were not studied in phase 3 clinical trials. Based on the published literature, the initial dose and dose-titration algorithm for patients with post-transplant CKD Stages 3 and 4 and secondary hyperparathyroidism is the same as for patients with native CKD Stages 3 and 4 and secondary hyperparathyroidism. Serum calcium and phosphorus levels should be closely monitored after initiation, during dose titration periods, and with co-administration of strong cytochrome P450 3A inhibitors.

Paediatric population

Zemplar is not indicated for children and adolescents below 18 years of age.

Elderly

No overall differences in safety and effectiveness were observed between elderly patients (65-75 years) with regard to younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Method of administration

Zemplar can be taken with or without food.

4.3 Contraindications

Paricalcitol should not be given to patients with evidence of vitamin D toxicity, hypercalcaemia, or hypersensitivity to paricalcitol or any of the excipients listed in section 6.1.

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 low-turnover bone disease. Patient monitoring and individualised 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).

In pre-dialysis patients, paricalcitol, like other vitamin D receptor activators, may increase serum creatinine (and therefore decrease the estimated GFR [eGFR]) without changing true glomerular filtration rate (GFR).

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

Warning for excipients

This medicinal product contains small amounts of ethanol (alcohol), less than 100 mg per 1 microgram, capsule which may be harmful to those suffering from alcoholism (refer to sections 2 and 4.2). 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

Ketoconazole

Ketoconazole is known to be a nonspecific 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.The effect of multiple doses of ketaconazole 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 (see PRECAUTIONS section 4.4). The results of this study indicate that following either oral or intravenous administration of paricalcitol the maximum amplification of the paricalcitol AUCINF from a drug interaction with ketoconazole is not likely to be greater than about two-fold.

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

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 preparation 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 aluminium and aluminium bone toxicity may occur.

Drugs that impair intestinal absorption of fat-soluble vitamins, such as cholestyramine, may interfere with the absorption of Zemplar capsules.

4.6 Pregnancy and Lactation

Pregnancy

There are no adequate data on 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 be not be used unless clearly necessary.

Breastfeeding

It is not known whether paricalcitol is excreted in human milk. 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 Zemplar should be made taking into account the benefit of breast-feeding to the child and the benefit of Zemplar therapy to the woman.

4.7 Effects on ability to drive and use machines

Zemplar has negligible influence on ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of paricalcitol capsules has been evaluated in three 24-week, double-blind, placebo-controlled, multi-centre clinical trials involving 220 CKD Stage 3 and 4 adult patients and in one 12-week, double-blind, placebo-controlled, multi-centre clinical trial involving 88 CKD Stage 5 adult patients. In addition, there is postmarketing experience with paricalcitol capsules from three additional studies, and paediatric experience from two studies. The most commonly reported adverse reactions for paricalcitol treated patients were hypercalcaemia and calcium phosphate product increased.

In the Stage 3/4 and Stage 5 clinical trials, the incidence of hypercalcaemia was Zemplar (3/167, 2%) vs placebo (0/137, 0%) and elevated calcium phosphate product was Zemplar (19/167, 11%) vs placebo (8/137, 6%).

Tabulated list of adverse reactions

All adverse reactions associated with Zemplar capsules are displayed in Table 3 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 (cannot be estimated from the available data).

Table 3: Adverse Reactions Reported With Zemplar Capsules in Clinical Trials and From Post Marketing Experience

System Organ Class	Frequency*	Adverse Reaction
Infections and infestations	Uncommon	Pneumonia
Immune system disorders	Uncommon	Hypersensitivity
	Not known*	Angioedema, laryngeal oedema
Endocrine Disorders	Uncommon	Hypoparathyroidism
Metabolism and nutrition disorders	Common	Hypercalcaemia, hyperphosphataemia
	Uncommon	Decreased appetite, hypocalcaemia
Nervous system disorders	Uncommon	Dizziness, dysgeusia, headache
Cardiac disorders	Uncommon	Palpitations
Gastrointestinal disorders	Uncommon	Abdominal discomfort, abdominal pain upper, constipation, diarrhoea, dry mouth, gastroesophageal reflux disease, nausea, vomiting
Skin and subcutaneous tissue disorders	Uncommon	Acne, pruritus, rash, urticaria
Musculoskeletal and connective tissue disorders	Uncommon	Muscle spasms, myalgia
Reproductive system and breast disorders	Uncommon	Breast tenderness
General disorders and administration site conditions	Uncommon	Asthenia, malaise, oedema peripheral, pain
Investigations	Common	Calcium phosphate product increased
	Uncommon	Blood creatinine increased†, hepatic enzyme abnormal

*Frequencies for adverse reactions from post marketing experience cannot be estimated and have been reported as "Not Known."
†This adverse reaction has been observed in studies in predialysis patients (see also section 4.4).

Reporting of suspected adverse reactions
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

Excessive administration of Zemplar capsules can cause hypercalcaemia, hypercalciuria, hyperphosphataemia, and over suppression of parathyroid hormone. High intake of calcium and phosphate concomitant with Zemplar capsules may lead to similar abnormalities.

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.

Signs and symptoms of vitamin D intoxication associated with hypercalcaemia include:

Early: Weakness, headache, somnolence, nausea, vomiting, dry mouth, constipation, muscle pain, bone pain and metallic taste.

Late: Anorexia, weight loss, conjunctivitis (calcific), pancreatitis, photophobia, rhinorrhoea, pruritus, hyperthermia, decreased libido, elevated BUN, hypercholesterolaemia, elevated AST and ALT, ectopic calcification, hypertension, cardiac arrhythmias, somnolence, death and rarely, overt psychosis.

Serum calcium levels should be monitored frequently until normocalcaemia ensues.
Paricalcitol is not significantly removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic 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 (D_2) 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 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 normalisation of calcium and phosphorus homeostasis, may prevent or treat the metabolic bone disease associated with chronic kidney disease.

Clinical Efficacy

Chronic Kidney Disease, Stages 3-4

The primary efficacy endpoint of at least two consecutive ≥30 % reductions from baseline iPTH was achieved by 91% of paricalcitol capsules-treated patients and 13% of the placebo patients ($p<0.001$). Serum bone specific alkaline phosphatase like serum osteocalcin were significantly reduced ($p<0.001$) in patients treated with paricalcitol capsules compared to placebo, which is associated with a correction of the high bone turnover due to secondary hyperparathyroidism. No

deterioration in the kidney function parameters of estimated glomerular filtration rate (via MDRD formula) and serum creatinine was detected in paricalcitol capsules treated patients in comparison to placebo treated patients. Significantly more of paricalcitol capsules treated patients experienced a reduction in urinary protein, as measured by semi quantitative dipstick, compared to placebo treated patients.

Chronic kidney disease, Stage 5

The primary efficacy endpoint of at least two consecutive ≥ 30 % reductions from baseline iPTH was achieved by 88% of paricalcitol capsules treated patients and 13% of the placebo patients ($p < 0.001$).

5.2 Pharmacokinetic properties

Absorption

Paricalcitol is well absorbed. In healthy adult subjects, following oral administration of paricalcitol at 0.24 micrograms/kg, the mean absolute bioavailability was approximately 72%; the maximum plasma concentration (C_{max}) was 0.630 ng/ml (1.512 pmol/ml) at 3 hours and area under the concentration time curve ($AUC_{0-\infty}$) was 5.25 ng•h/ml (12.60 pmol•h/ml). The mean absolute bioavailability of paricalcitol in haemodialysis (HD) and peritoneal dialysis (PD) patients is 79% and 86%, respectively, with the upper bound of 95% confidence interval of 93% and 112%, respectively. A food interaction study in healthy subjects indicated that the C_{max} and $AUC_{0-\infty}$ were unchanged when paricalcitol was administered with a high fat meal compared to fasting. Therefore, Zemplar capsules may be taken without regard to food.

The C_{max} and $AUC_{0-\infty}$ of paricalcitol increased proportionally over the dose range of 0.06 to 0.48 micrograms/kg in healthy subjects. Following multiple dosing, either as daily or three times a week in healthy subjects, steady-state exposure was reached within seven days.

Distribution

Paricalcitol is extensively bound to plasma proteins (> 99%). The ratio of blood paricalcitol to plasma paricalcitol concentration averaged 0.54 over the concentration range of 0.01 to 10 ng/ml (0.024 to 24 pmol/ml) indicating that very little drug associated with blood cells. The mean apparent volume of distribution following a 0.24 micrograms/kg dose of paricalcitol in healthy adult subjects was 34 litres.

Biotransformation

After oral administration of a 0.48 micrograms/kg dose of ^{3}H-paricalcitol, parent drug was extensively metabolised, with only about 2% of the dose eliminated unchanged in the faeces, and no parent drug found in the urine. Approximately 70% of the radioactivity was eliminated in the faeces and 18% was recovered in the urine. Most of the systemic exposure was from the parent drug. Two minor metabolites, relative to paricalcitol, were detected in human plasma. One metabolite was identified as 24(R)-hydroxy paricalcitol, while the other metabolite was unidentified. The 24(R)-hydroxy paricalcitol is less active than paricalcitol in an *in vivo* rat model of PTH suppression.

In vitro data suggest that paricalcitol is metabolised by multiple hepatic and non-hepatic enzymes, including mitochondrial CYP24, as well as CYP3A4 and UGT1A4. The identified metabolites include the product of 24(R)-hydroxylation, as well as 24,26- and 24,28-dihydroxylation and direct glucuronidation.

Elimination

Paricalcitol is eliminated primarily via hepatobiliary excretion.

In healthy subjects, the mean elimination half-life of paricalcitol is five to seven hours over the studied dose range of 0.06 to 0.48 micrograms/kg. The degree of accumulation was consistent with the half-life and dosing frequency. Haemodialysis procedure has essentially no effect on paricalcitol elimination.

Special Populations

Elderly

The pharmacokinetics of paricalcitol have not been investigated in patients greater than 65 years.

Gender

The pharmacokinetics of paricalcitol following single doses over 0.06 to 0.48 micrograms/kg dose range were gender independent.

Hepatic Impairment

In a study performed with Zemplar intravenous, the disposition of paricalcitol (0.24 micrograms/kg) was compared in patients with mild (n = 5) and moderate (n = 5) hepatic impairment (in accordance with the Child-Pugh method) and subjects with normal hepatic function (n = 10). The pharmacokinetics of unbound paricalcitol was similar across the range of hepatic function evaluated in this study. No dosing adjustment is required in patients with mild to moderate hepatic impairment. The influence of severe hepatic impairment on the pharmacokinetics of paricalcitol has not been evaluated.

Renal Impairment

Paricalcitol pharmacokinetics following single dose administration were characterised in patients with CKD Stage 3 or moderate renal impairment (n = 15, GFR = 36.9 to 59.1 ml/min/1.73 m^2), CKD Stage 4 or severe renal impairment (n = 14, GFR = 13.1 to 29.4 ml/min/1.73 m^2), and CKD 5 or end-stage renal disease [n = 14 in haemodialysis (HD) and n = 8 in peritoneal dialysis (PD)]. Similar to endogenous $1,25(OH)_2 D_3$, the pharmacokinetics of paricalcitol following oral administration were affected significantly by renal impairment, as shown in Table 4. Compared to healthy subjects' results obtained, CKD Stage 3, 4, and 5 patients showed decreased CL/F and increased half-life.

Table 4 Comparison of Mean ± SD Pharmacokinetic Parameters in Different Stages of Renal Impairment *versus* Healthy Subjects

Pharmacokinetic Parameter	Healthy Subjects	CKD Stage 3	CKD Stage 4	CKD Stage 5	
				HD	PD
n	25	15	14	14	8
Dose (micrograms/kg)	0.240	0.047	0.036	0.240	0.240
CL/F (l/h)	3.6 ± 1.0	1.8 ± 0.5	1.5 ± 0.4	1.8 ± 0.8	1.8 ± 0.8
$t_{½}$(h)	5.9 ± 2.8	16.8 ± 2.6	19.7 ± 7.2	13.9 ± 5.1	17.7 ± 9.6
f_u^* (%)	0.06 ± 0.01	0.06 ± 0.01	0.07 ± 0.02	0.09 ± 0.04	0.13 ± 0.08

***** Measured at 15 nM paricalcitol concentration.

Following oral administration of paricalcitol capsules, the pharmacokinetic profile of paricalcitol for chronic kidney disease, Stages 3 to 5 was comparable. Therefore, no special dosing adjustments are required other than those recommended (see section 4.2).

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

Triglycerides, Medium Chain
Gelatin
Glycerol, Anhydrous
Ethanol, anhydrous
Titanium Dioxide
Iron Oxide (Black)
Butylhydroxytoluene (BHT)
Ink, Opacode® WB, Black

Purified Water

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

This medicinal product does not require any special storage conditions.
It is recommended to store in a cool dry place.

6.5 Nature and contents of container

PVC/PVDC/aluminium blister strips containing 7 capsules. Each carton contains 1 or 4 blister strips.Packaged in outer cartons containing either 7 or 28 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MANUFACTURER

AbbVie Ltd., Vanwall Road, Maidenhead, Berkshire SL6 4UB, United Kingdom

8. MARKETING AUTHORISATION HOLDER
AbbVie Biopharmaceuticals Ltd., Israel

9. Registration Number:
141-12-31816

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