

## NAME OF THE MEDICINAL PRODUCT

Zemplar® 5 micrograms/ml Solution for injection

### COMPOSITION

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

### PHARMACEUTICAL FORM

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

### CLINICAL PARTICULARS

#### Therapeutic indications

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

#### Posology and method of administration

Zemplar solution for injection is administered via haemodialysis access.

#### 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:

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

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

and administered as an intravenous (IV) bolus dose no more frequently than 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<sup>2</sup>/l<sup>2</sup> (65 mg<sup>2</sup>/dl<sup>2</sup>) 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 Zemplar in children have not been established. There is no data available on children under 5 years. The currently available data on paediatric patients are described in Pharmacodynamic properties section.

#### Geriatric population (>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.

#### Contraindications

Hypersensitivity to active substance or to any of the excipients. Vitamin D toxicity  
Hypercalcaemia.

#### 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. Digitalis toxicity is potentiated by hypercalcaemia of any cause, so caution should be applied when digitalis is prescribed concomitantly with paricalcitol. Caution should be exercised if co-administering paricalcitol with ketoconazole. This medicinal product contains 20% v/v of ethanol (alcohol). Each dose may contain up to 1.3 g ethanol. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breastfeeding women, children and high risk groups such as patients with liver disease or epilepsy.

#### Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with paricalcitol injection. However, an interaction study between Ketoconazole 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 aluminum and aluminium bone toxicity may occur. Magnesium-containing preparations (e.g. antacids) should not be taken concomitantly with vitamin D preparations, because hypermagnesaemia 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. 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 C<sub>max</sub> of paricalcitol was minimally affected, but AUC<sub>0-∞</sub> 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<sub>0-∞</sub> 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.

#### Pregnancy and lactation

##### Pregnancy:

There are no adequate data from the use of paricalcitol in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Zemplar should not be used in pregnancy unless clearly necessary.

##### Lactation:

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.

#### Effects on ability to drive and use machines

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

#### Undesirable effects

Approximately 600 patients were treated with Zemplar in Phase II/III/IV clinical trials. Overall, 6% of the Zemplar treated patients reported adverse reactions. The most common adverse reaction associated with Zemplar 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, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10,000, < 1/1000); very rare (< 1/10000), not known (can not be estimated from the available data).

System Organ Class	Preferred Term	Frequency
Investigations	Bleeding time prolonged, aspartate aminotransferase increased, laboratory test abnormal, weight decreased	Uncommon
Cardiac disorders	Cardiac arrest, arrhythmia, atrial flutter	Uncommon
Blood and lymphatic system disorders	Anaemia, leukopenia, lymphadenopathy	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

Respiratory, thoracic and mediastinal disorders	Pulmonary oedema, asthma, dyspnoea, epistaxis, cough	Uncommon
Gastrointestinal disorders	Rectal haemorrhage, colitis, diarrhoea, gastritis, dyspepsia, dysphagia, abdominal pain, constipation, nausea, vomiting, dry mouth, gastrointestinal disorder	Uncommon
	Gastrointestinal haemorrhage	unknown
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
Endocrine Disorders	Hypoparathyroidism	Common
	Hyperparathyroidism	Uncommon
Metabolism and nutrition disorders	Hypercalcaemia, Hyperphosphataemia	Common
	Hyperkalaemia, hypocalcaemia, anorexia	Uncommon
Infections and infestations	Sepsis, pneumonia, infection, pharyngitis, vaginal infection, influenza	Uncommon
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Breast cancer	Uncommon
Vascular disorders	Hypertension, hypotension	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
Immune system disorders	Hypersensitivity	Uncommon
	Laryngeal oedema, angioedema, urticaria	Not Known
Reproductive system and breast disorders	Breast pain, erectile dysfunction	Uncommon
Psychiatric disorders	Confusional state, delirium, depersonalization, agitation, insomnia, nervousness	Uncommon

### Overdose

No case of overdose has been reported. Overdosage of paricalcitol may lead to hypercalcaemia, hypercalcaemia, hyperphosphatemia, and over suppression of PTH. In the event of an overdose, signs and symptoms of hypercalcaemia (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. Zemplan solution for injection contains 30% 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 Zemplan administration as propyleneglycol is eliminated during the dialysis process, the risk of toxic effect in overdosing situations has to be taken into account.

## PHARMACOLOGICAL PROPERTIES

### Pharmacodynamic properties

#### 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.

Paediatric clinical data: The safety and effectiveness of Zemplan 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 Zemplan-treated patients in the study were 5 - 12 years old. The initial dose of Zemplan was 0.04 microgram/kg 3 times per week, based on baseline iPTH level of less than 500 pg/mL, or 0.08 microgram/kg 3 times a week based on baseline iPTH level of  $\geq$  500 pg/mL, respectively. The dose of Zemplan was adjusted in 0.04 microgram/kg increments based on the levels of serum iPTH, calcium, and Ca x P. 67% of the Zemplan-treated patients and 14% placebo-treated patients completed the trial. 60% of the subjects in the Zemplan 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 Zemplan group or placebo group developed hypercalcaemia. No data are available for patients under the age of 5.

### 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 <sup>3</sup>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.

#### Metabolism

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 <sub>max</sub> (5 minutes after bolus)	6	1850 ± 664 (pg/mL)
AUC <sub>0-∞</sub>	5	27382 ± 8230 (pg•hr/mL)
CL	5	0.72 ± 0.24 (L/hr)
V <sub>ss</sub>	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.

## PHARMACEUTICAL PARTICULARS

### List of excipients

Ethanol (20 % v/v), Propylene glycol, Water for Injections

### Incompatibilities

In the absence of compatibility studies, this medicinal product should not be mixed with other medical products. Propylene glycol interacts with heparin and neutralises its effect. Zemplan solution for injection contains propylene glycol as an excipient and should be administered through a different injection port than heparin.

### Special precautions for storage

Do not store above 30°C.

### How supplied

Each Type 1 glass ampoule contains 1mL or 2mL of solution for injection.

The presentations of Zemplan 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.

### 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.

### Manufacturer

See outer pack

### MARKETING AUTHORISATION HOLDER

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abbvie

### DATE OF REVISION OF THE TEXT

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