Summary of Product Characteristic (SmPC)

1. Name of the medical product

OSSEKA 1 capsule contains calcitriol 0.25 mcg

2. Quality and Quantitative Composition

Each capsule contains calcitriol 0.25 mcg

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Soft capsule, 0.25 mcg: Oval Opaque orange.

4. Clinical particulars

4.1 Therapeutic indication

OSSEKA is indicated for

- Management of post-menopausal osteoporosis.

- Management of hypocalcemia in patient with chronic renal failure or in patient with hypoparathyroidism.

4.2 Posology and method of administration

- Post-menopausal osteoporosis: 1 capsule twice daily or as directed by the physician.

- Hypocalcemia in patient with chronic renal failure or in patient with hypoparathyroidism: 1 capsule once daily or as directed by the physician

4.3 Contraindication

OSSEKA is contraindicated:

• in all diseases associated with hypercalcaemia

• in patients with evidence of metastatic calcification

• in patients with known hypersensitivity to calcitriol (or drugs of the same class) and any of the constituent excipients

• if there is evidence of vitamin D toxicity.

4.4 Special warning and precautions for use

Patient with hypercalcaemia

There is a close correlation between treatment with calcitriol and the development of hypercalcaemia.

All other vitamin D compounds and their derivatives, including proprietary compounds or foodstuffs which may be “fortified” with vitamin D, should be withheld during treatment with OSSEKA.

An abrupt increase in calcium intake as a result of changes in diet (e.g. increased consumption of dairy products) or uncontrolled intake of calcium preparations may trigger hypercalcaemia. Patients and their families should be advised that strict adherence to the prescribed diet is mandatory and they should be instructed on how to recognise the symptoms of hypercalcaemia.

As soon as the serum calcium levels rise to 1 mg/100 ml (250 µmol/l) above normal (9-11 mg/100 ml or 2250-2750µmol/l), or serum creatinine rises to >120 µmol/L, treatment with calcitriol should be stopped immediately until normocalcaemia ensues (see section 4.2).

Immobilised patients, e.g. those who have undergone surgery, are particularly exposed to the risk of hypercalcaemia.

Patient with renal failure

Calcitriol increases inorganic phosphate levels in serum. While this is desirable in patients with hypophosphataemia, caution is called for in patients with renal failure because of the danger of ectopic calcification. In such cases, the plasmaphosphate level should be maintained at the normal level (2-5 mg/100 ml or 0.65-1.62 mmol/l) by the oral administration of appropriate phosphate-binding agents and low phosphate diet.

The serum calcium times phosphate (Ca x P) product should not be allowed to exceed 70 mg^2/dl^2.

Patient with vitamin D-resistant rickets

Patients with vitamin D-resistant rickets (familial hypophosphataemia) who are being treated with calcitriol must continue their oral phosphate therapy. However, possible stimulation of intestinal absorption of phosphate by calcitriol should be taken into account since this effect may modify the need for phosphate supplementation.

Patients who switched from other derivatives of vitamin D.

Since calcitriol is the most effective vitamin D metabolite available, no other vitamin D preparation should be prescribed during treatment with, thereby ensuring that the development of hypervitaminosis D is avoided.

If the patient is switched from a long-acting vitamin D preparation (e.g. ergocalciferol (vitamin D2) or colecalciferol) to calcitriol, it may take several months for the ergocalciferol level in the blood to return to the baseline value, thereby increasing the risk of hypercalcaemia (see section 4.9).

Patients with normal renal function who are taking calcitriol should avoid dehydration. Adequate fluid intake should be maintained.

In patients with normal renal function, chronic hypercalcaemia may be associated with an increase in serum creatinine.

Warnings due to the Public Health Ministry Announcement

1. The drug may be accumulated in the body and may be leading cause of harmful poisoning. Therefore, do not exceed recommended dosage and should avoid prolonged use of this drug.

2. The drug should be used under a physician's prescription.

4.5 Interaction with other medicinal products and other forms of interaction

Dietary instructions, especially concerning calcium supplements, should be strictly observed, and uncontrolled intake of additional calcium-containing preparations avoided.

Concomitant treatment with a thiazide diuretic increases the risk of hypercalcaemia. Calcitriol dosage must be determined with care in patients undergoing treatment with digitalis, as hypercalcaemia in such patients may precipitate cardiac arrhythmias (see section 4.4).

A relationship of functional antagonism exists between vitamin D analogues, which promote calcium absorption, and corticosteroids, which inhibit it.

Magnesium-containing drugs (e.g. antacids) may cause hypermagnesaemia and should therefore not be taken during therapy with calcitriol by patients on chronic renal dialysis.

Since calcitriol also has an effect on phosphate transport in the intestine, kidneys and bones, the dosage of phosphate-binding agents must be adjusted in accordance with the serum phosphate concentration (normal values: 2-5 mg/100 ml or 0.65-1.62 mmol/l).

Patients with vitamin D-resistant rickets (familial hypophosphataemia) should continue their oral phosphate therapy. However, possible stimulation of intestinal phosphate absorption by calcitriol should be taken into account since this effect may modify the requirement for phosphate supplements.

Bile acid sequestrants including cholestyramine and sevelamer can reduce intestinal absorption of fat-soluble vitamins and therefore may impair intestinal absorption of calcitriol.

4.6 Pregnancy and lactation

The safety of Calcitriol during pregnancy has not been established.

Supravalvular aortic stenosis has been produced in foetuses by near-fatal oral doses of vitamin D in pregnant rabbits. There is no evidence to suggest that vitamin D is teratogenic in humans even at very high doses. Calcitriol should be used during pregnancy only if the benefits outweigh the potential risk to the foetus.

It should be assumed that exogenous calcitriol passes into breast milk. In view of the potential for hypercalcaemia in the mother and for adverse reactions from OSSEKA in nursing infants, mothers may breastfeed while taking calcitriol, provided that the serum calcium levels of the mother and infant are monitored.

4.7 Effects on ability to drive and use machine

On the basis of the pharmacodynamic profile of reported adverse events, this product is presumed to be safe or unlikely to adversely affect such activities.

4.8 Undesirable effects

The most commonly reported adverse reaction was hypercalcaemia.

The ADRs listed in Table 1 are presented by system organ class and frequency categories, defined using the following convention: 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 1 Summary of ADRs Occurring in Patients Receiving Calcitriol

System Organ Class	Very Common	Common	Uncommon	Not known
Immune System Disorders				Hypersensitivity, Uriticaria
Metabolism and Nutrition Disorders	Hypercalcaemia		Decreased appetite	Polydipsia, Dehydration, Weight decreased
Psychiatric Disorders				Apathy, Psychiatric disturbances
Nervous System Disorders		Headache		
Cardiac Disorders				Cardiac arrhythmias
Gastrointestinal Disorders		Abdominal pain, Nausea	Vomiting	Constipation, Abdominal pain upper, Paralytic ileus
Skin and subcutaneous tissue disorders		Rash		Erythema, Pruritus
Musculoskeletal and Connective Tissue Disorders				Growth retardation
Renal and Urinary Disorders		Urinary tract infection		Polyuria, Nocturia
General disorders and administration site conditions				Calcinosis, Pyrexia, Thirst
Investigations			Blood creatinine increased	

Since calcitriol exerts vitamin D activity, adverse effects may occur which are similar to those found when an excessive dose of vitamin D is taken, i.e. hypercalcaemia syndrome or calcium intoxication (depending on the severity and duration of hypercalcaemia) (see sections 4.2 and 4.4*)*. Occasional acute symptoms include decreased appetite, headache, nausea, vomiting, abdominal pain or abdominal pain upper and constipation.

Because of the short biological half-life of calcitriol, pharmacokinetic investigations have shown normalisation of elevated serum calcium within a few days of treatment withdrawal, i.e. much faster than in treatment with vitamin D3 preparations.

Chronic effects may include muscular weakness, weight decreased, sensory disturbances, pyrexia, thirst, polydipsia, polyuria, dehydration, apathy, growth retardation and urinary tract infections.
In concurrent hypercalcaemia and hyperphosphataemia of > 6 mg/100 ml or > 1.9 mmol/l, calcinosis may occur; this can be seen radiographically.

Hypersensitivity reactions including rash, erythema, pruritus and urticaria may occur in susceptible individuals.

Laboratory Abnormalities

In patients with normal renal function, chronic hypercalcaemia may be associated with a blood creatinine increase.

4.9 Overdose

Treatment of asymptomatic hypercalcaemia (see section 4.2).

Since calcitriol is a derivative of vitamin D, the symptoms of overdose are the same as for an overdose of vitamin D. Intake of high doses of calcium and phosphate together with calcitriol may give rise to similar symptoms. The serum calcium times phosphate (Ca x P) product should not be allowed to exceed 70 mg^2 / dl^2. A high calcium level in the dialysate may contribute to the development of hypercalcaemia.

Acute symptoms of vitamin D intoxication: anorexia, headache, vomiting, constipation.

Chronic symptoms: dystrophy (weakness, loss of weight), sensory disturbances, possibly fever with thirst, polyuria, dehydration, apathy, arrested growth and urinary tract infections. Hypercalcaemia ensues, with metastatic calcification of the renal cortex, myocardium, lungs and pancreas.

The following measures should be considered in treatment of accidental overdosage: immediate gastric lavage or induction of vomiting to prevent further absorption. Administration of liquid paraffin to promote faecal excretion. Repeated serum calcium determinations are advisable. If elevated calcium levels persist in the serum, phosphates and corticosteroids may be administered and measures instituted to bring about adequate diuresis.

Hypercalcaemia at higher levels (>3.2 mmol/L) may lead to renal insufficiency particularly if blood phosphate levels are normal or elevated due to impaired renal function.

Should hypercalcaemia occur following prolonged treatment, calcitriol should be discontinued until plasma calcium levels have returned to normal. A low-calcium diet will speed this reversal. Calcitriol can then be restarted at a lower dose or given in the same dose but at less frequent intervals than previously.

In patients treated by intermittent haemodialysis, a low concentration of calcium in the dialysate may also be used. However, a high concentration of calcium in the dialysate may contribute to the development of hypercalcaemia.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Calcitriol is the most active known form of vitamin D3 in stimulating intestinal calcium transport. It is normally formed in the kidneys from its immediate precursor, 25-hydroxycholecalciferol. In physiological amounts it augments the intestinal absorption of calcium and phosphate and plays a significant part in the regulation of bone mineralisation. The defective production of calcitriol in chronic renal failure contributes to the abnormalities of mineral metabolism found in that disorder.

The biological effects of calcitriol are mediated by the vitamin D receptor, a nuclear hormone receptor expressed in most cell types and functioning as a ligand-activated transcription factor that binds to DNA sites to modify the expression of target genes.

Osseka is a synthetic preparation of calcitriol. Oral administration of Osseka to patients with chronic renal failure compensates for impaired endogenous production of calcitriol which is decreased when the glomerular filtration rate falls below 30 ml/min. Consequently, intestinal malabsorption of calcium and phosphate and the resulting hypocalcaemia are improved, thereby reversing the signs and symptoms of bone disease.

In patients with established post-menopausal osteoporosis, Osseka increases calcium absorption, elevates circulating levels of calcitriol and reduces vertebral fracture frequency.

The onset and reversal of the effects of Osseka are more rapid than those of other compounds with vitamin D activity and adjustment of the dose can be achieved sooner and more precisely. The effects of inadvertent overdosage can also be reversed more readily.

5.2 Pharmacokinetic properties

Absorption

Calcitriol is rapidly absorbed from the intestine. Peak serum concentrations following a single oral dose of 0.25-1 µg calcitriol in healthy subjects were found within 2-6 hours.

After a single oral dose of 0.5 mcg calcitriol in healthy subjects, the average serum concentrations of calcitriol rose from a baseline value of 40.0 ± 4.4 pg/ml to 60.0 ± 4.4 pg/ml after two hours, and then fell to 53.0 ± 6.9 after four hours, to 50.0 ± 7.0 after eight hours, to 44 ± 4.6 after twelve hours and to 41.5 ± 5.1 pg/ml after 24 hours.

Distribution

During transport in the blood at physiological concentrations, calcitriol is mostly bound to a specific vitamin D binding protein (DBP), but also, to a lesser degree, to lipoproteins and albumin. At higher blood calcitriol concentrations, DBP appears to become saturated, and increased binding to lipoproteins and albumin occurs.

Metabolism

Calcitriol is hydroxylated and oxidised in the kidney and in the liver by a specific cytochrome P450 enzyme: CYP24A1.

Several metabolites with different degrees of vitamin D activity have been identified.

Elimination

The elimination half-life of calcitriol in plasma ranges between 5 to 8 hours. However, the pharmacological effect of a single dose of calcitriol lasts at least 4 days. The elimination and absorption kinetics of calcitriol remain linear in a very broad dose range and up to 165 µg single oral dose. Calcitriol is excreted in the bile and may undergo an enterohepatic circulation.

5.3 Preclinical safety data

Subchronic toxicity studies in rats and dogs indicated that calcitriol at an oral dose of 20 ng/kg/day (twice the usual human dosage) for up to 6 months produced no or minimal adverse effects. A dose of 80 ng/kg/day (8 times the usual human dosage) for up to 6 months produced moderate adverse effects; changes seen appeared to be primarily the result of prolonged hypercalcaemia.

Reproductive toxicity studies in rats indicated that oral doses up to 300 ng/kg/day (30 times the usual human dose) did not adversely affect reproduction. In rabbits, multiple foetal abnormalities were observed in two litters at an oral maternally toxic dose of 300 ng/kg/day and one litter at 80 ng/kg/day, but not at 20 ng/kg/day (twice the usual human dose). Although there were no statistically significant differences between treated groups and controls in the numbers of litters or foetuses showing abnormalities, the possibility that these findings were due to calcitriol administration could not be discounted.

6. Pharmaceutical particulars

6.1 List of excipients

Content

- Butylated Hydroxyanisole
- Butylated Hydroxytoluene
- Medium-chain Triglycerides

Shell

- Gelatin
- Glycerol
- Titanium Dioxide
- Sunset Yellow Lake
- Quinoline Yellow Lake
- Potassium Sorbate
- Purified Water

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

24 months

6.4 Special precautions for storage

Keep in tight containers, protect from light, store below 30ºC

6.5 Nature and contents of container

10 capsules in a blister pack (ALU-amber PVC) and then be closed in a secondary paper box containing 10 blisters.

7. Marketing authorization holder

Manufactured by **MacroPhar Co., Ltd.**

Bangkok Thailand

Distributed by **MacroPhar Lab Co., Ltd.**

28/8 Soi Pattanakarn 20 Yaek 4, SuanLuang, Bangkok 10250 Thailand.

Tel : (662)314-6671

8. Marketing authorization numbers

1A 37/67

9. Date of authorization

April 5, 2024

10. Date of revision of the text

March 18, 2024