SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product :

1.1 Product Name : MEDITROL

1.2 Strength : Calcitriol 0.25 mcg

1.3 Pharmaceutical Dosage Form : Soft gelatin capsules

2. Quality and Quantitative Composition:

2.1 Qualitative Declaration

2.2 Quantitative Declaration

Compositions	**Content / Capsule**
Active Ingredient:	
Calcitriol	0.25 mcg
Inactive ingredient:	
Butylated Hydroxyanisole	0.01375 mg
Butylated Hydroxytoluene	0.01375 mg
Fractionated Coconut Oil	160.00000 mg
Capsule shell:	
Gelatin	58.5375 mg
Glycerin	13.6134 mg
Sorbitol 70% solution	19.0587 mg
Purified water	4.2000 mg
Iron oxide yellow	0.0545 mg
Iron oxide red	0.2723 mg
Titanium dioxide (Red	0.1361 mg
Titanium dioxide (White	0.8168 mg

3. Pharmaceutical Form :

Pharmaceutical form: Clear, colourless, oily liquid, filled in 3 minim, oval, red and white, opaque soft gelatin shell capsules.

4. Clinical Particulars :

4.1 Therapeutic indications:

Established postmenopausal osteoporosis; renal osteodystrophy in patients with chronic renal failure, particularly those undergoing hemodialysis; post-surgical hypo-parathyroidism; idiopathic hypoparathyroidism; pseudohypoparathyroidisim; vitamin D-dependent rickets; hypophosphatemic vitamin D-resistant rickets.

4.2 Posology and method of administration:

Standard Dosage: The optimal daily dose of calcitriol must be carefully determined for each patient on the basis of the serum calcium level. Calcitriol therapy should always be started at lowest possible dose and should not be increased without careful monitoring of serum calcium.

When the optimal dosage of calcitriol has been determined, serum calcium levels should be checked every month. Samples for serum calcium estimation should be taken without a tourniquet. As soon as the serum calcium levels rise to 1 mg/100 mL above normal, or serum creatinine rises to >120 ¯mol/L the dosage of calcitriol should be substantially reduced or treatment stopped altogether until normocalcemia ensues.

During the periods of hypercalcemia, serum calcium and phosphate levels must be determined daily. When normal levels have been attained, treatment with calcitriol can be continued, at a daily dose 0.25 ¯g lower than that previously used. An estimate of daily dietary calcium intake should be made and the intake adjusted when indicated. A prerequisite for optimal efficacy of calcitriol is adequate but not excessive calcium intake (in adults: Approximately 800mg daily) at the beginning of therapy. Calcium supplements may be necessary.

Because of improved calcium absorption from the gastrointestinal tract, some patients on calcitriol may be maintained on a lower calcium intake. Patients who tend to develop hypercalcemia may require only low doses of calcium or no supplementation at all.

The total daily calcium intake (ie, from food, and where applicable from drugs) should average approximately 800 mg and should not exceed 1000 mg.

Special Dosage Instruction:

Postmenopausal Osteoporosis: The recommended dosage is 0.25mcg twice daily. Serum calcium and creatinine levels should be determined at 4 week, 3 and 6 months and at 6 monthly intervals thereafter.

Renal Osteodystrophy (Dialysis Patients): Initial daily dose should be 0.25mcg. In patients with normal or only slightly reduced serum calcium levels, doses of 0.25mcg every other day are sufficient.

If no satisfactory response in the biochemical parameters and clinical manifestations of the disease is observed within 2-4 weeks, the dosage may be increased by 0.25mcg/day for 2 to 4 week intervals. During this period, serum calcium levels should be determined at least twice weekly. Most patients respond to between 0.5 and 1mcg daily.

Hypoparathyroidism and Rickets: Recommended initial dose should be 0.25mcg/day given in the morning. If a satisfactory response in the biochemical parameters and clinical manifestations of the disease are not observed, the dose may be increased at 2 to 4 week

intervals. During this period, serum calcium levels should be determined at least twice weekly.

Malabsorption is occasionally noted in patients with hypoparathyroidism; hence, larger doses of calcitriol may be needed.

Elderly: No specific dosage modifications are required in elderly patients. The general recommendations for monitoring serum calcium and creatinine should be observed.

4.3 Contraindications:

In all diseases associated with hypercalcemia. Use in patients with known hypersensitivity to calcitriol (or drugs of the same class) and any of the constituent is contraindicated.

4.4 Special warning and precautions for use:

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

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

Immobilized patients, eg those who have undergone surgery, are particularly exposed to the risk of hypercalcemia.

Calcitriol increases inorganic phosphate levels in serum.

While this is desirable in patients with hypophosphatemia, caution is called for in patients with renal failure because of the danger of ectopic calcification.

Patients with vitamin D-resistant rickets (familial hypophosphatemia) 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. Since calcitriol is the most effective vitamin D metabolite available, no other vitamin D preparation should be prescribed during treatment with calcitriol, thereby ensuring that the development of hypervitaminosis D is avoided.

If the patient is switched from ergocalciferol (vitamin D2) to calcitriol, it may take several months for the ergocalciferol level in the blood to return to the baseline values.

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

Hypersensitivity reactions may occur in susceptible individuals.

4.5 Undesirable effects:

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. hypercalcemia syndrome or calcium intoxication (depending on the severity and duration of hypercalcemia). Occasional acute symptoms include anorexia, headache, vomiting and constipation. Chronic effects may include dystrophy, sensory disturbances, fever with thirst, polyuria, apathy, arrested growth and urinary tract infections.

In concurrent hypercalcemia and hyperphosphatemia of > 6 mg/100 mL or > 1.9 mmol/L, soft tissue calcification may occur; this can be seen radiographically. In patients with normal renal function, chronic hypercalcemia may be associated with an increase in serum creatinine.

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

4.6 Overdose and special antidotes:

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 will calcitriol may give rise to similar symptoms. A high calcium level in the dialysate may contribute to the development of hypercalcemia.

Acute Symptoms of Vitamin D Intoxication: Anorexia, headache, vomiting and constipation.

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

Treatment: 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 fecal 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.

5. Pharmacological Properties:

5.1 Pharmacodynamic Properties:

Calcitriol is one of the most important active metabolites of vitamin D3. It is normally formed in the kidneys from its precursor, 25-hydroxycholecalciferol (25-HCC). Physiological daily production is normally 0.5-1mcg, and is somewhat higher during periods of increased bone synthesis (eg, growth or pregnancy). Calcitriol promotes intestinal absorption of calcium and regulates bone mineralization. The pharmacological effect of a single dose of calcitriol lasts about 3-5 days. The key role of calcitriol in the regulation of calcium homeostatis, which includes stimulating effects on osteoblastic activity in the skeleton, provides a sound pharmacological basis for its therapeutic effects in osteoporosis.

In patients with marked renal impairment, synthesis of endogenous calcitriol is correspondingly limited or may even cease altogether. This deficiency plays a key role in the development of renal osteodystrophy.

In patients with renal osteodystrophy, oral administration of calcitriol normalizes reduced intestinal absorption of calcium, hypocalcemia, increased serum alkaline phosphatase and serum parathyroid hormone concentration. It alleviates bone and muscle pain and corrects the histological alterations that occur in osteitis fibrosa and other mineralization defects.

In patients with post-surgical hypoparathyroidism, idopathic hypoparathyroidism and pseudohypo-parathyrodism, hypocalcemia and its clinical manifestations are alleviated by calcitriol therapy.

In patients with vitamin D-dependent rickets, the serum levels of calcitriol are low or absent. As the endogenous production of calcitriol in the kidney is insufficient, calcitriol is considered as a replacement therapy.

Patients with vitamin D-resistant rickets and hypophosphatemia in whom plasma calcitriol levels are reduced, treatment with calcitriol reduces tubular elimination of phosphates and, in conjunction with concurrent phosphate treatment, normalizes bone development.

Patients with various other form of rickets, eg in association with neonatal hepatitis, biliary atresia, cystinosis and dietary calcium and vitamin D deficiency, have also benefited from calcitriol therapy.

5.2 Pharmacokinetic Properties:

Absorption: Calcitriol is rapidly absorbed from the intestine. Peak serum concentrations following a single oral dose of 0.25-1mcg Calcitriol were found within 3-6 hrs. Following multiple administration, serum calcitriol levels reached a steady state within 7 days, with a relationship to the dose of calcitriol administered.

Distribution: During transport in the blood, calcitriol and other vitamin D metabolites are bound to specific plasma proteins. It can be assumed that exogenous calcitriol passes from the maternal blood into fetal bloodstream and the breast milk.

Metabolism: Several metabolites of calcitriol, each exerting different vitamin D activities,have been identified: 1 ,25-dihydroxy-24-oxo-cholecaciferol, 1 ,23,25–trihydroxy-24-oxocholecalciferol,1 ,24R,25-trihydroxycholecalciferol, 1 ,25R-dihydroxycholecalciferol-26,23S-lactone, 1 ,25S,26-tripydroxycholecalciderol, 1 ,25-dihydroxy-23-oxo-cholecalciferol,1 ,25R,26-trihydroxy-23-oxo-cho-lecalciferol and 1 -hydroxy-23-carboxy-24,25,26,27-tetranorcholecalciferol.

Elimination: The elimination half-life of calcitriol in serum is 3-6 hrs. However, the pharmacological effect of single dose of calcitriol lasts about 3-5 days. Calcitriol is excreted in the bile and is subject to enterohepatic circulation.

5.3 Preclinical Safety Data: No information for preclinical safety data.

6. Pharmaceutical Particulars :

6.1 List of excipients:

Butylated hydroxyanisole, Butylated hydroxytoluene, Fractionated coconut oil Capsule shell: Gelatin, Glycerin, Sorbitol 70% solution, Purified water, Iron oxide red, Iron oxide yellow and Titanium dioxide

6.2 Incompatibilities: Not applicable.

6.3 Shelf life: 2 years from date of manufacture.

6.4 Special precautions for storage: Store below 30°C in a dry place, away from direct sunlight.

6.5 Nature and contents of container :

Blister film: Alu Alu blister

Outer carton: Printed cardboard carton

7. Marketing Authorization Holder:

Mega Lifesciences Public Company Limited.
384, Pattana 3 Road, Bangpoo Industrial
Estate, Samutprakarn 10280, Thailand

8. Marketing Authorization Numbers: Rwanda FDA-HMP-MA-0620

9. Date of first authorization / renewal of the authorization: N/A

10. Date of revision of the text: December 2023