NEW ZEALAND DATA SHEET

1. CALCITRIOL – AFT

Calcitriol – AFT capsules 0.25 µg
Calcitriol – AFT capsules 0.5 µg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Calcitriol – AFT 0.25 µg: Each capsule contains 0.25µg of synthetic calcitriol, a biologically active form of vitamin D3.

Calcitriol – AFT 0.5 µg: Each capsule contains 0.5µg of synthetic calcitriol, a biologically active form of vitamin D3.

Excipients with known effect:

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, liquid filled.

Calcitriol - AFT are oval, orange soft-gel capsules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

• Established postmenopausal osteoporosis.
• Renal osteodystrophy in patients with chronic renal failure, particularly those undergoing haemodialysis.
• Secondary hyperparathyroidism in patients with moderate to severe chronic renal failure (pre-dialysis).
• Postsurgical hypoparathyroidism.
• Idiopathic hypoparathyroidism.
• Pseudohypoparathyroidism.
• Vitamin D-dependent rickets.
• Hypophosphataemic vitamin D-resistant rickets.
• Prevention of corticosteroid induced osteoporosis

4.2 Dose and method of administration

Standard dosage

The optimal daily dose of Calcitriol-AFT must be carefully determined for each patient on the basis of the serum calcium level. Calcitriol-AFT therapy should always be started at the lowest possible dose and should not be increased without careful monitoring of serum calcium (see Patient monitoring).

A prerequisite for optimal efficacy of Calcitriol-AFT 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-AFT may be maintained on a lower calcium intake. Patients who tend to develop hypercalcaemia may require only low doses of calcium or no supplementation at all.
The total daily calcium intake (i.e. from food, and, where applicable, from medicines) should average approximately 800mg and should not exceed 1000mg.

Patient monitoring

During the stabilization phase of treatment with Calcitriol-AFT, serum calcium levels should be checked at least twice weekly. When the optimal dosage of Calcitriol-AFT has been determined, serum calcium levels should be checked every month (or as given below for individual indications). Samples for serum calcium estimation should be taken without a tourniquet.
As soon as the serum calcium levels rise to 1 mg/100ml (250µmol/l) above normal (9 to 11mg/100 ml, or 2250-2750µmol/l), or serum creatinine rises to > 120µmol/l, treatment with Calcitriol-AFT should be stopped immediately until normocalcaemia ensues.
During the periods of hypercalcaemia, serum calcium and phosphate levels must be determined daily. When normal levels have been attained, the treatment with Calcitriol-AFT can be continued, at a daily dose 0.25µg lower than that previously used. An estimate of daily dietary calcium intake should be made and the intake adjusted when indicated.

Special dosage instructions

Postmenopausal osteoporosis

The recommended dosage for Calcitriol-AFT is 0.25µg twice daily.
Serum calcium and creatinine levels should be determined at 1, 3 and 6 months and at 6-month intervals thereafter.
Renal osteodystrophy (dialysis patients)
The initial daily dose is 0.25µg. In patients with normal or only slightly reduced serum calcium levels, doses of 0.25µg 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 daily dosage may be increased by 0.25µg at two to
four-week intervals. During this period, serum calcium levels should be determined at least twice weekly. Most patients respond to between 0.5µg and 1.0µg daily.
An oral Calcitriol-AFT pulse therapy with an initial dosage of 0.1µg/kg/week split into two or three equal dosages given at night was found to be effective even in patients refractory to continuous therapy. A maximum total cumulative dosage of 12µg per week should not be exceeded.

Secondary hyperparathyroidism (pre-dialysis patients)

The recommended initial dosage of Calcitriol-AFT for the treatment of secondary hyperparathyroidism and resultant metabolic bone disease in patients with moderate to severe renal failure i.e. creatinine clearance (Ccr) 15 to 55ml/min, is 0.25µg/day in adults and in paediatric patients 3 years of age or older (corrected for a surface area of 1.73m2). This dosage may be increased if necessary to 0.5µg/day.

Hypoparathyroidism, rickets

The recommended initial dose of Calcitriol-AFT is 0.25µg/day given in the morning. If a satisfactory response in the biochemical parameters and clinical manifestations of the disease is not observed, the dose may be increased at two to four-week intervals. During this period, serum calcium levels should be determined at least twice weekly. If hypercalcaemia is noted, Calcitriol-

AFT should be immediately discontinued until normocalcaemia ensues. Careful consideration should also be given to lowering the dietary calcium intake.
Malabsorption is occasionally noted in patients with hypoparathyroidism; hence, larger doses of Calcitriol-AFT may be needed.
If the physician decides to prescribe Calcitriol-AFT to a pregnant woman with hypoparathyroidism, an increased dose may be required during the latter half of gestation, with dose reduction postpartum or during lactation.

Prevention of corticosteroid induced osteoporosis

The recommended dosage range for the prevention of corticosteroid induced osteoporosis is 0.5-0.75µg per day. Serum calcium and creatinine levels should be obtained at 2-4 weeks after initiating treatment then at 3 and 6 months and every 6 months thereafter. If hypercalcaemia is noted, the medicine should be immediately discontinued until normocalcemia ensues. While an adequate dietary calcium intake is important, ordinarily it is more convenient to titrate medicine dosage around the customary calcium intake of the patient.

Elderly patients

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

Infants and children

During the first 2 years of life, a daily dosage of 0.01-0.1µg/kg bodyweight is recommended as a guideline.

4.3 Contraindications

- Calcitriol-AFT is contraindicated in all diseases associated with hypercalcaemia.
- Use of Calcitriol-AFT in patients with known hypersensitivity to calcitriol or medicines of the same class and any of the constituent excipients is contraindicated.
- Calcitriol-AFT is contraindicated if there is evidence of vitamin D toxicity.

4.4 Special warnings and precautions for use

There is a close correlation between treatment with calcitriol and the development of hypercalcaemia. 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 1mg/100 ml (250µmol/l) above normal (9-11mg/100 ml, or 2250-2750µmol/l), or serum creatinine rises to >120µmol/l, treatment with Calcitriol-AFT should be stopped immediately until normocalcaemia ensues (see Dosage and Administration).
Immobilised patients, e.g. those who have undergone surgery, are particularly exposed to the risk of hypercalcaemia.
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. In such cases, the plasma phosphate level should be maintained at the normal level (2-5mg/100ml or 0.65-1.62mmol/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 70mg2/dl2.
Patients with vitamin D-resistant rickets (familial hypophosphatemia) who are being treated with Calcitriol-AFT must continue their oral phosphate therapy. However, possible stimulation of

intestinal absorption of phosphate by Calcitriol-AFT should be taken into account since this effect may modify the need for phosphate supplementation. The regular laboratory investigations that are required include serum determinations of calcium, phosphorus, magnesium and alkaline phosphatase and of the calcium and phosphate content in 24-hour urine. During the stabilisation phase of treatment with Calcitriol-AFT, serum calcium levels should be checked at least twice weekly (see Dosage Administration).
Since calcitriol is the most effective vitamin D metabolite available, no other vitamin D preparation should be prescribed during treatment with Calcitriol-AFT, 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 value (see Overdosage).
Patients with normal renal function who are taking Calcitriol-AFT should avoid dehydration. Adequate fluid intake should be maintained.

4.5 Interaction with other medicines and other forms of interaction

Since calcitriol is one of the most important active metabolites of vitamin D3, pharmacological doses of vitamin D and its derivatives should be withheld during treatment with Calcitriol-AFT to avoid possible additive effects and hypercalcaemia.
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 Warnings and Precautions).
A relationship of functional antagonism exists between vitamin D analogues, which promote calcium absorption, and corticosteroids, which inhibit it.
Magnesium-containing medicines (e.g. antacids) may cause hypermagnesemia and should therefore not be taken during therapy with Calcitriol-AFT by patients on chronic renal dialysis.
Since Calcitriol-AFT 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: 2-5mg/100ml, or 0.65-1.62mmol/l).
Patients with vitamin D-resistant rickets (familial hypophosphatemia) 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.
Administration of enzyme inducers such as phenytoin or phenobarbital may lead to increased metabolism and hence reduced serum concentrations of calcitriol. Therefore higher doses of calcitriol may be necessary if these medicines are administered simultaneously.
Cholestyramine can reduce intestinal absorption of fat-soluble vitamins and therefore may impair intestinal absorption of calcitriol.

4.6 Fertility, pregnancy and lactation

Category B3
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-AFT 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 the breast milk. In view of the potential for hypercalcaemia in the mother and for adverse reactions from Calcitriol-AFT in nursing infants, mothers may breastfeed while taking Calcitriol-AFT, provided that the serum calcium levels of the mother and infant are monitored.

4.7 Effects on ability to drive and use machines

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

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 Dosage and Administration and Warnings and Precautions). Occasional acute symptoms include anorexia, headache, nausea, vomiting, abdominal pain or stomach ache 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 dystrophy, sensory disturbances, fever with thirst, thirst/polydipsia, polyuria, dehydration, apathy, arrested growth and urinary tract infections.
The number of adverse effects reported from clinical use of calcitriol over a period of 15 years in all indications is very low with each individual effect, including hypercalcaemia, occurring at a rate of 0.001% or less.
In concurrent hypercalcaemia and hyperphosphatemia of > 6mg/100ml or > 1.9mmol/l, soft-tissue calcification may occur; this can be seen radiographically.
In patients with normal renal function, chronic hypercalcaemia may be associated with an increase in serum creatinine.
Hypersensitivity reactions (pruritis, rash, urticaria, and very rarely severe erythematous skin disorders) may occur in susceptible individuals.

4.9 Overdose

Treatment of asymptomatic hypercalcaemia: see Dosage and administration.
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-AFT may give rise to similar symptoms. The serum calcium times phosphate (Ca x P) product should not be allowed to exceed 70mg2/dl2. 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.

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 kidney from its precursor, 25-hydroxycholecalciferol (25-HCC). Physiological daily production is normally 0.5-1.0µg and is somewhat higher during periods of increased bone synthesis (e.g. growth or pregnancy). Calcitriol promotes intestinal absorption of calcium and regulates bone mineralisation. The pharmacological effect of a single dose of calcitriol lasts about 3-5 days.

The key role of calcitriol in the regulation of calcium homeostasis, 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-AFT normalises reduced intestinal absorption of calcium, hypocalcaemia, 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 mineralisation defects.
In patients with postsurgical hypoparathyroidism, idiopathic hypoparathyroidism, and pseudohypo-parathyroidism, hypocalcaemia and its clinical manifestations are alleviated by Calcitriol-AFT therapy.
In patients with vitamin D-dependent rickets, serum levels of calcitriol are low or absent. As the endogenous production of calcitriol in the kidney is insufficient, Calcitriol-AFT is considered as a replacement therapy.
In patients with vitamin D-resistant rickets and hypophosphatemia in whom plasma calcitriol levels are reduced, treatment with Calcitriol-AFT reduces tubular elimination of phosphates and, in conjunction with concurrent phosphate treatment, normalises bone development.
Patients with various other forms of rickets, e.g. in association with neonatal hepatitis, biliary atresia, cystinosis and dietary calcium and vitamin D deficiency, have also benefited from Calcitriol-AFT therapy.
The two known sites of action of calcitriol are intestine and bone.
A calcitriol receptor-binding protein appears to exist in the mucosa of human intestine. Additional evidence suggests that calcitriol may also act on the kidney and the parathyroid glands. Calcitriol is the most active known form of vitamin D3 in stimulating intestinal calcium transport. In acutely uremic rats calcitriol has been shown to stimulate intestinal calcium absorption.
The kidneys of uremic patients cannot adequately synthesize calcitriol, the active hormone formed from precursor Vitamin D. Resultant hypocalcaemia and secondary
hyperparathyroidism are a major cause of the metabolic bone disease of renal failure. However, other bone-toxic substances which accumulate in uremia (e.g., aluminium) may also contribute.
The beneficial effect of Calcitriol-AFT in renal osteodystrophy appears to result from correction of hypocalcaemia and secondary hyperparathyroidism. It is uncertain whether Calcitriol-AFT produces other independent beneficial effects.

5.2 Pharmacokinetic properties

Absorption

Calcitriol is rapidly absorbed from the intestine. Peak serum concentrations following a single oral dose of 0.25-1.0µg Calcitriol-AFT were found within 3 - 6 hours. Following multiple administration, serum calcitriol levels reached a steady state within 7 days, with a relationship to the dose of calcitriol administered.

Distribution

After a single oral dose of 0.5µg Calcitriol-AFT, the average serum concentrations of calcitriol rose from a baseline value of 40.0 ± 4.4pg/ml to 60.0 ± 4.4pg/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 ± 5.1pg/ml after 24 hours. 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 the foetal bloodstream and breast milk.

Metabolism

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

Elimination

The elimination half-life of calcitriol in serum is 9 - 10 hours.
However, the pharmacological effect of a single dose of calcitriol lasts at least 7 days. Calcitriol is excreted in the bile and is subject to enterohepatic circulation.
After i.v. administration of radioactive calcitriol in healthy subjects, about 27% of the radioactivity is found in the faeces and about 7% in the urine within 24 hours.
After oral administration of 1μg radioactive calcitriol in healthy subjects, about 10% of the entire radioactivity was found in the urine within 24 hours. On the sixth day after i.v. administration of radioactive calcitriol, urine and faeces accounted for an average of 16% and 49% respectively of the cumulative excretion of radioactivity.
Pharmacokinetics in special clinical situations
In patients with nephrotic syndrome or in those undergoing haemodialysis, serum levels of calcitriol were reduced and time to peak levels was prolonged.

5.3 Preclinical safety data

Acute toxicity studies in mice and rats indicated that the oral approximate lethal dose of calcitriol ranged from 1.35 to 3.9mg/kg. These values are several orders of magnitude higher than the proposed clinical dose of 0.25μg twice daily (approximately 8 - 10ng/kg/day).
Subchronic toxicity studies in rats and dogs indicated that calcitriol at an oral dose of 20ng/kg/day (twice the usual human dosage) for up to 6 months produced no or minimal adverse effects. A dose of 80ng/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 300ng/kg/day (30 times the usual human dose) did not adversely affect reproduction. In rabbits, calcitriol produced some maternal and foetotoxic effects at an oral dose of 300ng/kg/day, but did not show any adverse effect at 20 or 80ng/kg/day (8 times the usual human dose).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule shell

Gelatin 69.45mg, glycerol 15.78mg, iron oxide red 0.368mg, sodium ethyl hydroxybenzoate 0.316mg, sodium propyl hydroxybenzoate 0.151mg, sorbitol 16.668mg (70% solution), titanium dioxide 0.971 mg.

Other excipient

Acorbyl palmitate 0.002mg, butylated hydroxyanisole 0.016mg, medium-chain triglycerides 160mg.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original container.

6.5 Nature and contents of container

Packs of 100 capsules.

6.6 Special precautions for disposal

No special requirements.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

AFT Pharmaceuticals Ltd
PO Box 33-203
Takapuna
Auckland 0740
Phone: 0800 423 823
Email: customer.service@aftpharm.com

9. DATE OF FIRST APPROVAL

12 January 2006

10. DATE OF REVISION OF THE TEXT

24 February 2021

SUMMARY TABLE OF CHANGES

Date	Section(s) Changed	Change (s)
February 2021	2 and 3	Correction of typographic errors