Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

One-Alpha 0.25 microgram Soft Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 0.25micrograms of Alfacalcidol
Excipient:Sesame oil
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, soft (capsule)
Product imported from Greece:
Cream-coloured, egg shaped soft gelatin capsule holding 0.1g oily solution

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

One-Alpha is indicated in all conditions where there is a disturbance of calcium metabolism due to impaired 1 α-hydroxylation of vitamin D_3 such as when there is reduced renal function.

The main indications are:

a) Uraemic bone disease.
b) Hyperparathyroidism (with bone disease).
c) Hypoparathyroidism.
d) Post-menopausal, senile and steroid-induced osteoporosis.
e) Nutritional and malabsorptive rickets and osteomalacia.
f) Pseudo-deficiency (D-dependent) rickets.
g) Hypophosphataemic vitamin D resistant rickets and osteomalacia.
h) Prophylactic and therapeutic use in neonatal hypocalcaemia.

4.2 Posology and method of administration

Initial dosage for all indications is:

Adults & children over 20 kg bodyweight	1 microgram/day
Neonates and premature infants	0.05 -0.1 microgram/kg/day
Children under 20 kg bodyweight	0.05 microgram/kg/day
Elderly	0.5microgram/day may be sufficient

Regular monitoring of response by assays of serum calcium and phosphate, parathyroid hormone and alkaline phosphatase levels and urinary calcium may be used as a guide for subsequent dosage.

Most patients respond eventually to doses between 0.5 – 6 μg daily. The dosage requirements generally decrease in bone disorders at a time when there is biochemical or radiographic evidence of bone healing, and in hypoparathyroid patients after normal plasma calcium levels have been attained. Maintenance doses are generally in the range of 0.25 - 2 μg daily.

a) Renal bone disease

Most patients with osteitis fibrosa and osteomalacia show a rapid symptomatic and a gradual biochemical, radiographic and histological improvement. In these patients, the only unwanted effects of One Alpha appears to be hypercalcaemia which is more likely when there is evidence of bone healing. Patients with relatively high initial calcium levels may have autonomous hyperparathyroidism which is often unresponsive to One-Alpha. In these cases other therapeutic measures may be indicated.

Before and during treatment with One-Alpha, phosphate-binding agents should be considered to prevent hyperphosphataemia, which is known to increase the risk of metastatic calcification, especially when associated with hypercalcaemia. It is particularly important to make frequent plasma calcium measurements in patients with chronic renal failure because prolonged hypercalcaemia may aggravate the decline of renal function.

Early hypercalcaemia is more likely in patients with autonomous hyperparathyroidism, those with histologically 'pure' osteomalacia related possibly to phosphate depletion or aluminium intoxication, and those dialysed against a high dialysate calcium concentration.

b) Hypoparathyroidism

In contrast to the response to parent vitamin D, low plasma calcium levels are restored to normal relatively quickly with One-Alpha. Severe hypocalcaemia (e.g. after extensive neck surgery) is corrected and symptoms abolished even more rapidly with higher doses of One-Alpha (e.g. 3-5 μg) together with calcium supplements. Normocalcaemia may be maintained with smaller doses within a relatively narrow dose range.

c) Hyperparathyroidism

Following parathyroidectomy, patients with primary or tertiary hyperparathyroidism and bone disease often require large doses of vitamin D and intravenous calcium to avoid severe hypocalcaemia. Preliminary studies suggest that pre-operative treatment with One Alpha for 2 to 3 weeks alleviates bone pain and myopathy when present without aggravating pre-operative hypercalcaemia. Continued post-operative treatment decreases post-operative hypocalcaemia and should be continued until the plasma alkaline phosphatase level falls to normal or hypercalcaemia occurs.

d) Hypophosphataemic vitamin D-resistant rickets and osteomalacia

These conditions are characterised by hypophosphataemia due to defective tubular reabsorption and intestinal absorption of phosphorous. Neither large doses of parent vitamin D nor phosphate supplements are entirely satisfactory, the latter tending to produce hypocalcaemia and hyperparathyroidism. Treatment of children and adults with One Alpha rapidly relieves myopathy when present, increases calcium and phosphorous retention and promotes bone healing. Phosphate supplements may also be required in some patients.

e) Pseudo-deficiency (D-dependent) rickets

Although large doses of parent vitamin D would be required (probably because of an inherent defect in the production of 1, 25-$(OH)_2D_3$), effective doses of One-Alpha are similar to those required to heal nutritional Vitamin D deficiency rickets.

f) Nutritional and malabsorptive rickets and osteomalacia

Nutritional rickets and osteomalacia can be cured rapidly with 'physiological' doses of One-Alpha. Limited experience suggests that patients with malabsorptive osteomalacia (responding only to large doses of parenterally administered vitamin D) will respond to small doses of One-Alpha.

g) Osteoporosis

Patients with post-menopausal and senile osteoporosis are said to have low levels of plasma 1, 25-$(OH)_2D_3$, even though their nutritional vitamin D status is normal. This may explain why some of these patients have calcium malabsorption, which is relatively resistant to vitamin D but responsive to small doses of One Alpha. Many post-menopausal osteoporotic women appear to have both oestrogen deficiency and calcium malabsorption. To avoid hypercalcaemia, a daily dose of 1 μg of One Alpha should not be exceeded and excessive calcium supplementation is not indicated.

h) Neonatal hypocalcaemia

Although the normal starting dose of One-Alpha is 0.05-0.1 μg /kg/day (and subsequent adjustment is by careful titration), in severe cases doses of up to 2 μg /kg/day may be required. Whilst ionised serum calcium levels may provide a guide to response, measurement of plasma alkaline phosphatase activity may be more useful. Levels of alkaline phosphatase may be markedly raised in the pre-term low birthweight infant. Whilst levels of 5 times the normal adult laboratory value may be usual in this group, alkaline phosphatase levels above 7.5 times the adult range indicate active disease. A dose of 0.1 μg/kg/day has proved effective as prophylaxis against early neonatal hypocalcaemia in premature neonates.

4.3 Contraindications

Hypercalcaemia.

Hypersensitivity to any of its constituents.

4.4 Special warnings and precautions for use

During treatment with One-Alpha, serum calcium and serum phosphate should be monitored regularly, especially in the early stages of treatment. Calcium supplements may also be required.

To maintain serum phosphates at an acceptable level in patients with renal bone diseases a phosphate binding agent may be used.

Hypercalcaemia might appear in patients treated with One-Alpha. Patients with renal failure, tertiary hyper-parathyroidism, or those on regular haemodialysis (potentially phosphates depleted) are particularly prone to develop hypercalcaemia. For this reason, patients should be informed about the clinical symptoms connected with hypercalcaemia. The early signs of hypercalcaemia are polyuria, polydipsia, weakness, headache, nausea, dry mouth, constipation, muscle pain, bone pain and metallic taste.

Hypercalcaemia can be rapidly corrected by stopping treatment until plasma calcium levels return to normal (in about one week).

One-Alpha may then be restarted at a reduced dose (half the previous dose). Caution in patients under treatment with cardioactive glycosides or digitalis as hypercalcaemia may lead to arrhythmia in such patients.

Caution should be paid to patients with neophrolithiasis.

One-Alpha capsules contain sesame oil which may rarely cause severe allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Patients taking barbiturates or anti-convulsants may require larger doses of One-Alpha to produce the desired effect due to the induction of hepatic detoxification enzymes.

Concomitant administration of colestyramine may interfere with the intestinal absorption of One-Alpha.

4.6 Fertility, pregnancy and lactation

There is no clinical experience.

One-Alpha should only be used in pregnancy if considered essential by the physician as hypercalcaemia during pregnancy may produce congenital disorders in the offspring.

Although it has not been established, it is likely that increased amounts of 1, 25 dihydroxyvitamin D_3 will be found in the milk of lactating mothers treated with One-Alpha. This may influence calcium metabolism in the infant therefore, it is advised that if possible women receiving vitamin D do not breastfeed their infants as this may lead to the development of hypercalcaemia in the infant.

4.7 Effects on ability to drive and use machines

No or negligible influence.

4.8 Undesirable effects

The most frequently reported undesirable effects are hypercalcaemia and various skin reactions such as rash.

Symptoms and signs which occur in associations with hypercalcaemia are diarrhoea, constipation, nausea, vomiting, dry mouth, metallic taste, hypercalciuria, polyuria, polydipsia, headache, dizziness, confusional state, myalgia, bone pain, irregular heartbeat, pruritus and fatigue. Prolonged hypercalcaemia can result in nephrocalcinosis and renal impairment.

Based on post-marketing data the total undesirable effect ‘reporting rate’ is rare or very rare being approximately 1:10,000 patient’s treatment years.

Metabolism and Nutrition Disorders

- Hypercalcaemia
- Hyperphosphataemia

Skin and Subcutaneous Tissue Disorders

- Pruritus
- Rash
- Urticaria

Renal and Urinary Disorders

- Nephrocalcinosis
- Renal impairment

4.9 Overdose

Hypercalcaemia is treated by suspending the administration of One-Alpha. In severe cases of hypercalcaemia general supportive measures should be undertaken: keep the patients well hydrated by I.V. infusion of saline (force diuresis), measure electrolytes, calcium and renal functions indices, assess electrocardiographic abnormalities, especially on patients on digitalis.

More specifically, treatment with glucorticosteroids, loop diuretics, bisphosphonates, calcitonin and eventually haemodialysis with low calcium content should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: A11C C03
Alfacalcidol is converted rapidly in the liver to 1, 25 dihydroxyvitamin D_3. This is the metabolite of vitamin D_3 which acts as a regulator of calcium and phosphate metabolism. Since this conversion is rapid, the clinical effects of One-Alpha and 1, 25 dihydroxyvitamin D_3 are very similar.

Impaired renal 1 -hydroxylation reduces 1, 25 dihydroxyvitamin D_3 production. This contributes to the disturbances in mineral metabolism found in several disorders, including renal bone disease, hypoparathyroidism, neonatal hypocalcaemia and vitamin D dependent rickets. These disorders, which require high doses of parent vitamin D for their correction, will respond to small doses of One-Alpha.

The delay in response and high dosage required in treating these disorders with parent vitamin D makes dosage adjustment difficult. This can result in unpredictable hypercalcaemia which may take weeks or months to reverse. The major advantage of One-Alpha is the more rapid onset of response, which allows a more accurate titration of dosage. Should inadvertent hypercalcaemia occur it can be reversed within days of stopping treatment.

5.2 Pharmacokinetic properties

Serum levels of 1,25 dihydroxyvitamin D_3 reach peak concentrations approximately 8-12 hours after a single dose of One-Alpha with a half-life of 1,25-$(OH)_2$ -D_3 of about 35 hours.

The metabolism is similar to that of vitamin D after the 25-hydroxylation to 1, 25 dihydroxyvitamin D_3.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sesame Oil
dl-α-tocopherol
Capsule Shell
Gelatin
Glycerol (E422)
Potassium Sorbate (E202)
Titanium Dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The shelf-life expiry date of this product is the date shown on the blister and outer carton of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

Blister foils containing 100 capsules in an overlabelled outer container

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

G & A Licencing Limited
Ballymurray
Co Roscommon
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1447/036/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24th July 2009

10 DATE OF REVISION OF THE TEXT