Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Egostar 22400 IU film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet of Egostar contains 560 micrograms (22 400 IU) of cholecalciferol (vitamin D3).

Excipients with known effect:
Each tablet contains 429.60 mg of lactose monohydrate and 175 mg of sucrose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Egostar 22 400 IU tablets are white, convex oblong 18 mm x 8 mm, film coated and engraved with a "V3" mark on one of the sides of the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prevention of vitamin D deficiency in patients with an identified risk.
Initial treatment of clinically relevant vitamin D deficiency.
As an adjunct to specific therapy for osteoporosis in patients with vitamin D deficiency or at risk of vitamin D insufficiency.

Egostar is indicated in adults.

4.2 Posology and method of administration

Posology
Adults
Dose should be established on an individual basis depending on the extent of the necessary vitamin D supplementation. The patient's dietary habits should be carefully evaluated and artificially added vitamin D content of certain food types should be taken into consideration.

Prevention of Vitamin D deficiency:
One tablet (22 400 IU) once every 28 days.

Initial treatment of Vitamin D deficiency:
One tablet (22 400 IU) once a week for four weeks. After four weeks, lower doses may be considered, dependent upon desirable serum levels of 25 hydroxycolecalciferol (25(OH)D), the severity of the disease and/or the patient´s response to treatment.

As an adjunct to specific therapy for osteoporosis:
One tablet (22 400 IU) once every 28 days.

Medical supervision is necessary as dose requirements may vary dependent on patient response (see section 4.4).

Paediatric population

This medicinal product should not be given to children (see section 4.4).

Special populations

Patients with hepatic impairment

No posology adjustment is required in patients with hepatic impairment.

Patients with renal impairment

This medicine should be administered with caution in patients with kidney disease and should not be used in patients with severe renal impairment (see sections 4.3 and 4.4).

Certain populations are at high risk of vitamin D deficiency, and may require higher doses and monitoring of serum 25(OH)D:
- Institutionalised or hospitalised individuals
- Dark skinned individuals
- Individuals with limited effective sun exposure due to protective clothing or consistent use of sun screens
- Obese individuals
- Patients being evaluated for osteoporosis
- Use of certain concomitant medications (e.g., anticonvulsant medications, glucocorticoids)
- Patients with malabsorption, including inflammatory bowel disease and coeliac disease
- Those recently treated for vitamin D deficiency, and requiring maintenance therapy.

Method of administration

Tablets should be orally administrated and swallowed whole with water.

Patients should be advised to take Egostar preferably with a meal.
Treatment duration is based upon the indication, the severity of the disease and the patient's response to treatment.

4.3 Contraindications

- Hypersensitivity to the active substance or any of the excipients listed in section 6.1.
- Hypervitaminosis D.
- Nephrolithiasis.
- Diseases or conditions resulting in hypercalcaemia and/or hypercalciuria.
- Severe renal impairment.

4.4 Special warnings and precautions for use

- Egostar should not be administered to patients with hypercalcaemia.
- This medicinal product should be used with caution in patients with impairment of renal function (or calculi) and the effect on calcium and phosphate levels should be monitored.
- Caution is required in patients receiving treatment for cardiovascular disease (e.g. digitalis).
- Caution is required in patients suffering from sarcoidosis because of the risk of increased metabolism of vitamin D to its active form. These patients should be monitored with regard to the calcium content in serum and urine.
- Allowances should be made for vitamin D supplements from other sources.
- The need for additional calcium supplementation should be considered for individual patients. Calcium supplements should be given under close medical supervision.
- Medical supervision is required whilst on treatment to prevent hypercalcaemia.
- It is advised that patients receiving pharmacological doses of vitamin D should have their plasma-calcium concentration monitored at regular intervals, especially initially or if symptoms suggest toxicity.

Paediatric population

This medicinal product should not be given to children.

Monitoring of plasma-calcium concentration, at regular intervals is advised in infants breastfed by mothers receiving pharmacological doses of vitamin D.

Similar monitoring is recommended in infants if they are breastfed by mothers receiving pharmacological doses of vitamin D.

Special populations

Hepatic impairment

No dosage adjustments are known in patients with hepatic impairment.

Renal *impairment*

Egostar should be administered with caution to patients with renal failure and is contraindicated in patients with severe renal impairment.

Long-term treatment

During long-term treatment serum levels of calcium and renal function should be monitored regularly, particularly in elderly patients on concomitant treatment with cardiac glycosides or diuretics and in patients with tendency to calculus formation. In case of hypercalcemia, or renal function impairment signals the dose should be reduced or discontinued treatment.

Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet that is to say essentially "sodium-free".

Sucrose
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

Vitamin A: Vitamin A might antagonise the actions of vitamin D.

Magnesium: elevation of plasma magnesium increases the secretion of parathyroid hormone (PTH), which stimulates the synthesis of 1,25(OH)2D (calcitriol or 1,25-di-hydroxyvitamin D - active form). Magnesium deficiency in humans, on the other hand, may result in an impaired PTH secretion followed by hypocalcaemia and a reduced serum concentration of 1,25(OH)2D.

Antiepileptics drugs: carbamazepine, phenobarbital, phenytoin, and primidone may increase vitamin D requirements, by increase the breakdown of vitamin D and reduce calcium absorption.

Rifampicin and isoniazid: may increase vitamin D metabolism and reduce the effectiveness of vitamin D.

Cardiac glycosides (digitalis): hypercalcaemia may increase the toxicity of cardiac glycosides during treatment with calcium and vitamin D. Patients should be monitored with regard to electrocardiogram (ECG) and serum calcium levels.

Systemic corticosteroids: may counteract the effect of vitamin D and therefore, reduce calcium absorption. It may be necessary to increase the dose of Egostar 22400 IU tablets. Concomitant use of glucocorticoids can decrease the effect of vitamin D.

Cytotoxic agents (actinomycin) and imidazole antifungal agents: interfere with vitamin D activity by inhibiting the conversion of 25-hydroxyvitamin D (calcidiol - [25(OH)D]) to 1,25-dihydroxyvitamin D by the kidney enzyme, 25-hydroxyvitamin D-1-hydroxylase.

Thiazide diuretics: increase the tubular reabsorption of calcium, enhancing the hypercalcaemic effect of a high dose of vitamin D. Monitoring of serum calcium concentration is recommended.

Ion exchange resins: simultaneous treatment with ion exchange resins such as cholestyramine or laxatives (e.g., paraffin oil) may reduce the gastrointestinal absorption of vitamin D.

Both the weight-loss drug orlistat and the cholesterol-lowering drug cholestyramine can reduce the absorption of vitamin D.

4.6 Fertility, pregnancy and lactation

Pregnancy
Egostar 22 400 IU tablets is not recommended in pregnancy. A low strength formulation should be used.

There are no or limited amount of data from the use of cholecalciferol in pregnant women.
Studies in animals have shown reproductive toxicity (see section 5.3). The recommended daily intake for pregnant women is 400 IU, however, in women who are considered to be vitamin D deficient a higher dose may be required.
During pregnancy women should follow the advice of their medical practitioner as their requirements may vary depending on the severity of their disease and their response to treatment.
Hypercalcaemia during pregnancy may produce congenital disorders in the offspring, and neonatal hypoparathyroidism. However, the risks to the foetus of untreated maternal hypoparathyroidism are considered greater than the risks of hypercalcaemia due to vitamin D therapy.

Breastfeeding
Egostar 22 400 IU tablets is not recommended in breastfeeding women. A low strength formulation should be used.
Vitamin D and its metabolites are excreted in breast milk. Its concentration appears to correlate with the amount of vitamin D in the serum of exclusively breast-fed infants.

Overdose in infants induced by nursing mothers has not been observed. However, infants should be closely monitored for hypercalcaemia or clinical manifestations of vitamin D toxicity if the mother is taking pharmacological doses of vitamin D.
When prescribing additional vitamin D to a breast-fed child the practitioner should consider the dose of any additional vitamin D given to the mother.

4.7 Effects on ability to drive and use machines

There are no data about the effect of this product on driving capacity. An effect is, however, unlikely.

4.8 Undesirable effects

Adverse reactions are listed below, by system organ class and frequency. Frequencies are defined as: (>1/1,000, <1/100) or rare (>1/10,000, <1/1,000).
Very common (³1/10)
Common (³1/100, <1/10)
Uncommon (³1/1.000, <1/100)
Rare (³1/10.000, <1/1.000)
Very rare (<1/10.000)
Not known (cannot be estimated from the available data)

Metabolism and nutrition disorders
Uncommon: Hypercalcaemia and hypercalciuria.

Skin and subcutaneous disorders
Rare: Pruritus, rash and urticaria.

Long-term treatment
In case of hypercalcemia, or renal function impairment signals the dose should be reduced or the treament discontinued (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the HPRA:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

The most serious consequence of acute or chronic overdose is hypercalcaemia due to vitamin D toxicity.
Symptoms may include arrhythmia, nausea, vomiting, anorexia, constipation, polydipsia, polyuria, dehydration, hypercalciuaria with kidney stones, nephrocalcinosis, muscle weakness, apathy, weakness or altered consciousness, etc. In addition, chronic overdoses can lead to vascular and organ calcification.

The symptoms and findings associated with vitamin D intoxication are closely related to serum calcium concentration and duration of hypercalcaemia. In patients with vitamin D intoxication, hypercalcaemia, normal or high serum phosphorus levels, normal or low levels of alkaline phosphatase, high levels of serum 25-OHD, low serum PTH, and high urine calcium/creatinine are usually present.

Treatment for vitamin D intoxication includes: discontinuation of intake, a diet with low calcium and phosphorus content, intravenous hydration with saline solutions, loop diuretics, glucocorticoids, calcitonin, and bisphosphonates.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vitamin D and analogues
ATC code: A11CC05

Mechanism of action

Cholecalciferol (vitamin D3) is important for calcium homeostasis and for optimal skeletal health. Its major function is to increase the efficiency of calcium absorption from the small intestines. Vitamin D also enhances the absorption of phosphorus from the distal small bowel. Adequate calcium and phosphorus absorption from the intestine is important for proper mineralisation of the bone. The second major function of vitamin D is involvement in the maturation of osteoclasts, which resorb calcium from the bones.
The UV-B irradiation of skin triggers photolysis of 7-dehydrocholesterol (provitamin D3) to previtamin D3 in the plasma membrane of human skin keratinocytes. Once formed in the skin, cell plasma membrane previtamin D3 is rapidly converted to vitamin D3 by the skin's temperature. Vitamin D3 from the skin and vitamin D from the diet undergo two sequential hydroxylations, first in the liver to 25(OH)D and then in the kidney to its biologically active form, D 1,25[OH]2D.
The 1,25(OH)2D ligand binds with high affinity to the VDR and triggers an increase in intestinal absorption of both calcium and phosphorus. In addition, vitamin D is involved in bone formation, resorption, and mineralization and in maintaining neuromuscular function. Circulating 1,25(OH)2D reduces serum PTH levels directly by decreasing parathyroid gland activity and indirectly by increasing serum calcium. The 1,25(OH)2D regulates bone metabolism in part by interacting with the VDR in osteoblasts to release biochemical signals, leading to formation of mature osteoclasts. The osteoclasts release collagenases and hydrochloric acid to dissolve the matrix and mineral, releasing calcium into the blood.

When vitamin D levels are inadequate, calcium and phosphorus homeostasis becomes impaired. The body responds by increasing the production and release of PTH into the circulation. The increase in PTH restores calcium homeostasis by increasing tubular reabsorption of calcium in the kidney, increasing bone calcium mobilization from the bone, and enhancing the production of 1,25(OH)2D.

Elderly and fracture/fall prevention

Other studies suggest that treatment doses of 700 IU to 1000 IU supplemental vitamin D daily could reduce the risk of falling among older individuals. This benefit may not depend on additional calcium supplementation.

Daily vs intermittent high dose regimens

Several studies aimed to determine whether the same cumulative dose of vitamin D3 produces different effects if it is given daily, weekly, or monthly. Major concern was if large intermittent, monthly doses of vitamin D might cause transient hypercalcaemia because of a mass-action effect on the production of 1,25(OH)2D.
These studies allow concluding that if the cumulative vitamin D dose and the vehicle of administration are the same, then similar serum 25(OH)D concentrations will be attained. In one clinical study, despite the initial dose of 45,000 IU vitamin D3 having produced an initial transient increase in serum 1,25(OH)2D, this did not cause hypercalcaemia, and the transient increase did not recur on the subsequent dose. Therefore, in conclusion, the doses studied in this clinical study were safe, and the related dosing interval can be selected freely, based upon the individually tailored regimen that the clinician considers most likely to maximise long-term adherence with vitamin D supplementation.

Postmenopausal women

A study including healthy postmenopausal women (aged 57 to 90 years who were at least 7 years postmenopausal) with vitamin D insufficiency to whom were randomly assigned the administration of placebo or vitamin D3, 400, 800, 1600, 2400, 3200, 4000, or 4800 IU once daily demonstrated that serum 25(OH)D increased with higher dosages of vitamin D3 and tended to plateau with vitamin D3 dosages of 3200 to 4800 IU/day. Vitamin D3, 800 IU/day, increased 25(OH)D levels in 97.5% of women. This level is associated with significant reductions in hip fractures.

Osteoporosis in patients with vitamin D deficiency or at risk of vitamin D insufficiency

A meta-analysis of randomised, controlled fracture prevention trials with vitamin D reported that oral vitamin D supplementation between 700 to 800 IU/day appeared to reduce the risk of hip and any nonvertebral fractures in ambulatory or institutionalised elderly persons.
Another recent review has confirmed that a number of studies suggest that the combination of calcium and vitamin D3 is effective in osteoporosis prevention and treatment when administered at the respective dosages of at least 1200 mg and 800 IU/day.

5.2 Pharmacokinetic properties

Vitamin D is a group of fat-soluble prohormones with the two major biologically inert precursors being vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol). Vitamin D3 is formed when 7-dehydrocholesterol in the skin is exposed to solar ultraviolet B (UVB, 290-320 nm).

Cholecalciferol is considered an inactive form of vitamin D that, after intestinal absorption, is first metabolized to calcidiol (25-hydroxyvitamin D [25(OH)D]) in the liver, and then to calcitriol (1,25-dihydroxyvitamin D [1,25(OH)2D3]) by means of an hydroxylation in the kidney. Calcitriol is the active form of vitamin D and the main responsible for its pharmacologic effects although it has been established and accepted that calcidiol should be used as an indicator of vitamin D status in the body. The circulating level of this 25-hydroxyvitamin D, due to its ease of measurement, long half-life in circulation (approximately 2 or 3 weeks), and high correlation of its level with clinical disease states, make this intermediate metabolite an optimal parameter to determine if there is a deficient state of vitamin D in the clinical setting.

Absorption
Vitamin D3 is almost completely absorbed from the gastro-intestinal tract after oral administration, if the lipid absorption is normal.

Distribution
In plasma, vitamin D3 is transported to the liver via binding protein vitamin D, where the first hydroxylation occurs. The concentration of circulating 25(OH)D (calcidiol) are an indicator of vitamin D state.

Biotransformation
25(OH)D undergoes hydroxylation in the kidney to form 1,25(OH)D (calcitriol).
Cholecalciferol and its metabolites can be stored in the muscle and fat tissues during several months.

Elimination
Calcitriol undergoes further hydroxylations before being eliminated. The primary route of elimination of vitamin D and its hydroxylated derivatives and sulfates is through the bile with about 2% excreted in the urine.

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on the results of studies of acute toxicity, chronic toxicity and genotoxicity.

No data are available concerning long-term studies in animals on the carcinogenic potential of vitamin D.

Reproductive toxicity studies performed with high doses of vitamin D3 showed embryonic malformations, some of which related to excessive deposition of calcium.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Sodium ascorbate
All-rac-α-tocopherol
Modified starch
Sucrose
Medium chain triglycerides
Silicon dioxide, colloidal
Lactose monohydrate
Povidone
Crospovidone
Sodium stearyl fumarate.

Film-coating:
Hypromellose
Titanium dioxide (E171)
Macrogol 6000
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

The product does not require any special storage conditions.

6.5 Nature and contents of container

Egostar film-coated tablets are available in white opaque PCTFE/PE.EVOH.PE/PVC/Alu blister packs of 1, 3 and 6 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Jaba Recordati S.A.
Av. Jacques Delors
Ed. Inovação 1.2
Piso 0 - Taguspark
2740-122 Porto Salvo
Portugal

8 MARKETING AUTHORISATION NUMBER

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10 DATE OF REVISION OF THE TEXT