SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Hidroferol 0.266 mg soft capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 0.266 mg of calcifediol (equivalent to 15.960 UI of Vitamin D).

Excipients with known effect:
Each capsule contains 4.98 mg of ethanol, 31.302 mg of sorbitol (E-420), 0.958 mg of sunset yellow (E-110) and other excipients.

For the full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Soft capsule
Orange, oval soft gelatine capsule

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In adults:
Treatment of vitamin D deficiency, in those cases where the initial administration of high doses is required or administration spaced in time is preferred, as in the following situations:

- As adjuvant for the treatment of osteoporosis
- In patients with malabsorption syndrome
- Renal ostheodystrophy
- Bone diseases induced by treatment with corticosteroid drugs.

4.2 Posology and method of administration

Posology

Dietary intake of vitamin D and sun exposure vary among patients and should be taken into account when calculating the appropriate dose of vitamin D analogue drugs such as calcifediol.
The dose, frequency and duration of the treatment will be determined according to plasma levels of 25-OH-cholecalciferol, type and condition of the patient and other comorbidities such as obesity, malabsorption syndrome, treatment with corticosteroids. The dose to be administered should produce serum calcium levels between 9-10 mg/dl.

Determination of 25-OH-cholecalciferol in plasma is considered the most accepted way to diagnose vitamin D deficiency. It is accepted that Vitamin D deficiency exists when serum levels of 25-OH-cholecalciferol are < 20 ng/ml, while insufficiency of vitamin D exists when serum levels of 25-OH-cholecalciferol are between 20 and 24 ng/ml.
In normal subjects mean serum concentrations are between 25 and 40 ng/ml of 25-OH-cholecalciferol.

The recommended dose is one capsule (0.266 mg of calcifediol) once a month.

- Vitamin D insufficiency: administration of one capsule (0.266 mg of calcifediol) per month for 2 months is recommended.
- Vitamin D deficiency: initial administration of one capsule (0.266 mg of calcifediol) per month for 4 months is recommended.
- As adjuvant for the treatment of osteoporosis in patients with vitamin D deficiency, administration of one capsule (0.266 mg of calcifediol) per month for 3-4 months is recommended.

In populations at high risk of vitamin D deficiency administration of higher doses or with longer duration might be necessary, after analytical verification of the extent of the deficiency and under regular monitoring of serum levels of 25-OH-cholecalciferol:

- Renal osteodystrophy: one capsule (0.266 mg of calcifediol) weekly or biweekly.
- Bone diseases induced by corticosteroid medications: one capsule (0.266 mg of calcifediol) monthly.
- Patients with higher vitamin D deficiencies or malabsorption syndrome: repetition of the initial dose a week after starting the treatment, followed by one capsule once a month for four months, controlling plasma concentration of 25-OH- cholecalciferol. Depending on these levels an increase in dose or frequency of administration might be required. Once the value is stabilized within the range either the therapy should be discontinued or the pattern spaced.

In general terms, doses should be reduced when the symptoms improve since the requirements of analogous drugs to vitamin D usually lessen after bone recovery.

It is convenient to check serum concentrations of 25-OH-cholecalciferol after 3 months of supplementation in order to confirm that they are within the desired or preferred range (30 - 60 ng/ml). Once the value is stabilized within this range the treatment should be discontinued or the frequency of administration should be lowered.
Paediatric population
For use in children, other presentations with lower dose strength are recommended.

Method of administration
Oral administration
The capsule may be taken with water, milk or juice.

4.3 Contraindications

- Hypersensitivity to the active ingredient or to any of the excipients listed in section 6.1.
- Hypercalcemia (serum calcium > 10.5 mg/dl), hypercalciuria (increased urinary elimination of calcium)
- Calcium lithiasis

- Hypervitaminosis D.

4.4 Special warnings and precautions for use

- Serum levels of 25-OH-cholecalciferol reflect vitamin D status of the patient. However, in order to obtain an adequate clinical response to oral administration of calcifediol, an appropriate dietary calcium intake is also required. Therefore, to control the therapeutic effects, the following parameters should be monitored, in addition to 25-OH cholecalciferol: serum calcium, phosphorus and alkaline phosphatase as well as urinary calcium and phosphorus in 24 hours. A decrease in serum levels of alkaline phosphatase normally precedes the onset of hypercalcemia. Once parameters are stabilized and the patient is under maintenance treatment, the above mentioned determinations should be performed regularly, especially for serum levels of 25-OH-calciferol and calcium.
- Liver or biliary insufficiency: In case of liver failure, an inability to absorb calcifediol may occur since no bile salts are produced.
- Renal impairment: To be administered with caution. Use of this drug in patients with chronic kidney disease should be accompanied by periodic monitoring of serum calcium and phosphorus, and hypercalcemia prevention. Transformation to calcitriol takes place in the kidney; thus, in case of severe renal impairment (creatinine clearance of less than 30 ml/min) a very significant reduction in the pharmacological effects may occur.
- Heart failure: Special caution is required. The patient's serum calcium should be monitored constantly, especially in patients on digitalis, because hypercalcemia may occur and arrhythmias appear. Twice-a- week determinations are recommended at the beginning of treatment.
- Hypoparathyroidism: 1-alpha-hydroxylase is activated by parathyroid hormone. As a result, in case of parathyroid insufficiency the activity of calcifediol may decrease.
- Kidney stones: Calcemia should be monitored, since vitamin D increases absorption of calcium and may aggravate the situation. In these patients supplements of vitamin D should be administered only if the benefits outweigh the risks.
- In patients with prolonged immobilization it may be necessary to reduce rthe dose in order to avoid hypercalcemia.
- Some diseases reduce the ability of the intestine to absorb vitamin D, as in the case of malabsorption syndrome or Crohn's disease.
- Patients with sarcoidosis, tuberculosis or other granulomatous diseases: to be administered with caution, since these conditions lead to a greater sensitivity to the effect of vitamin D as well as to an increase of the risk of adverse effects at doses lower than the recommended dose. It is necessary to monitor serum and urinary calcium concentrations in these patients.
- Patients and their families and/or caregivers should be informed of the importance of complying with the prescribed dosage and with recommendations about diet and concomitant intake of calcium supplements in order to prevent overdosing.
- Interference with laboratorytests: Patients should be warned that this drug contains a component that can alter the results of laboratory tests:
  Determination of cholesterol: calcifediol may interfere with Zlatkis-Zak method, leading to false increases in serum cholesterol levels.

Elderly patients:
Elderly people generally have greater needs for vitamin D due to a decreased ability of the skin to produce cholecalciferol from its precursor 7-dehydrocholesterol, to a reduction of exposure to the sun, to changes in renal function or to digestive disorders that decrease absorption of vitamin D.

Warnings on excipients
This medicine contains 1% ethanol (alcohol), which corresponds to 4.98 mg/capsule.
This medicine contains sorbitol. Patients with hereditary fructose intolerance should not take this drug.
This medicine may cause allergic reactions because it contains sunset yellow (E-110). It can cause asthma, especially in patients allergic to acetylsalicylic acid.

4.5 Interaction with other medicinal products and other forms of interaction

- **Phenytoin, phenobarbital, primidone** and other enzyme inducers: enzyme inducers may reduce plasma concentrations of calcifediol and inhibit its effects by inducing its hepatic metabolism.
- **Cardiac glycosides:** Calcifediol can cause hyperglycemia, which can, in turn, enhance the inotropic effects of digoxin and its toxicity, producing cardiac arrhythmias.
- Drugs that decrease the absorption of calcifediol such as **cholestyramine, colestipol or orlistat**, which can result in decreased effects. It is recommended to space doses of these medicines and vitamin D supplements at least 2 hours.
- **Paraffin and mineral oil**: Due to liposolubility of calcifediol, the product can dissolve in paraffin and intestinal absorption may decrease. Using other types of laxatives or at least spacing doses is recommended.
- **Thiazide diuretics**: Co-administration of a thiazide diuretic (hydrochlorothiazide) with vitamin D supplements in patients with hypoparathyroidism may lead to hypercalcemia, which may be temporary or require the interruption of the treatment with the vitamin D analogue.
- Some antibiotics, such as **penicillin, neomycin** and **chloramphenicol** can increase calcium absorption.
- **Phosphate-binding agents such as magnesium salts**: Since vitamin D has an effect on phosphate transport in the intestine, kidney and bone, hypermagnesemia may occur. The dosage of agents that bind to phosphate shall be adjusted according to phosphate concentrations in serum.
- **Verapamil:** Some studies show potential inhibition of antianginal action, due to antagonism of their actions.
- **Vitamin D:** Co-administration of any vitamin D analogue should be avoided as additive effects and hypercalcemia can occur.
- **Calcium supplements:** Uncontrolled intake of additional preparations containing calcium should be avoided.
- **Corticosteroids:** They counteract the effects of vitamin D analogue drugs such as calcifediol.

Interaction with food and drinks
Food supplemented with vitamin D should be taken into account, since additive effects may occur.

4.6 Fertility, pregnancy and lactation

Pregnancy
No controlled studies with calcifediol in pregnant women have been performed.
Studies performed in animals have shown toxicity for reproduction (see section 5.3).

Do not use calcifediol 0.266 mg soft capsules during pregnancy.

Breast-feeding
Calcifediol is excreted into breast milk.
The risk in newborns/infants cannot be excluded. Maternal ingestion of high doses of calcifediol can produce high levels of calcitriol in milk and cause hypercalcemia in infants.

This medicine should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Calcifediol capsules has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions to calcifediol are generally uncommon (≥ 1/1,000 to <1/100) but sometimes they are moderately significant.

The most significant adverse effects are related to excessive intake of vitamin D, i.e. they are often associated with overdose or prolonged treatment, especially when associated with high doses of calcium. The doses of vitamin D analogues required for hypervitaminosis vary considerably from one subject to another. The most common adverse reactions are due to the hypercalcemia which can occur initially or at a later stage:

Endocrine disorders:
Pancreatitis, among the late symptoms of hypercalcemia

Metabolism and nutrition disorders:
Elevation of blood urea nitrogen (BUN), albuminuria, hypercholesterolemia, hypercalcemia

Nervous system disorders:
In case of moderate hypercalcemia the following symptoms may appear: weakness, fatigue, drowsiness, headache, irritability.

Eye disorders:
Rarely (≥1/10,000 to <1/1,000), at very high doses photophobia and conjunctivitis with corneal calcifications may occur.

Cardiac disorders:
In case of hypercalcemia cardiac arrhythmias may occur.

Gastrointestinal disorders:
Nausea, vomiting, dry mouth, constipation, taste disturbances, with a metallic taste, abdominal cramps. If hypercalcemia progresses anorexia may occur.

Hepatobiliary disorders:
High calcemia levels can lead to increased transaminase (SGOT and SGPT).

Musculoskeletal and connective tissue disorders:
Bone and muscle pain may occur in early stages of hypercalcemia, calcification in soft tissues.

Renal and urinary disorders:
Manifestations of hypercalcemia are: nephrocalcinosis and deterioration of kidney function (with polyuria, polydipsia, nocturia and proteinuria).

General disorders and alterations in the place of administration:
Later symptoms of hypercalcemia include: rhinorrhea, pruritus, hyperthermia, decreased libido.

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 national reporting system listed in Appendix V.

4.9 Overdose

Symptoms:
Administration of vitamin D in high doses or for long periods of time may cause hypercalcemia, hypercalciuria, hyperphosphatemia and renal failure. As early symptoms of overdose, weakness, fatigue, drowsiness, headache, anorexia, dry mouth, metallic taste, nausea, vomiting, abdominal cramps, polyuria, polydipsia, nocturia, constipation or diarrhea, dizziness, tinnitus, ataxia, rash, hypotonia (especially in children), muscle or bone pain and irritability may appear.
Among later symptoms of hypercalcemia the following are included: runny nose, itching, decreased libido, nephrocalcinosis, renal failure, osteoporosis in adults, growth retardation in children, weight loss, anemia, conjunctivitis with calcification, photophobia, pancreatitis, elevated blood urea nitrogen (BUN), albuminuria, hypercholesterolemia, increased transaminases (SGOT and SGPT), hyperthermia, generalized vascular calcification, convulsions, soft tissue calcification. Rarely, patients may develop hypertension or psychotic symptoms; serum alkaline phosphatase may decrease; electrolyte imbalances together with moderate acidosis can lead to cardiac arrhythmias.
In the most serious cases, where serum calcium exceeds 12 mg/dl, syncope, metabolic acidosis and coma may happen. Although symptoms of overdose are usually reversible an overdose might lead to kidney or heart failure.
It is accepted that serum levels of 25-OH-cholecalciferol above 150 ng/ml may be associated with an increased incidence of adverse effects.
Increased calcium, phosphate, albumin and urea nitrogen in blood as well as cholesterol and blood transaminases are typical of this kind of overdose.

Treatment:
Treatment of calcifediol overdose consists of:

1. Withdrawal of treatment (with calcifediol) and with any calcium supplement being administered.
2. Follow a diet low in calcium. Administration of large volumes of liquids, both orally and parenterally, is advisable to increase calcium excretion. If necessary, administer steroids and induced forced diuresis with loop diuretics such as furosemide.
3. If intake has occurred in the previous 2 hours, gastric emptying and forced emesis are advisable. If vitamin D has already passed through the stomach, a laxative (paraffin or mineral oil) can be administered. If vitamin D has already been absorbed, hemodialysis or peritoneal dialysis with a dialysis solution free of calcium can be performed.

Hypercalcemia derived from prolonged administration of calcifediol persists for approximately 4 weeks after discontinuation of treatment. Signs and symptoms of hypercalcemia are usually reversible. However, metastatic calcification can cause serious kidney or heart failure and death.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vitamin D and analogues, ATC code: A11CC06

Mechanism of action

Vitamin D has two main forms: D2 (ergocalciferol) and D3 (cholecalciferol). Vitamin D3 is synthesized in the skin by exposure to sunlight (ultraviolet radiation) and is obtained from the diet. Vitamin D3 must undergo a two-step metabolic process to be active; the first step occurs in the microsomal fraction of the liver where Vitamin D is hydroxylated at position 25 (25-hydroxycholecalciferol or calcifediol); the second step takes place in the kidney where 1,25-dihydroxycholecalciferol or calcitriol is formed due to the activity of enzyme 25-hydroxycholecalciferol 1-hydroxylase; conversion to 1,25-dihydroxycholecalciferol is regulated by its own concentration, by parathyroid hormone (PTH) and by serum calcium and phosphate concentration. Other metabolites with unknown function exist. 1,25-dihydroxycholecalciferol is transported from the kidney to target tissues (intestine, bone and possibly kidney and parathyroid gland) by binding to specific plasma proteins.

Pharmacodynamic effects

Vitamin D increases absorption of calcium and phosphorus in the intestine and improves normal bone formation and mineralization and acts on three levels:
Intestine: Vitamin D enhances absorption of calcium and phosphorus in the small intestine. Bone: calcitriol enhances bone formation by increasing levels of calcium and phosphate and stimulates action of osteoblasts.
Kidney: calcitriol enhances tubular reabsorption of calcium.
Parathyroid glands: vitamin D inhibits the secretion of parathyroid hormone.

5.2 Pharmacokinetic properties

Absorption
Calcifediol or 25-hydroxycholecalciferol, as an analogue to vitamin D, is well absorbed in the intestine if fat absorption is normal, through chylomicrons, mainly in the middle portions of the small intestine; approximately 75-80% is absorbed through this process.

Distribution
Calcifediol is the major circulating form of vitamin D. Serum concentrations of 25-OH-cholecalciferol reflect the vitamin D stored in the body, usually from 25 to 40 ng/ml (62.5 to 100 nmol/l) in healthy subjects. Following oral administration of calcifediol, the maximum serum concentration is reached after 4 hours approximately. Its half-life is around 18 to 21 days and storage in adipose tissue is less significant than vitamin D, due to its lower lipid solubility. Calcifediol is stored in adipose tissue and muscle for prolonged periods.

Metabolism or Biotransformation

Elimination
Calcifediol is primarily excreted in the bile.

5.3 Preclinical safety data

High doses of vitamin D (4 to 15 times the recommended dose in humans) have proved to be teratogenic in animals, but there are few studies in humans. Vitamin D can cause hypercalcemia in pregnant women, which could lead to a syndrome of supravalvar aortic stenosis, retinopathy and mental retardation in infants and newborn.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol, anhydrous
Medium chain triglycerides
Gelatine
Vegetable glycerin
Sorbitol (70%) (E-420)
Titanium dioxide (E171)
Sunset yellow (E-110)
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

This medicine is packed in PVC / PVDC-Al blisters containing 5 or 10 capsules.

6.6 Special precautions for disposal and other handling

No special requirements for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

FAES FARMA S.A.
Máximo Aguirre, 14
48940 Leioa (Bizkaia)
SPAIN

8. MARKETING AUTHORISATION NUMBER

80.095

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

5th August 2015

10. DATE OF REVISION OF THE TEXT

August 2015