SPC (Summary of product characteristic)

1. Name of medical product

Zanotazon 50000IU Softgel capsules

2.Qualitative and quantitative composition

Each capsule contains 50,000 IU cholecalciferol (equivalent to 1.25 mg vitamin D3)
Excipients with known effect: Methyl Parahydroxybenzoate(E218) and Propyl Parahydroxybenzoate (E216).
For the full list of excipients, see section6.1.

3. Pharmaceutical Form

Pharmaceutical form and strengths
Soft capsule

Zanotazon 50,000 IU is a yellow oval-shaped, soft capsule. It contains a slightly yellow oily liquid.

4. Clinical particulars

4.1 Therapeutic indications

The treatment of vitamin D3 deficiency.

4.2 Posology and method of administration

Posology

1 capsule contains 50,000 IU vitamin D3.

▪ Paediatric posology

- Due to lack of clinical data, Zanotazon is not recommended.

▪ Pregnancy and breastfeeding

- Due to lack of clinical data, Zanotazon is not recommended.

▪ Adults

Higher doses may be required in certain situations, see below.

- Treatment of vitamin D3 deficiency (<25 nmol/l) 50,000 IU/week (1 capsule) for 6-8 weeks, followed by maintenance therapy (1400-2000 IU/day may be required, such as 1 capsule per month; follow up 25(OH)D measurements should be made approximately three to four months after initiating maintenance therapy to confirm that the target level has been achieved.)

▪ Certain populations are at high risk of Vitamin D3 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 (eg, anticonvulsant medications, glucocorticoids)

- Patients with malabsorption, including inflammatory bowel disease and coeliac disease

- Those recently treated for Vitamin D3 deficiency, and requiring maintenance therapy.

Special populations

Renal impairment

Zanotazon should not be used in combination with calcium in patients with severe renal impairment.

Hepatic impairment

No posology adjustment is required in patients with hepatic impairment.

Method of administration

Oral – The capsules should be swallowed whole with water.

Patients should be advised to take Zanotazon preferably with a meal (see section 5.2 Pharmacokinetic properties - "Absorption").

4.3 Contraindications

• Hypersensitivity to the active substance(s) or to any of the excipients.

• Hypercalcaemia and/or hypercalciuria.

• Nephrolithiasis and/or nephrocalcinosis

• Serious renal impairment

• Hypervitaminosis D

• Pseudohypoparathyroidismas the vitamin D requirement may be reduced due to phases of normal vitamin D sensitivity, involving the risk of prolonged overdose. Better-regulatable vitamin D derivatives are available for this.

• Pregnancy

• Children and adolescents (under 18 years of age)

4.4 Special warnings and precautions for use

- *Concomitant calcium administration:* Adequate dietary calcium is necessary for a clinical response to vitamin D therapy.

Hypercalcemia: Calcium phosphate may precipitate if the product of serum calcium multiplied by phosphate (Ca.P) exceeds 70. Progressive hyper-calcemia due to overdosage of vitamin D and its metabolites may require

- emergency attention. Chronic hypercalcemia can lead to generalized vascular calcification,

nephrocalcinosis and other soft tissue calcification.

- Radiographic or slit lamp evaluation of suspect anatomical regions may be useful for early

detection.

In patients with normal renal function, chronic hypercalcemia may be associated with an increase in serum creatinine. While this is usually reversible, it is important to pay careful attention to factors that may lead to hypercalcemia.

A fall in serum alkaline phosphatase levels usually precedes hypercalcemia. Should

hypercalcemia develop, discontinue the drug immediately. After achieving normocalcemia, readminister at a lower dosage.

- *Hypersensitivity reactions:* Hypersensitivity to vitamin D may be one etiological factor in infants with idiopathic hypercalcemia. In these cases, severely restrict vitamin D intake.
- *Renal function impairment:* The kidneys of uremic patients cannot adequately synthesize calcitriol, the active hormone formed from parathyroidism are a major cause of the metabolic bone disease of renal failure.
- *Pregnancy:* Category A. (Category C when used in doses that exceed the RDA). Safety of

vitamin D in amounts > 400 IU/day is not established. Avoid doses greater than the RDA during a normal pregnancy.
Animal studies have shown fetal abnormalities associated with hyper-vitaminosis D.
There are no adequate and well controlled studies in pregnant women use during pregnancy only if the potential benefits outweigh the potential hazards to the fetus.

- *Lactation:* Vitamin D is excreted in breast milk in limited amounts. In a mother given large

doses of vitamin D, 25-hydroxycholecalciferol appeared in the milk and caused hypercalcemia in the child. Monitoring of the infant's serum calcium concentration was required.

- *Children:* Safety and efficacy of vitamin D and its metabolites in children in doses exceeding

the RDA and in children undergoing dialysis have not been established.

- This medicinalproductcontainsmethylparahydroxybenzoateandpropylparahydroxywenzoatewhichmaycauseallergicreactions

4.5 Interaction with other medicinal products and other forms of interaction
Concomitant use of anticonvulsants (such as phenytoin) or barbiturates (and possibly other drugs that induce hepatic enzymes) may reduce the effect of Vitamin D3 by metabolic inactivation.

In cases of treatment with thiazide diuretics, which decrease urinary elimination of calcium, monitoring of serum calcium concentration is recommended.

Concomitant use of glucocorticoids can decrease the effect of Vitamin D3.

In cases of treatment with drugs containing digitalis and other cardiac glycosides, the administration of Vitamin D3 may increase the risk of digitalis toxicity (arrhythmia).

Strict medical supervision is needed, together with serum calcium concentration and electrocardiographic monitoring if necessary.

Simultaneous treatment with ion exchange resin such as cholestyramine, colestipol hydrochloride, orlistat or laxative such as paraffin oil may reduce the gastrointestinal absorption of Vitamin D3,.

The cytotoxic agent actinomycin and imidazole antifungal agents interfere with Vitamin D3 activity by inhibiting the conversion of 25-hydroxyVitamin D3 to 1,25- dihydroxyVitamin D3 by the kidney enzyme, 25-hydroxyVitamin D3-1-hydroxylase.

4.6 Fertility, pregnancy and lactation
In pregnancy and lactation the high strength formulation is not recommended and a low strength formulation should be used.

<u>Pregnancy</u>

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 Preclinical safety data). The recommended daily intake for pregnant women is 400 IU, however, in women who are considered to be Vitamin D3 deficient a higher dose may be required (up to 2000 IU/day- 10 drops with the oral drops presentation).

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 Vitamin D3 and its metabolites are excreted in breast milk.

Breast-feeding

Vitamin D3 can be prescribed while the patient is breast-feeding if necessary. This supplementation does not replace the administration of Vitamin D3 in the neonate

Fertility

There is no data regarding treatment with vitaminD3 and its effects on fertility.

4.7 Effects on ability to drive and use machines
There are no data on the effects of Zanotazon on the ability to drive. However, an effect on this ability is unlikely.

4.8 Undesirable effects
Adverse reactions are listed below, by system organ class and frequency. Frequencies are defined as: uncommon (>1/1,000, <1/100) or rare (>1/10,000, <1/1,000).

Metabolism and nutrition disorders

Uncommon: Hypercalcaemia and hypercalciuria

Skin and subcutaneous disorders:

Rare: pruritus, rash, and urticaria.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose
Symptoms of overdose

Ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) have a relatively low therapeutic index. The threshold for vitamin D intoxication is between 40,000 and 100,000 IU daily for 1 to 2 months in adults with normal parathyroid function. Infants and small children may react sensitively to far lower concentrations. Therefore, it is warned against intake of vitamin D without medical supervision.

Overdose leads to increased serum and urinary phosphorus levels, as well as hypercalcaemic syndrome and consequently calcium deposits in the tissues and above all in the kidneys (nephrolithiasis, nephrocalcinosis) and the vessels.

Discontinue Zanotazon when calcaemia exceeds 10.6 mg/dl (2.65 mmol/l) or if the calciuria exceeds 300 mg/24 hours in adults or 4-6 mg/kg/day in children.

Chronic overdosage may lead to vascular and organ calcification, as a result of hypercalcaemia.

The symptoms of intoxication are little characteristic and manifest as nausea, vomiting, initially also diarrhoea, later constipation, loss of appetite, weariness, headache, muscle pain, joint pain, muscle weakness, persistent sleepiness, azotaemia, polydipsia and polyuria and, in the final stage, dehydration. Typical biochemical findings include hypercalcaemia, hypercalciuria, as well as increased serum 25 hydroxycholecalciferol concentrations.

Treatment of overdose

Symptoms of chronic vitamin D overdosage may require forced diuresis as well as administration of glucocorticoids or calcitonin.

Overdosage requires measures for treating the - often persisting and under certain circumstances life- threatening - hypercalcaemia.

The first measure is to discontinue the vitamin D preparation; it takes several weeks to normalisehypercalcaemia caused by vitamin D intoxication.

Depending on the degree of hypercalcaemia, measures include a diet that is low in calcium or free of calcium, abundant liquid intake, increase of urinary excretion by means of the drug furosemide, as well as the administration of glucocorticoids and calcitonin.

If kidney function is adequate, calcium levels can be reliably lowered by infusions of isotonic sodium chloride solution (3–6 liters in 24 hours) with addition of furosemide and, in some circumstances, also 15 mg/kg body weight/hour sodium edetate accompanied by continuous calcium and ECG monitoring. In oligoanuria, in contrast, haemodialysis (calcium-free dialysate) is necessary.

No special antidote exists.

It is recommended to point out the symptoms of potential overdose to patients under chronic therapy with higher doses of vitamin D (nausea, vomiting, initially also diarrhoea, later constipation, anorexia, weariness, headache, muscle pain, joint pain, muscle weakness, persistent sleepiness, azotaemia, polydipsia and polyuria).

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vitamin D and analogues, cholecalciferol ATC Code: A11CC05

In its biologically active form Vitamin D3 stimulates intestinal calcium absorption , incorporation of calcium into the osteoid, and release of calcium from bone tissue. In the small intestine it promotes rapid and delayed calcium uptake. The passive and active transport of phosphate is also stimulated. In the kidney, it inhibits the excretion of calcium and phosphate by promoting tubular resorption. The production of parathyroid hormone (PTH) in the parathyroids is inhibited directly by the biologically active form of vitamin D3. PTH secretion is inhibited additionally by the increased calcium uptake in the small intestine under the influence of biologically active Vitamin D3.

5.2 Pharmacokinetic properties

The pharmacokinetics of Vitamin D3 is well known.

Absorption

Vitamin D3 is well absorbed from the gastro-intestinal tract in the presence of bile, so the administration with the major meal of the day might therefore facilitate the absorption of Vitamin D3.

Distribution and biotransformation

It is hydroxylated in the liver to form 25-hydroxy-cholecalciferol and then undergoes further hydroxylation in the kidney to form the active metabolite 1, 25-dihydroxy- cholecalciferol (calcitriol).

6. Pharmaceutical particulars

6.1 List of Excipient

- Corn oil
- Butylated Hydroxyanisole(BHA)
- Butylated Hydroxytoluene (BHT)
- Gelatin
- Glycerin
- Methyl Parahydroxybenzoate
- Propyl Parahydroxybenzoate
- Purified water

6.2 Incompatibilities

Not applicable

The stability results show no incompatibility between drug substance and excipients and packaging materials.

6.3 Shelf life

3 years

6.4 Proposed storage condition

Store below 25°C protect from light and moisture.

6.5 Nature and contents of container (Packaging specification)

20 capsules packed in PVC /Aluminum foil blister, inserted into a cardboard carton.

6.6 Special precautions for disposal and other handling

Any unused product should be disposed of in accordance with the local requirements.

7. Marketing authorization holder

"Giga Farm" LLC
Gogunts 3/5 Street, Gyumri,
Armenia.

9. Date of first authorization / Renewal of the authorization

Date of first authorization: 12/Aug/2003
Renewal of the authorization is: 25/Apr/2009

Date of partial revision the text
February/2017