National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

1. Name of the medicinal product
Avrocal-D Caplet

2. Qualitative and quantitative composition
Each tablet contains:

Calcium	300mg (as Calcium Carbonate)
Vitamin D3	200 I.U (as Cholecalciferol)
Magnesium	100mg (as Magnesium Hydroxide)
Zinc	4mg (as Zinc Sulphate)

For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Tablet
Orange, biconvex, oblong tablets, with a score line on one side and embossed "AVC-D" on the other side.

4. Clinical particulars
4.1 Therapeutic indications
- Boosts the immune system
- For strong and healthy bones and teeth
- Prevents osteoporosis and bone loss
- Regulates heart and blood pressure
- Promotes normal muscle and nerve function

4.2 Posology and method of administration
Posology
Adults: One caplet 2 to 3 times daily.
Children 7 – 12 years: Half a caplet 2 to 3 times daily.

May be taken with or without food or as prescribed by the physician.

Method of administration
For oral administration.

4.3 Contraindications
- Avrocal-D is contra-indicated in patients with known hypersensitivity to calcium, Vitamin D, Magnesium and Zinc.
- It is contraindicated in patients with renal impairment or diseases associated with hypercalcaemia such as sarcoidosis and some malignancies.
- It is contraindicated in patients hyperphosphataemia.
- It is contra-indicated in patients with calcium renal calculi or a history of renal calculi and in patients with heart disease who might be at risk of organ damage if hypercalcaemia occurred
- It should not be used in infants, who may have increased sensitivity to the effects of Vitamin D.

4.4 Special warnings and precautions for use
Patients receiving other single vitamins or multivitamin preparations, any other medication or those under medical care should consult a health care professional before taking this product.

This preparation must be taken with particular caution together with other products, including supplements and/or fortified foods/drinks containing Vitamin D, since large daily doses may cause hypervitaminosis D.

As calcium and Vitamin D may have an effect on stone formation, patients with nephrolithiasis or urolithiasis should use caution when using vitamin supplements.

Seek medical advice before taking this medicine if you are:

- Pregnant or breastfeeding
- Allergic to any of the components of the medication
- Have high Calcium or Vitamin D (hypercalcaemia or hypervitaminosis D)
- Have malabsorption syndrome
- Have heart, kidney or live disease, carcoidosis, Chron's disease, achlorhydria, low level of bile or other stomach or intestinal problems
- Problems of phosphate imbalance or biabetes

4.5 Interaction with other medicinal products and other forms of interaction

CALCIUM

There is an increased risk of hypercalcaemia if calcium salts are given with vitamin D or thiazide diuretics. Vitamin D increases the gastrointestinal absorption of calcium and thiazide diuretics decrease its urinary excretion. Plasma-calcium concentrations should be monitored in patients receiving the drugs together.

Bran decreases the gastrointestinal absorption of calcium and may therefore decrease the efficacy of calcium supplements. Corticosteroids also reduce calcium absorption.

Calcium enhances the effects of digitalis glycosides on the heart and may precipitate digitalis intoxication.

Calcium salts reduce the absorption of bisphosphonates, fluoride, some fluoroquinolones and tetracyclines. Doses should be separated by at least 3 hours.

VITAMIN D

Some antiepileptics may increase vitamin D requirements (e.g. carbamazepine, Phenobarbital, phenytoin, and primidone).

Rifampicin and isoniazid may reduce the effectiveness of vitamin D. Corticosteroids may counteract the effects of vitamin D.

MAGNESIUM

Oral magnesium salts decreases the absorption of tetracyclines and bisphosphonates and doses should be separated by a number of hours. Magnesium salts also interact with many other drugs both by alterations in gastric pH and emptying and by formation of complexes that are not absorbed. Interactions may be minimised by giving magnesium and any other medications 2 to 3 hours apart.

ZINC

The absorption of zinc may be reduced by iron supplements, penicillamine, phosphorus-containing preparations and tetracyclines. Zinc supplements reduce the absorption of copper, fluoroquinolones, iron, penicillamine and tetracyclines.

Drug-Food Interactions: Since oxalic acid (found in spinach and rhubarb) and phytic acid (found in whole cereals) may inhibit calcium absorption, it is not recommended to take this product within two hours of eating foods containing high oxalic acid or phytic acid concentrations.

4.6 Fertility, pregnancy and lactation

Pregnancy

Hypercalcaemia during pregnancy may produce congenital disorders in the offspring, and neonatal hypoparathyroidism. However, the risk to the foetus of untreated maternal hypoparathyroidism are considered greater than the risks of hypercalcaemia due to vitamin D therapy.

Indeed, one report noted increased requirements for vitamin D preparations during pregnancy for the treatment of hypoparathyroidism; the dose needed tended to increase during the second half of pregnancy. In one woman in whom the dose of calcitriol remained raised after delivery, hypercalcaemia developed. This did not occur in two women who did not breast feed and in whom the dose of the vitamin D preparations was reduced soon after delivery.

Magnesium crosses the placenta. When used in pregnant women, foetal heart rate should be monitored and use within 2 hours of delivery should be avoided.

Zinc requirements are increased in pregnancy. Although it is unclear to what extent this has clinical consequences, some have suggested that supplementation with modest doses of zinc (less than 45mg daily) during pregnancy may have beneficial effects on foetal growth and development and lead to improved pregnancy outcomes. A controlled study in Peru found that addition of oral zinc (25mg of zinc daily as zinc sulphate) to iron and folate supplementation improved foetal bone growth, as measured by femur length.

Breast-feeding
Permanent overdose of vitamin D might be harmful to the neonate. The vitamins and minerals in this preparation are secreted into breast milk. This must be taken into consideration if the infant is receiving any respective supplements.
For lactating women the Institute of Medicine (USA) has set the Tolerable Upper Intake Levels (UL) of vitamin D of 100 µg (4000IU) per day, which is considered as safe. Avrocal-D contains 200IU/tablet (5 µg/tablet).

Fertility
There are no data on the effect of the medicinal product on fertility.

4.7 Effects on ability to drive and use machines
Avrocal-D has no influence on the ability to drive and use machines.

4.8 Undesirable effects
Calcium carbonate may occasionally cause constipation. Flatulence from released carbon dioxide may occur in some patients.

Vitamin D is usually well tolerated and has no reported side effect when taken at normal doses.

Magnesium Hydroxide may cause gastrointestinal irritation and watery diarrhoea, an effect that is dose-dependent. Taking with food may decrease the incidence of diarrhoea.

The most common effects of zinc salts given orally are gastrointestinal and include abdominal pain, dyspepsia, nausea, vomiting, diarrhoea, gastric irritation and gastritis. These are particularly common if zinc salts are taken on an empty stomach and may be reduced by giving them with meals.

4.9 Overdose
There is no evidence that this product can lead to an overdose when used as recommended. Most, if not all reports concerning overdoses of vitamins and minerals are associated with concomitant intake of high dosed single and/or multivitamin preparations.
Acute or long-term overdose can cause hypervitaminosis D and hypercalcaemia.

Symptoms
CALCIUM
High doses or prolonged use of calcium carbonate can lead to gastric hypersecretion and acid rebound. Like other calcium salts calcium carbonate may lead to hypercalcaemia, particularly in patients with renal failure or after high doses. Symptoms of hypercalcaemia include anorexia, nausea, vomiting, constipation, abdominal pain, muscle weakness, fatigue, confusion, mental disturbances, thirst, polyuria, nephrocalcinosis, renal calculi and in severe cases, cardiac arrhythmias and coma.

VITAMIN D
Excessive intake of vitamin D leads to the development of hyperphosphataemia or hypercalcaemia. Doses of 60,000 units daily can cause hypercalcaemia. Associated effects of hypercalcaemia include muscle weakness, apathy, bone pain, proteinuria, hypercalciuria, ectopic calcification and renal and cardiovascular damage including hypertension and cardiac arrhythmias. Chronic hypercalcaemia can lead to generalised vascular calcification, nephrocalcinosis and rapid deterioration of renal function.
Symptoms of Vitamin D overdosage include anorexia, nausea and vomiting, lassitude, constipation or diarrhoea, polyuria, nocturia, sweating, headache, thirst, somnolence and vertigo.

Interindividual tolerance to vitamin D varies considerably; infants and children are generally more susceptible to its toxic effects. The vitamin should be withdrawn if toxicity occurs.
Large doses of vitamin D have resulted in chronic hypercalcaemia in children with renal osteodystrophy.

MAGNESIUM
Hypermagnesaemia due to oral intake is uncommon as the kidneys are able to excrete a relatively large magnesium load. However it may occur in patients with impaired renal function taking large amounts of magnesium. Symptoms of hypermagnaesaemia include are CNS and respiratory depression and loss of deep tendon reflexes, both due to neuromuscular blockade. Other symptoms may include nausea, vomiting, flushing of the skin, thirst, hypotension due to peripheral vasodilatation, drowsiness, confusion, slurred speech, double vision, muscle weakness, bradycardia, coma and cardiac arrest.

ZINC
Acute toxicity of zinc is characterised by dehydration, electrolytic imbalance, stomach pain, lethargy, dizziness, muscular incoordination and renal failure.
Prolonged use of zinc supplements leads to copper deficiency due to lowered copper absorption with associated sideroblastic anaemia and neutropenia; therefore zinc supplements should be taken only with adequate intakes of copper and full blood counts and serum cholesterol should be monitored to detect early signs of copper deficiency. High serum zinc concentrations may be reduced by using a chelating drug such as sodium calcium edetate.

Management
Treatment of severe hypercalcaemia requires prompt rehydration regardless of the cause. Where hypercalcaemia is due to excessive doses of a vitamin D analogue, it should be discontinued until normocalcaemia is achieved. Corticosteroids effectively reduce the gastrointestinal absorption of calcium, and these may be used intravenously as adjuncts to rehydration in severe hypercalcaemia, and orally for milder hypercalcaemia or longer term therapy. Oral sodium cellulose phosphate, which binds calcium in the gastrointestinal tract, and a low calcium diet may also be considered. Oral chloroquine or hydroxylchloroquine have been used in hypercalcaemia associated with sarcoidosis. Ketoconazole may be useful as an alternative to corticosteroids.

Treatment of mild hypermagnaesaemia is usually limited to restricting magnesium intake. In severe hypermagnaesaemia, ventilatory and circulatory support may be required. Slow intravenous injection of calcium gluconate is recommended to reverse the effects on cardiovascular and respiratory systems. If renal function is normal, adequate fluids should be given to promote renal magnesium clearance. This may be increased by the use of furosemide. Haemodialysis using a magnesium-free dialysis solution effectively removes magnesium, and this may be necessary in patients with renal impairment, or for whom other methods prove ineffective.

In acute overdosage zinc salts are corrosive, due to the formation of zinc chloride by stomach acid; treatment consists of giving milk or alkali carbonates and activated charcoal. The use of emetics or gastric lavage should be avoided.

5. Pharmacological properties
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Multivitamins and minerals / trace elements,
ATC code: A 11A A03

CALCIUM
Calcium is essential for the development and maintenance of normal bone. It is the most abundant mineral in the body and an essential body electrolyte. The adult body contains about 1.2kg of calcium, of which about 99% is incorporated into the skeleton where its primary role is structural. The remaining 1% is found in body tissues and fluids and is essential for normal nerve conduction, muscle activity and blood coagulation.

Calcium salts are used as calcium supplement in the management of hypocalcaemia and calcium deficiency states resulting from dietary deficiency or ageing and as an adjunct in the management of osteoporosis and corticosteroid-induced osteoporosis. Calcium salts may be indicated in the treatment of some bone disorders associated with calcium deficiency, such as osteomalacia and rickets.
Hypocalcaemia, a decrease in plasma-calcium concentration below the normal range, may be due to impaired or reduced absorption of calcium from the gastrointestinal tract, as with vitamin D deficiency disorders, chronic renal failure, deficient parathyroid hormone secretion and/or action as in hypoparathyroidism and hypomagnesaemia. Where symptoms of hypocalcaemia occur, they are typically associated with increased neuromuscular excitability; paraesthesias can occur and in more severe cases, carpopedal spasm, muscle cramps, tetany and convulsions may develop. Other symptoms include ECG changes and mental disturbances such as irritability and depression. Prolonged hypocalcaemia can lead to dental defects, cataract formation, and in children can result in mental retardation.
In simple deficiency states calcium salts may be given orally, usually in doses of 10 to 50 mmol (400mg to 2g) of calcium daily, adjusted to the individual patient's requirwements. Vitamin D supplements are widely used to enhance calcium absorption and correct vitamin D deficiency disorders and hypoparathyroidism.

VITAMIN D

Vitamin D compounds are fat-soluble sterols, sometimes considered to be hormones or hormone precursors, which are essential for the proper regulation of calcium and phosphate homoeostasis and bone mineralisation.
Mechanisms by which vitamin D acts to maintain normal concentrations of calcium and phosphate in plasma are to facilitate their absorption by the small intestine, to interact with parathyroid hormone to enhance their mobilization from the bone, and to decrease their excretion by the kidney. A direct role of vitamin in bone mineralization has been difficult to validate; rather, the predominant view is that normal bone formation occurs when calcium and phosphate concentration in the plasma are adequate. Colecalciferol and ergocalciferol are traditionally considered equal in potency and have a slow onset and relatively prolonged duration of action.
Vitamin D deficiency develops when there is inadequate exposure to sunlight or lack of the vitamin in diet. It may occur in some infants who are breast fed without supplemental vitamin D or exposure to sunlight, in the elderly whose mobility and thus exposure to sunlight may be impaired, and in persons with fat malabsorption syndromes; certain disease states such as renal failure may also affect the metabolism of vitamin D substances to metabolically active forms and thus result in deficiency. Deficiency leads to the development of a syndrome characterised by hypocalcaemia, hypophospahataemia, undermineralisation or demineralisation of bone, bone pain, bone fractures, and muscle weakness, known in adults as osteomalacia. In children, in whom there may be growth retardation and skeletal deformity, especially of the long bones, it is known as rickets.

MAGNESIUM

Magnesium is an essential body cation that is involved in numerous enzymatic reactions and physiological processes including energy transfer and storage, skeletal development, nerve conduction, and muscle contraction. Over half of the magnesium in the body is found in bone, about 40% is present in muscle and soft tissue, and only about 1% is present in the extracellular fluid. A normal concentration for magnesium in plasma is from about 0.7 to 1.0mmol/litre.
Magnesium salts are given as a source of magnesium ions in the treatment of magnesium deficiency and hypomagnesaemia which may result from a reduced magnesium intake as in dietary deficiency or malabsorption syndromes. Alternatively it may be due to excessive magnesium loss, either via the kidney because of inadequate reabsorption, or more often from the gut, for example during chronic diarrhoea.
Hypomagnesaemia is closely associated with hypocalcaemia and hypokalaemia and rarely occurs alone. Specific symptoms are therefore difficult to determine but may include anorexia, nausea, weakness, neuromuscular dysfunction such as tetany, tremor and muscle fasciculations, and rarely seizures. Cardiac arrhythmias may occur, but the relative contribution of hypomagnesaemia and hypokalaemia to these is uncertain.

ZINC

Zinc is an essential element of nutrition and traces are present in a wide range of foods. It is a constituent of many enzyme systems and is present in all tissues. Zinc is required for the growth of every animal species studied; therefore, growth depression of young animals is invariably observed if the zinc deprivation is severe enough. Features of zinc deficiency include growth retardation and defects of rapidly-dividing tissues such as the skin, the immune system and the intestinal mucosa. Other characteristics of deficiency include skin lesions, alopecia, deformed and poorly mineralized bones, hyperkeratinisation of the oesophagus, reduced numbers of circulating lymphocytes, impaired reproduction in males and females, foetal abnormalities and decreased learning ability. Water-soluble zinc salts are used as supplements to correct zinc deficiency.

5.2 Pharmacokinetic properties

CALCIUM

Calcium carbonate is converted to calcium chloride by gastric acid. Some of the calcium is absorbed from the intestines and the unabsorbed portion is excreted in the faeces.
Calcium is absorbed mainly from the small intestine by active transport and passive diffusion. About one third of ingested calcium is absorbed although this can vary depending upon dietary factors and the state of the small intestine; also absorption is increased in calcium deficiency and during periods of high physiological requirements such as during childhood or pregnancy and lactation. 1,25-Dihydroxycholecalciferol (calcitriol) a metabolite of vitamin D enhances the active phase of absorption.
Excess calcium is excreted renally. Unabsorbed calcium is eliminated in the faeces, together with that secreted in the bile and pancreatic juice. Minor amounts are lost in the sweat, skin, hair and nails. Calcium crosses the placenta and is distributed into breast milk.

VITAMIN D

Vitamin D is well absorbed from the gastrointestinal tract. Absorption may be increased in patients with decreased fat absorption. Vitamin D also circulate in the blood bound to a specific alpha globulin. It can be stored in adipose and muscle tissue for long periods of time. It is slowly released from such storage sites and from the skin where it is formed in the presence of sunlight or ultraviolet light. Cholecalciferol and ergocalciferol are hydroxylated in the liver by the enzyme vitamin D 25-hydroxylase to form 25-hydroxycholecalciferol and 25-hydroxyergocalciferol respectively. These compounds undergo further hydroxylation in the kidneys.

Cholecalciferol has a slow onset and a long duration of action. It is excreted mainly in the bile and faeces with only small amounts appearing in urine. Certain vitamin D substances may be distributed into breast milk.

MAGNESIUM

Magnesium Hydroxide given orally reacts relatively rapidly with hydrochloric acid in the stomach to form magnesium chloride and water. About 30% of magnesium is absorbed from the small intestine after oral doses and even soluble magnesium salts are generally very slowly absorbed. The fraction of magnesium absorbed increases if magnesium intake decreases. Absorption of magnesium from the gastrointestinal tract is enhanced to some extent by 1,2,5-dihydroxycholecalciferol (calcitriol).
In plasma about 25 to 30% of magnesium is protein bound. Oral doses are eliminated in the urine (absorbed fraction) and the faeces (unabsorbed fraction). Small amounts are distributed into breast milk. Magnesium crosses the placenta.

ZINC

Zinc is absorbed mainly from the duodenum. Absorption of zinc from the gastrointestinal tract is incomplete, and is reduced in the presence of some dietary constituents such as phytates. It binds to all proteins of the plasma; however, it is bound most loosely to albumin, and this may be important for transport to and from tissues. Bioavailability of dietary zinc varies widely between different sources, but is about 20 to 30%. Zinc is distributed throughout the body with the highest concentrations found in muscle, bone, skin, eye and prostatic fluids. It is primarily excreted in the faeces and regulation of faecal losses is important in zinc homoeostasis. Small amounts are lost in urine and perspiration.

5.3 Preclinical safety data
There are no other preclinical 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
Lactose
Gelatin Powder
Sodium Lauryl Sulphate
Crospovidone
FD & C Yellow No 6 (Al Lake)
Stearic Acid

6.2 Incompatibilities
None.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store below 30^{o}C. Protect form light.

6.5 Nature and contents of container
Alu/PVC blisters of 3 x 10 and 10 x 10 caplets.

6.6 Special precautions for disposal and other handling
No special instructions.

7. Applicant/manufacturer
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