For the use only of Registered Medical Practitioners

OSTOCALCIUM B_{12} SUSPENSION

1. GENERIC NAME

Suspension of Calcium with Vitamins D_3 and B_{12} with Banana flavour /
Suspension of Calcium with Vitamins D_3 and B_{12} with Lemon Lime flavour

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml (1 teaspoonful) contains:

Vitamin D_3 (Cholecalciferol) I.P.	200 IU
Vitamin B_{12} I.P.	2.5 mcg
Calcium Phosphate equivalent to elemental Calcium	82 mg

in a flavoured syrup base.
Colour: Erythrosine

3. DOSAGE FORM AND STRENGTH

Oral liquid (Suspension)

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

OSTOCALCIUM B_{12} SUSPENSION is indicated for:

- Correction of combined vitamin D_3, calcium and vitamin B_{12} deficiencies

4.2 Posology and Method of Administration

The calcium dose should be calculated on the basis of elemental calcium daily needs for the different ages and metabolic situations and the amount of calcium in food.

The necessary daily intake of cholecalciferol (vitamin D_3) and vitamin B_{12} will depend on the different metabolic situations.

Route of Administration

For oral use only.

Adults

The daily dose of *OSTOCALCIUM B_{12} SUSPENSION* for correction of deficiency states is 2 to 4 teaspoonful (equivalent to 164-328 mg of elemental calcium, 400-800 I.U. of vitamin D and 5-10 mcg of vitamin B_{12}), divided into 1 or 2 doses.

Calcium should be provided from diet or from other sources for additional calcium requirements. The duration of therapy will depend upon the response to therapy.

Children

The daily doses for children are

For children below 1 year of age:

1 teaspoonful daily (equivalent to 82 mg of calcium, 200 I.U. of vitamin D_3 and 2.5 mcg of vitamin B_{12}) or as advised by the doctor.

For children above 1 year of age:

1-2 teaspoonful daily (equivalent to 82-164 mg of calcium, 200-400 I.U. of vitamin D_3 and 2.5-5 mcg of vitamin B_{12}) or as advised by the doctor.

Calcium should be provided from diet or from other sources for additional calcium requirements. The duration of therapy will depend upon the response to therapy.

Renal impairment

Calcium/cholecalciferol should not be used in patients with severe renal impairment (see Sections 4.3 *Contraindications*; 4.4 *Special Warnings and Precautions for Use*). Using in patients with renal failure is contraindicated (see Section 4.3 *Contraindications*).

Hepatic impairment

No dose adjustment is required.

4.3 Contraindications

OSTOCALCIUM B_{12} SUSPENSION is contraindicated in:

- hypersensitivity to the active substances or to any of the excipients,
- hypercalcaemia, hypercalciuria,
- nephrocalcinosis, nephrolithiasis,
- disease and/or conditions which leads to hypercalcaemia and/or hypercalciuria (e.g. primary hyperparathyroidism, myeloma, bone metastases),
- hypervitaminosis D,
- severe renal impairment and renal failure *(*see Section 4.4 *Special Warnings and Precautions for Use)*.

4.4 Special Warnings and Precautions for Use

Long term treatment

During long-term treatment, serum calcium levels should be followed and renal function should be monitored through measurements of serum creatinine. Monitoring is especially important in patients on concomitant treatment with cardiac glycosides or thiazide diuretics

(see Section 4.5 *Drug Interactions*) and in patients with a high tendency to calculus formation. In case of hypercalcaemia or signs of impaired renal function the dose should be reduced or the treatment discontinued. Therapy should be reduced or preliminary interrupted, if urinary calcium level exceeds 7.5 mmol/24 h (300 mg/24 h).

Sarcoidosis

Calcium/cholecalciferol should be prescribed with caution to patients suffering from sarcoidosis, due to the risk of increased metabolism of vitamin D into its active form. These patients should be monitored with regard to the calcium content in serum and urine.

Immobilised patients with osteoporosis

Calcium/cholecalciferol should be used cautiously in immobilised patients with osteoporosis due to increased risk of hypercalcaemia.

Renal impairment

Vitamin D should be used with caution in patients with impairment of renal function and the effect on calcium and phosphate levels should be monitored. Patients with renal impairment are at potential risk of hyperphosphaetemia, nephrolithiasis and nephrocalcinosis. The risk of soft tissue calcification should be taken into account. In patients with severe renal insufficiency, vitamin D in the form of cholecalciferol is not metabolised normally and other forms of vitamin D should be used *(*see Section 4.3 *Contraindications)*.

Milk-alkali syndrome

Milk-alkali syndrome (Burnett´s syndrome) i.e. hypercalcemia, alkalosis and renal impairment, can develop when large amounts of calcium are ingested with absorbable alkali.

Other medicinal products containing calcium or vitamin D

The content of vitamin D in calcium/cholecalciferol should be considered when prescribing other medicinal products containing vitamin D. Additional doses of calcium or vitamin D should be taken under close medical supervision. In such cases it is necessary to monitor serum calcium levels and urinary calcium excretion frequently. Calcium and vitamin D intake from other sources (food, dietary supplements) should be estimated, before prescribing the product.

Tetracyclines or quinolones

Co-administration with tetracyclines or quinolones is usually not recommended, or must be done with precaution (see Section 4.5 *Drug Interactions*).

Vision disorders

OSTOCALCIUM B_{12} SUSPENSION should not be used in Leber's disease or tobacco amblyopia since these optic neuropathies may degenerate further due to Cyanocobalamin (vitamin B_{12}).

Treatment preparation and monitoring

This medicinal product should, if possible, not be given to patients with suspected vitamin B_{12} deficiency without first confirming the diagnosis.

4.5 Drug Interactions

Phenytoin, barbiturates

Concomitant use of phenytoin or barbiturates may reduce the effect of vitamin D_3 since the metabolism increases.

Thiazide diuretics

Thiazide diuretics reduce the urinary excretion of calcium. Due to increased risk of hypercalcaemia, serum calcium should be regularly monitored during concomitant use of thiazide diuretics.

Corticosteroids

Systemic corticosteroids reduce calcium absorption. During concomitant use, it may be necessary to increase the dose of calcium/cholecalciferol.

Ion exchange resins, liquid paraffin

Simultaneous treatment with ion exchange resins such as cholestyramine or laxatives such as paraffin oil may reduce the gastrointestinal absorption of vitamin D. Therefore a time interval as long as possible between the intakes should be recommended.

Tetracyclines

Calcium may interfere with the absorption of concomitantly administered tetracycline preparations. For this reason, tetracycline preparations should be administered at least two hours before or four to six hours after oral intake of calcium.

Quinolone

The absorption of quinolone antibiotics may be impaired if administered concomitantly with calcium. Quinolone antibiotics should be taken two hours before or six hours after intake of calcium.

Cardiac glycosides

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.

Bisphosphonate

If a bisphosphonate is used concomitantly, this preparation should be administered at least one hour before the intake of calcium/cholecalciferol since gastrointestinal absorption may be reduced.

Sodium fluoride

Calcium may also reduce absorption of sodium fluoride, and such preparations should be administered at least three hours before the intake of calcium/cholecalciferol.

Iron, zinc and strontium ranelate

Calcium salts may decrease the absorption of iron, zinc and strontium ranelate. Consequently, iron, zinc or strontium ranelate preparations should be taken at least two hours before or after calcium/cholecalciferol.

Oxalic acid, phytic acid

Oxalic acid (found in spinach and rhubarb) and phytic acid (found in whole cereals) may inhibit calcium absorption through formation of insoluble compounds with calcium ions. The patient should not take calcium products within two hours of eating foods high in oxalic acid and phytic acid.

Levothyroxine

The efficacy of levothyroxine can be reduced by the concurrent use of calcium, due to decreased levothyroxine absorption. Administration of calcium and levothyroxine should be separated by at least four hours.

Orlistat

Treatment with orlistat may potentially impair the absorption of fat-soluble vitamins, e.g. vitamin D_3.

Neomycin

Neomycin used orally may reduce the absorption of vitamin B_{12}.

Rifampicin and isoniazid

Rifampicin and isoniazid may reduce the effectiveness of vitamin D.

Oral contraceptives

Serum concentration of vitamin B_{12} may be decreased by use of oral contraceptives.

Omeprazole

Omeprazole has been reported to impair the bioavailability of vitamin B_{12}.

Other

Absorption of vitamin B_{12} from the gastrointestinal tract may be reduced by aminosalicylic acid, histamine H_2-antagonists, and colchicine.

4.6 Use in Special Populations

Pregnancy and Lactation

Fertility

Normal endogenous levels of calcium, vitamin D and vitamin B_{12} are not expected to have any adverse effects on fertility

Pregnancy

Studies in animals have shown reproductive toxicity of high doses of vitamin D.

In pregnant women, overdoses of calcium and vitamin D should be avoided as permanent hypercalcaemia has been related to adverse effects on developing foetus.

Lactation

Calcium passes slightly into breast-milk, without having a negative effect on children.

Vitamin D and its metabolites also pass into breast-milk. This should be considered when giving additional vitamin D to the child.

Pregnant and nursing mother should only use doses of Vitamin B_{12} higher than 12 mcg daily only if recommended by their physician.

4.7 Effects on Ability to Drive and Use Machines

An unfavourable effect of the preparation on the ability to drive or operate machines is very unlikely.

4.8 Undesirable Effects

Post Marketing Data

For calcium / Cholecalciferol:

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency.
Frequencies are defined as:
Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1000 to <1/100

Rare ≥1/10000 to <1/1000
Very rare <1/10000
Not known (cannot be estimated from the available data).

Immune system disorders

Not known: hypersensitivity reactions *(see Skin and subcutaneous tissue disorders; Respiratory, thoracic and mediastinal disorders)*, anaphylactic reaction

Metabolism and nutrition disorders

Uncommon: hypercalcaemia, hypercalciuria

Respiratory, thoracic and mediastinal disorders

Not known: laryngeal oedema

Gastrointestinal disorders

Rare: nausea, diarrhea, abdominal pain, constipation, flatulence, abdominal distension
Not known: vomiting

Skin and subcutaneous tissue disorders

Rare: rash, pruritus, urticaria
Not known: angioedema

For Vitamin B_{12}:

Oral vitamin B_{12} is well tolerated at high doses. There are occasional reports of hypersensitivity reactions (urticaria, rash, pruritis) in those receiving parenteral vitamin B_{12}. Those who have experienced hypersensitivity reactions from the use of parenteral B_{12} may experience similar reactions from oral vitamin B_{12} although there are very few reports of this occurring.

4.9 Overdose

Symptoms and signs

Overdose can lead to hypervitaminosis and hypercalcaemia. Symptoms of hypercalcaemia may include anorexia, nausea, vomiting, thirst, polydipsia, polyuria, constipation, abdominal pain, muscle weakness, fatigue, mental disturbances, bone pain, nephrocalcinosis, renal calculi and in severe cases, cardiac arrhythmias. Extreme hypercalcaemia may result in coma and death. Persistently high calcium levels may lead to irreversible renal damage and soft tissue calcification.

The threshold for vitamin D intoxication is between 40,000 and 100,000 I.U./day for 1-2 months in persons with normal parathyroid function, for calcium in excess of 2.000 mg per day.

There are no report of Vitamin B_{12} overdosage in the literature.

Treatment

In the case of intoxication, treatment should be stopped immediately and the fluid deficiency should be balanced. Treatment with thiazide diuretics, lithium, vitamin A, vitamin D and cardiac glycosides must also be discontinued.

Rehydration and, according to severity, isolated or combined treatment with loop diuretics, bisphosphonates, calcitonin and corticosteroids should be given. Serum electrolytes, renal function and diuresis must be monitored. In severe cases ECG and CVP should be followed.

Further management should be as clinically indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

Vitamin D is involved in calcium-phosphorus metabolism. It allows the active absorption of calcium and phosphorus from the intestine and their uptake by bone. Supplementation with calcium and vitamin D_3 corrects latent vitamin D deficiency and secondary hyperparathyroidism.

Administration of calcium and vitamin D_3 counteracts the increase of parathyroid hormone (PTH) which is caused by calcium deficiency and which cause increased bone resorption.

Vitamin B_{12} (cyanocobalamin) is essential for erythropoiesis, formation of myelin sheet and synthesis of the DNA.

5.2 Pharmacodynamic Properties

Pharmacotherapeutic group: Mineral supplements; calcium, combinations with vitamin D and/or other drugs; ATC Code**:** A12AX.

5.3 Pharmacokinetic Properties

Calcium

Absorption: The amount of calcium absorbed through the gastrointestinal tract is approximately 30 % of the swallowed dose. The bioavailability of calcium can be slightly increased by concomitant intake of food.

Distribution: 99 % of the calcium in the body is concentrated in the hard structure of bones and teeth. The remaining 1 % is present in the intra- and extracellular fluids.

Metabolism: About 50 % of the total blood-calcium content is in the physiologically active ionised form with approximately 10 % being complexed to citrate, phosphate or other anions, the remaining 40 % being bound to proteins, principally albumin.

Elimination: Calcium is eliminated through faeces, urine and sweat. Renal excretion depends on glomerular filtration and calcium tubular reabsorption.

Vitamin D

Absorption: Vitamin D is easily absorbed in the small intestine.

Distribution: Cholecalciferol and its metabolites circulate in the blood bound to a specific globulin. Vitamin D which is not metabolised is stored in adipose and muscle tissues.

Metabolism: Cholecalciferol is converted in the liver by hydroxylation to the active form 25-hydroxycholecalciferol. It is then further converted in the kidneys to 1,25-dihydroxycholecalciferol. 1,25 dihydroxycholecalciferol is the metabolite responsible for increasing calcium absorption.

Elimination: Vitamin D is excreted in faeces and urine.

Vitamin B_{12}

Two mechanisms exist for cobalamin absorption. One is passive, occurring equally through buccal, duodenal, and ileal mucosa; it is rapid but extremely inefficient, with <1% of an oral dose being absorbed by this process. The normal physiologic mechanism is active; it occurs through the ileum and is efficient for small (a few micrograms) oral doses of cobalamin, and it is mediated by gastric intrinsic factor (IF). Dietary cobalamin is released from protein complexes by enzymes in the stomach, duodenum, and jejunum; it combines rapidly with a salivary glycoprotein that belongs to the family of cobalamin-binding proteins known as haptocorrins (HCs). In the intestine, the HC is digested by pancreatic trypsin and the cobalamin is transferred to IF.

Between 0.5 and 5 g of cobalamin enter the bile each day. This binds to IF, and a major portion of biliary cobalamin normally is reabsorbed together with cobalamin derived from sloughed intestinal cells. Because of the appreciable amount of cobalamin undergoing enterohepatic circulation, cobalamin deficiency develops more rapidly in individuals who malabsorb cobalamin than it does in vegans, in whom reabsorption of biliary cobalamin is intact.

5.4 Clinical Studies

Not relevant for this product

6. NONCLINICAL PROPERTIES

At vitamin D doses far higher than the human therapeutic range teratogenicity has been observed in animal studies.

There are no relevant data available for Vitamin B_{12}.

7. DESCRIPTION

Oral liquid (Suspension)

Each 5 ml (1 teaspoonful) contains:

Vitamin D_3 (Cholecalciferol) I.P.	200 IU
Vitamin B_{12} I.P.	2.5 mcg
Calcium Phosphate equivalent to elemental Calcium	82 mg

in a flavoured syrup base.
Colour: Erythrosine

8. PHARMACEUTICAL PARTICULARS

List of Excipients

Sucrose, Phosphoric Acid, Calcium Hydroxide, Benzoic Acid, Sodium Methyl Hydroxybenzoate, Polysorbate 80, Propylene Glycol, Colour Erythrosine, Flavour Banana or Lemon lime, Sodium Hydroxide or Phosphoric acid, purified water.

8.1 Incompatibilities

There are no relevant data available.

8.2 Shelf Life

The expiry date is indicated on the label and packaging.

8.3 Packaging Information

Bottle in a carton.

All pack presentations may not be marketed in the country.

8.4 Storage and Handling Instructions

Store in a well closed container at temperature not exceeding 30°C. Protect from direct sunlight. Do not freeze.

Keep out of reach of children.

Shake the bottle before use.

There are no other special requirements for use or handling of this product.

9. PATIENT COUNSELLING INFORMATION

Registered Medical Practitioners may counsel their patients (and/or patient's caregiver as applicable) about the special warnings and precautions for use, drug interactions, undesirable effects, and any relevant contra-indications of *OSTOCALCIUM B_{12} SUSPENSION*. Patients (and/or patient's caregiver) may also be informed about posology, method of administration and storage/handling information as applicable.

10. DETAILS OF MANUFACTURER

The Manufacturing Site details are mentioned on the label and packaging.

For further information please contact:
GlaxoSmithKline Pharmaceuticals Limited.
Registered Office
Dr. Annie Besant Road, Worli,
Mumbai 400 030, India.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Manufacturing License number is indicated on the label and packaging.

12. DATE OF REVISION

21-JAN-2022

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Version OSB/PI/IN/2022/01

Adapted from:

- *Calcium/cholecalciferol (CHEWCAL / OSTOCALCIUM / OSTOCALCIUM FORTE) NCDS Version 05 dated 21 Oct 2019.*
- *Vitamins and Minerals (VITAMAX) NCDS Version 05 dated 26 October 2018.*
- *PDR for Nutritional Supplements 2nd edition.*
- *Harrison's Principles of Internal Medicine 20th ed. Chapter 95 Megaloblastic Anemias*