PRESCRIBING INFORMATION
INCLUDING PATIENT MEDICATION INFORMATION

Pr AG-Vitamine D Tablets

Cholecalciferol Tablets USP
Tablets, 10 000 Units, Oral

Vitamin D product

Angita Pharma Inc.
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Boucherville, Quebec
J4B 5H3, Canada

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Control No. 287100

RECENT MAJOR LABEL CHANGES

Not Applicable	

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1. INDICATIONS

AG-Vitamine D Tablets at 10 000 Units is indicated for:

- the treatment of hypophosphatemic rickets (vitamin D – resistant rickets)
- the treatment of hypoparathyroidism.

2. CONTRAINDICATIONS

- Abnormal sensitivity to the toxic effect of vitamin D
- Hypercalcemia and/or hypercalciuria
- Hypersensitivity to vitamin D, any of its analogues and derivatives or to any ingredient in the formulation component of the container (see Dosage Form, Composition, and Packaging).
- Hypervitaminosis D
- Malabsorption syndrome
- Nephrolithiasis (renal calculi)
- Sarcoidosis
- Severe renal impairment

4. DOSAGE AND ADMINISTRATION

4.1 Dosing Consideration

At the higher doses of Vitamin D used for active treatment, the range between therapeutic and toxic doses is narrow.

The dosage of vitamin D_3 must be individualized with careful monitoring of serum-calcium levels. Readjust therapeutic dosage as soon as there is clinical improvement. Careful titration is necessary to avoid overdose. Dietary and other sources of vitamin D must be considered. Calcium intake should be adequate.

Blood calcium, phosphorus and urea determinations must be made every two weeks or more frequently if necessary.

The bones should be x-rayed every month until the condition is corrected and stabilized.

4.2 Recommended Dose and Dosage Adjustment

For the treatment of Vitamin D resistant rickets: 20,000 to 500,000 IU (0.5-12.5 mg) daily.

For the treatment of hypoparathyroidism: 50,000 to 200,000 IU (1.25 - 5 mg) daily. Calcium supplementation is also required.

The dosage of vitamin D depends on severity of the disease, as well as patient's response to treatment. The dosage and the frequency of administration has to be established individually by a physician.

Not all given recommended doses can be achieved with this product. When a higher daily dose of more than 100,000 IU (2.5 mg) is needed, it is recommended to use other Vitamin D products

with higher strength.

4.5 Missed Dose

If a dose of this medication has been missed, it should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not take a double dose to make up for the missed dose.

5. OVERDOSAGE

Symptoms: Acute intoxication with Vitamin D_3 (cholecalciferol) may cause hypervitaminosis D, manifested by hypercalcemia and its sequelae. Hypercalcemia is usually reversible, however, if metastatic calcification has occurred, severe renal or cardiac failure or even death may result (see WARNINGS AND PRECAUTIONS).

Treatment: Treatment of acute or chronic intoxication includes withdrawal of the Vitamin D_3 and any calcium supplements, maintenance of low-calcium diet, administration of oral IV fluids and, if needed, corticosteroids or calciuric diuretics, such as furosemide and ethacrymic acid, to decrease serum calcium concentrations. Peritoneal or hemodialysis with calcium free dialysate will help remove calcium.

If acute ingestion is recent, gastric lavage or emesis may minimize further absorption. If the drug has already passed through the stomach, administration of mineral oil may promote faecal elimination.

Hypercalcemia is usually reversible, however, if metastatic calcification has occurred, severe renal or cardiac failure or even death may result.

For management of a suspected drug overdose, contact your regional poison control centre.

6. DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablets, 10 000 Units	sodium ascorbate, all-rac-α-tocopherol, modified starch, sucrose, medium chain triglycerides, colloidal silicon dioxide, microcrystalline cellulose, polacrilin potassium, croscarmellose sodium, silica colloidal anhydrous, magnesium stearate, hypromellose, diethyl phthalate, ethyl cellulose, talc, titanium dioxide, polydextrose, maltodextrin and may contain traces of methylene chloride and isopropyl alcohol.

Description

AG-Vitamine D Tablets is a white to off-white coloured, round, biconvex, film coated tablet, scored on one side and embossed with "D" on other side, and contains 10 000 Units (0.25 mg) of Vitamin D3 (Cholecalciferol).

Available in HDPE bottles of 60, 250, 500 tablets and blister pack of 10 (1x10) tablets and 100 (10 x 10) tablets.

7. WARNINGS AND PRECAUTIONS

General

Chronic or acute administration of excessive doses may lead to hypervitaminosis D, manifested by hypercalcemia and its sequelae.

The therapeutic index of Vitamin D products is narrow, and there is great interindividual variation in the dose that will lead to chronic toxicity. Daily doses of cholecalciferol ranging from 50,000 to 100,000 IU (1.25 to 2.5 mg) in adults and 1000 IU (25 mcg) in children may result in hypervitaminosis. Other Vitamin D products with shorter duration of action may have a lower propensity to accumulate and to cause hypercalcemia.

Cardiovascular

Caution is required for patients receiving treatment for cardiovascular disease. (See DRUG INTERACTIONS)

Endocrine and Metabolism

Hypercalcemia

Early symptoms of hypercalcemia may include weakness, fatigue, somnolence, headache, anorexia, dry mouth, metallic taste, nausea, vomiting, vertigo, tinnitus, ataxia and hypotonia.

Later and possibly more serious manifestation include nephrocalcinosis, renal dysfunction, osteoporosis in adults, impaired growth in children, anemia, metastatic calcification, pancreatitis, generalized vascular calcification and seizures. Extreme hypercalcaemia may result in coma and death.

Immune

AG-Vitamine D Tablets should not be prescribed in patients with sarcoidosis, as there is increased conversion of vitamin D to its active metabolite. (See CONTRAINDICATIONS). High doses of Vitamin D can induce hypercalcemia and hypercalcuria. Serum and urinary calcium levels should be monitored.

Monitoring and Laboratory Tests:

Periodic monitoring of serum calcium, phosphate, magnesium, and alkaline phosphatase is recommended for patients taking Vitamin D3. Serum calcium should be maintained in the range

of 2.25-2.5 mmol/L and not allowed to exceed 2.75 mmol/L.

The best indicator of vitamin D status is 25-hydroxyvitamin D or 25(OH)D serum concentration, as this level reflects total vitamin D exposure (from skin synthesis, food and supplements). However, there is no clinical benefit in monitoring vitamin D levels unless a clinical condition, such as malabsorption syndromes, chronic renal or liver failure, unexplained bone pain, unusual fractures, and other evidence of metabolic bone disorders, predisposes the patient to vitamin D deficiency. Other clinical situations where vitamin D testing is indicated include hypo- or hypercalcemia/hyperphosphatemia, hypo-or hyperparathyroidism, unexplained increases in serum alkaline phosphatase or patients with symptoms suggesting hypervitaminosis D. Testing for vitamin D levels may also be indicated when a patient is on medications that affect vitamin D metabolism or absorption (see Table 1)

Renal

AG-Vitamine D Tablets should not be used in patients with severe renal impairment and should be used with caution in patients with mild and moderate impairment of renal function. (See CONTRAINDICATIONS). The effect on calcium and phosphate levels should be monitored. The risk of soft tissue calcification should be taken into account.

There is no clear evidence for causation between vitamin D supplementation and renal stones, but the risk is plausible, especially in the context of concomitant calcium supplementation. The need for additional calcium supplementation should be considered for individual patients. Calcium supplements should be given under close medical supervision.

During treatment, the serum and urinary calcium levels should be monitored and the kidney function checked by measurement of serum creatinine. These checks are particularly important in concomitant treatment with diuretics. In the case of hypercalcaemia or signs of impaired kidney function, the dose must be reduced or treatment interrupted. It is recommended to reduce the dose or to interrupt treatment if the urinary calcium level exceeds 7.5 mmol/24 hours (300 mg/24 hours).

Vitamin D must be used with particular caution in patients with disturbed urinary excretion of calcium and phosphate, in treatment with benzothiadiazine derivatives. Plasma and urinary calcium levels should be monitored in these patients.

7.1 Special Populations

7.1.1 Pregnant Women

The recommended daily dose of Vitamin D in pregnant women in Canada is 600 IU (15 mcg) daily. Studies have shown safe use of Vitamin D at doses up to 4000 IU (100 mcg) daily during pregnancy although studies in animals have shown reproductive toxicity. Avoid the use of vitamin D in excess of the recommended dietary allowance during pregnancy unless potential benefits outweigh the possible adverse effects. Hypercalcemia during pregnancy may also lead to suppression of parathyroid hormone release in the neonate, resulting in hypocalcemia, tetany and seizures.

Severe deficiency of vitamin D during pregnancy can result in maternal osteomalacia and lead to significant morbidity in both mother and fetus.

7.1.2 Breast-feeding

The recommended daily dose of Vitamin D in nursing women is 600 IU (15 mcg). Vitamin D and its metabolites are excreted in breast milk. However, Vitamin D may be deficient in maternal milk; therefore, breastfed infants may require supplementation. Use of excessive amounts of Vitamin D in nursing mothers may result in hypercalcemia in infants. A daily dose of 4,000 IU (100 mcg) should not be exceeded. 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.

8. ADVERSE REACTIONS

Vitamin D_3 (cholecalciferol) is generally well tolerated in doses that do not exceed the recommended daily intake. Chronic excessive dosing can lead to toxicity (see precautions). Possible side effects include symptoms of hypercalcaemia and hypercalciuria (see WARNINGS AND PRECAUTIONS). Rare cases of pruritus, rash and urticarial have been reported.

9. DRUG INTERACTIONS

Table 1: Drug-Drug Interactions

Interacting Drug	Effect	Clinical Comment
Antacids (aluminum-containing)	Increased intestinal absorption of aluminum may lead to increased aluminum levels.	Avoid this combination if possible.
Antacids (magnesium-containing)	Hypermagnesemia may develop when these agents are used concurrently with vitamin D.	Monitor magnesium levels particularly in patients with chronic renal failure.
Anticonvulsants (e.g., phenytoin, phenobarbital, carbamazepine)	Strong CYP3A4 inducers can reduce vitamin D levels, potentially causing vitamin D deficiency.	Consider prophylactic vitamin D supplementation. Monitor serum 25(OH)D every 2 years; supplement with vitamin D if necessary
Cholestyramine, colestipol	Intestinal absorption of vitamin D may be impaired.	Patients should be advised to allow as much time as possible between the ingestion of these drugs and vitamin D.
Danazol	Danazol may increase the hypercalcemic response to vitamin D.	Monitor serum calcium levels.

Digoxin	Vitamin D or any analogues should be used with caution in patients taking digoxin. Hypercalcemia (which may result from concomitant use) may enhance the arrhythmogenic effects of digoxin.	Strict medical supervision is required. Monitor serum calcium levels.
Efavirenz	Increased metabolism of vitamin D via CYP24A induction leads to a deficiency state.	Consider prophylactic vitamin D supplementation.
Mineral oil	Intestinal absorption of vitamin D may be impaired.	Patients should be advised to allow as much time as possible between the ingestion of these drugs.
Orlistat	Intestinal absorption of vitamin D may be impaired.	Patients should be advised to allow as much time as possible between the ingestion of these drugs.
Sevelamer	Sevelamer may decrease the serum concentration of orally administered vitamin D.	Monitor serum 25(OH)D levels and adjust vitamin D or analogue dose if necessary.
Sucralfate	Increased intestinal absorption of aluminum from sucralfate may lead to increased aluminum levels.	Avoid this combination if possible.
Thiazide diuretics	Increased risk of hypercalcemia and associated calcium toxicity. Thiazides decrease renal excretion of calcium and increase calcium release from bone. Thiazides may also enhance the effect of parathyroid hormone and vitamin D on release of calcium from bone.	Monitor serum calcium levels with concomitant therapy.

Different Vitamin D products should not be administered concurrently.

10. CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Vitamin D is a fat-soluble vitamin that helps regulate serum calcium and phosphorous concentrations by enhancing the efficiency of the small intestine to absorb these minerals from

the diet. Vitamin D has two main forms: cholecalciferol (Vitamin D_3), and ergocalciferol (Vitamin D_2).

One microgram (mcg) is equivalent to 40 IU of vitamin D activity. Vitamin D is essential for the absorption and utilization of calcium and phosphate and aids in the mobilization of bone calcium and maintenance of serum calcium concentrations.

10.2 Pharmacodynamics

In humans, cholecalciferol (vitamin D_3) is synthesized in the skin, from 7-dehydrocholesterol, on exposure to ultraviolet radiation, and obtained from the diet from fish liver oils and salt water fish. In the absence of adequate sunlight exposure, vitamin D_3 is an essential dietary nutrient. Cholecalciferol is a prohormone with several active metabolites that act as hormones. It is metabolised by the liver to form 25-hydroxycholecalciferol (calcifediol), which is then converted in the kidneys to the active 1,25-dihydroxyvitamin D_3 (calcitriol).

In its biologically active form, vitamin D_3 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 D_3. PTH secretion is inhibited further by the increased calcium uptake in the small intestine under the influence of biologically active vitamin D_3.

10.3 Pharmacokinetics

Vitamin D from nutritional sources and synthetic Vitamin D products are readily absorbed from the small intestine in the presence of dietary lipids and bile acids. Cholecalciferol is metabolised by the microsomal enzyme vitamin D-25-hydroxylase to form 25-hydroxycolecalciferol (25(OH)D3, calcidiol), the primary storage form of vitamin D_3. 25(OH)D3 undergoes a secondary hydroxylation within the kidney to form the predominant active metabolite 1,25-hydroxycolecalciferol (1,25(OH)2D3, calcitriol). The conversion to calcitriol is regulated by its own concentration, PTH, and serum concentrations of calcium and phosphate. The metabolites circulate in the blood bound to a specific α-globin. Vitamin D and its metabolites are excreted mainly in the bile and faeces.

11. STORAGE CONDITIONS

Blister: Store between 15-30°C. Protect from light.

Bottle: Store between 15-30°C, in a well closed container. Protect from light and moisture.

12. SPECIAL HANDLING INSTRUCTIONS

Do not use if safety seal is broken.
Keep out of reach and sight of children.

PATIENT MEDICATION INFORMATION
READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrAG-Vitamine D Tablets
Cholecalciferol Tablets USP

Read this carefully before you start taking **AG-Vitamine D Tablets** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **AG-Vitamine D Tablets**.

What is AG-Vitamine D Tablets used for?

AG-Vitamine D Tablets is used to treat:

- Vitamin D resistant rickets (a bone disease with low level of vitamin D, calcium, or phosphorus in the body).
- Hypoparathyroidism (a condition where your body does not have enough chemical messenger (hormone) to manage the levels of calcium and phosphorus in your blood).

How does AG-Vitamine D Tablets work?

AG-Vitamine D Tablets helps:

- your body get calcium and phosphorus from your diet
- prevent calcium and phosphate loss from your kidneys
- build and maintains strong bones and teeth

What are the ingredients in AG-Vitamine D Tablets?

Medicinal ingredient: Vitamin D_3 (Cholecalciferol)

Non-medicinal ingredients: sodium ascorbate, all-rac-α-tocopherol, modified starch, sucrose, medium chain triglycerides, colloidal silicon dioxide, microcrystalline cellulose, polacrilin potassium, croscarmellose sodium, silica colloidal anhydrous, magnesium stearate, hypromellose, diethyl phthalate, ethyl cellulose, talc, titanium dioxide, polydextrose, maltodextrin and may contain traces of methylene chloride and isopropyl alcohol.

AG-Vitamine D Tablets comes in the following dosage forms:
Tablets; 10 000 Units

Do not use AG-Vitamine D Tablets if you have:

- known allergy:
  - to vitamin D or medicines like vitamin D
  - to any of the other ingredients in AG-Vitamine D Tablets
- too much calcium in your blood or urine
- kidney stones
- severe kidney disease

- a bowel problem where your body can't get nutrients from the food you eat.
- unusual sensitivity to vitamin D poisoning (for example when you have too much calcium in your body)
- too much vitamin D in your body

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take AG-Vitamine D Tablets. Talk about any health conditions or problems you may have, including if you are:

- pregnant or planning on becoming pregnant
- breastfeeding or planning to breastfeed

Other warnings you should know about:

Treatment with AG-Vitamine D Tablets can increase your risk of certain side effects, including:

- hypervitaminosis D (too much vitamin D in your body).
- hypercalcemia too much calcium in your blood).

Monitoring and Laboratory Tests: While taking AG-Vitamine D Tablets, your healthcare professional may check calcium, phosphate, and magnesium levels in your blood.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with AG-Vitamine D Tablets:

- Heartburn medicines (Antacids):
    - hagnesium-containing antacids. If you have kidney problems and taking AG-Vitamine D Tablets with magnesium-containing antacids, your healthcare professional may do blood tests.
    - hluminum-containing antacids. Avoid taking aluminum-containing antacids with AG-Vitamine D Tablets.
- anti-seizure medicines (such as phenytoin, phenobarbital and carbamazepine)
- medicines used to lower cholesterol (such as cholestyramine and colestipol). Allow as much time as possible between taking cholesterol lowering medicines and AG-Vitamine D Tablets.
- digoxin (used to treat heart failure)
- efavirenz (used to treat HIV)
- orlistat (used in medications for weight loss)
- sevelamer (used to treat high phosphorous levels)
- mineral oil. Allow as much time as possible between taking mineral oils and AG-Vitamine D Tablets.
- Sucralfate (used to treat ulcers). Avoid taking sucralfate with AG-Vitamine D Tablets.
- thiazide diuretics, also known as “water pills” (such as hydrochlorothiazide, used to treat high blood pressure)
- danazol

Do **not** take AG-Vitamine D Tablets along with any other products that may contain Vitamin D unless advised by your healthcare professional.

How to take AG-Vitamine D Tablets:

While taking AG-Vitamine D Tablets, your healthcare professional:

- will monitor you closely
- may check your blood calcium, magnesium, phosphorus and urea level every two weeks as needed
- may do an x-ray every month to check your bones
- may also prescribe a calcium supplement depending on the type of treatment you are receiving.

Usual dose:

Take exactly as prescribed by your healthcare professional. Do not change your dose on your own. Your healthcare professional will decide when to end your treatment.

Overdose:

If you think you, or a person you are caring for, have taken too much AG-Vitamine D Tablets, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Taking too much AG-Vitamine D Tablets can cause high levels of calcium in your body (hypercalcemia). See **What are possible side effects from using AG-Vitamine D Tablets?**

Missed Dose:

If you miss a dose of this medication, take the next dose as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not take a double dose to make up for the missed dose.

What are possible side effects from using AG-Vitamine D Tablets?

These are not all the possible side effects you may feel when taking AG-Vitamine D Tablets. If you experience any side effects not listed here, contact your healthcare professional.

Side effects include:

- itching
- rash
- itchy bumps on your skin (hives)
- hypercalcaemia (high blood calcium). May cause:
    - early symptoms such as:
        - weakness
        - feeling tired and sleepy
        - headache
        - loss of appetite

- dry mouth
- a metallic taste
- nausea and vomiting
- dizziness
- ringing in the ears

issues with balance, coordination and speech (ataxia)

- low muscle tone (hypotonia)

- later and long term serious symptoms: See Serious side effects table below

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Hypercalcaemia (too much calcium in the blood). May lead to: • **anemia** (low number of red blood cells): tiredness, weakness and shortness of breath • **kidneys problems** o **nephrocalcinosis** (buildup of too much calcium in the kidneys): blood in the urine, fever and chills, severe pain in the belly area, sides of the back (flank), groin, or testicles o **renal dysfunction** (kidneys no longer working properly): little or no urine, swelling of the legs, ankles or feet • **calcification** (buildup of too much calcium in your body). This may cause hardening of blood vessels and soft tissues such as the heart and lungs, leading to high blood pressure…. • **pancreatitis** (pain and swelling of the pancreas): upper belly pain, fever, rapid heartbeat, nausea and vomiting, tenderness when touching the belly • **seizures** (fits) • **osteoporosis** (thin, fragile bones): broken bones, pain, back pain that gets worse when standing or walking • **grow problems** (in children)		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Blister: Store between 15-30°C. Protect from light.
Bottle: Store between 15-30°C, in a well closed container. Protect from light and moisture.

Keep out of reach and sight of children.

If you want more information about AG-Vitamine D Tablets:

- Talk to your healthcare professional
- Find the full Prescribing Information that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); or by calling 1-450-449-9272.

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