Package Insert

D – Bright®

Product Summary

1. Name of the medicinal product

D – Bright®

2. Qualitative and quantitative composition

Each soft gelatin capsule contains:

Vitamin D3 IP 60000 IU

Excipients q.s

3. Pharmaceutical form

Soft gelatin capsule

4. Clinical particulars

4.1 Therapeutic indications

Vitamin D3 is indicated in the treatment and prevention of vitamin D deficiency. Any of the following symptoms may represent vitamin D deficiency (associated with weak and fragile bones):

- Muscle pain and muscle cramp
- Chronic back pain
- Bone and joint pain
- Fatigue and weakness

4.2 Posology and method of administration

D – Bright® should be used as prescribed by the physician. The dosage is determined by the desired vitamin D levels. Softgel capsule of 60000 IU to be given once a week, followed by daily dose of 1000 IU capsule per day.

4.3 Contraindications

Contraindicated in patients with a hypersensitivity to any component of this product. Except under special circumstances, this medication should not be used when the following medical problems exist:

- Hypercalcaemia.
- Hypervitaminosis D.
- Renal osteodystrophy with hyperphosphataemia (risk of metastatic calcification; however, vitamin D therapy can begin once serum phosphate levels have stabilized).

4.4 Special warnings and precautions for use

The risk–benefit ratio should be considered when the following medical problems exist:

- Cholecalciferol should be used with caution in patients with renal impairment and the effect on calcium and phosphate levels should be monitored. The risk of soft tissue calcification should be taken into account. In patients with severe renal impairment, vitamin D in the form of cholecalciferol is not metabolized normally and another form of vitamin D should be used.
- During long-term treatment, serum and urinary calcium levels should be followed and renal function should be monitored through measurement of serum creatinine. Monitoring is especially important in elderly patients on concomitant treatment with cardiac glycosides or diuretics and in patients with a high tendency to calculus formation. Treatment must be reduced or suspended if urinary calcium exceeds 7.5 mmol/24 hours (300 mg/24 hours). In case of hypercalcaemia or signs of impaired renal function, treatment with cholecalciferol should be discontinued.
- The dose of cholecalciferol should be considered when prescribing other drugs 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.
- Cholecalciferol should be used with caution in patients suffering from sarcoidosis because of the risk of increased metabolism of vitamin D to its active metabolite. In these patients, serum calcium levels and urinary calcium excretion must be monitored.
- Cholecalciferol should be used with caution in immobilized patients with

osteoporosis due to the increased risk of hypercalcaemia. The cholecalciferol treatment should be discontinued in prolonged immobilization and should only be resumed once the patient becomes mobile again.

- Conditions like arteriosclerosis or cardiac function impairment may be exacerbated due to the possibility of hypercalcaemia and elevated serum cholesterol concentrations.
- Cholecalciferol should be administered with caution in patients with hyperlipidaemia as it could potentially exacerbate Low-density lipoprotein (LDL) elevation. Administration of cholecalciferol in patients with hyperphosphataemia may put the patient at risk of metastatic calcification; normalization of phosphate levels indicated prior to therapy. Liver disease may, in turn, impair the absorption of cholecalciferol.

Renal Impairment:
In patients with severe renal impairment, vitamin D in the form of cholecalciferol is not metabolized normally and another form of vitamin D should be used.

Hepatic Impairment: Liver disease may impair the absorption of cholecalciferol.

4.5 Interaction with other medicinal products and other forms of interaction
Cholestyramine: Cholestyramine has been reported to reduce intestinal absorption of fat-soluble vitamins; as such, it may impair the intestinal absorption of vitamin D.
Phenytoin/Phenobarbital: The co-administration of phenytoin or phenobarbital will not affect plasma concentrations of vitamin D, but may reduce endogenous plasma levels of calcitriol by accelerating metabolism. Since the blood level of calcitriol will be reduced, higher doses of cholecalciferol may be necessary if these drugs are administered simultaneously.
Thiazides: Thiazides are known to induce hypercalcaemia by the reduction of calcium excretion in urine. Some reports have shown that the concomitant administration of thiazides with vitamin D causes hypercalcaemia. Therefore, precaution should be taken when co-administration is necessary.
Digitalis: Vitamin D dosage must be determined with care in patients undergoing treatment with digitalis, as hypercalcaemia in such patients may precipitate cardiac arrhythmias.
Ketoconazole: Ketoconazole may inhibit both the synthetic and catabolic enzymes of

vitamin D. Reductions in serum endogenous vitamin D concentrations have been observed following the administration of 300 mg/day to 1200 mg/day ketoconazole for a week to healthy men. However, in vivo drug interaction studies of ketoconazole with vitamin D have not been investigated.

Corticosteroids: A relationship of functional antagonism exists between vitamin D analogues, which promote calcium absorption, and corticosteroids, which inhibit calcium absorption.

Phosphate-Binding Agents: Since vitamin D also has an effect on phosphate transport in the intestine, kidneys and bones, the dosage of phosphate-binding agents must be adjusted in accordance with the serum phosphate concentration.

Calcium Supplements: Uncontrolled intake of additional calcium-containing preparations should be avoided.

Magnesium: Magnesium-containing preparations (e.g. antacids) may cause hypermagnesaemia and should, therefore, not be taken during therapy with vitamin D by patients on long-term renal dialysis.

Geriatric Use

Studies have shown that the elderly may have an increased need for vitamin D due to a possible decrease in the capacity of the skin to produce pro-vitamin D3, or a decrease in exposure to the sun, or impaired renal function, or impaired vitamin D absorption.

4.6 Fertility, pregnancy and lactation

Pregnancy Category A

Controlled studies in women have failed to demonstrate a risk to the foetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of foetal harm remains remote. Maternal hypercalcaemia during pregnancy in humans may be associated with increased sensitivity to the effects of vitamin D, suppression of parathyroid function, or a syndrome of peculiar (elfin) facies, mental retardation and congenital aortic stenosis in infants.

Pregnancy Category D

If the dose is more than the recommended US RDA – There is positive evidence of human foetal risk, but the benefits from use in pregnant women may be acceptable

despite the risk (e.g. if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective). Overdosage of vitamin D has been associated with foetal abnormalities in animals. Lactation Only small amounts of vitamin D metabolites appear in human milk. Infants who are totally breastfed and have little exposure to the sun may require vitamin D supplementation. It is advised that patients receiving pharmacological doses of vitamin D should have their plasma-calcium concentration monitored at regular intervals, especially initially, and if the symptoms suggest toxicity, similar monitoring is recommended in infants if they are breastfed by mothers receiving vitamin D.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive or use machines have been performed. Cholecalciferol has no known side effects that are likely to affect the ability to drive and use or operate machines.

4.8 Undesirable effects

Vitamin D at normal doses usually has no side effects. Too much vitamin D can cause harmful high calcium levels. Some of the associated symptoms are as follows: nausea/vomiting, constipation, loss of appetite, increased thirst, increased urination, mental/mood changes, and unusual tiredness.

A very serious allergic reaction to this drug is rare. However, medical help may be needed in case of a serious allergic reaction, including rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, and trouble breathing. This is not a complete list of possible side effects.

Toxicity is much more likely to occur from high intakes of dietary supplements containing vitamin D. Vitamin D toxicity can cause non-specific symptoms such as anorexia, weight loss, polyuria, and heart arrhythmias. More seriously, it can also raise blood levels of calcium, which leads to vascular and tissue calcification, with subsequent damage to the heart, blood vessels and the kidneys.

The use of supplements of both calcium (1000 mg/day) and vitamin D (400 IU) by postmenopausal women was associated with a 17% increase in the risk of kidney stones over 7 years in the Women's Health Initiative. A serum calcidiol concentration consistently >500 nmol/L (>200 ng/mL) is considered to be potentially toxic. Long-term intakes above the upper limit increase the risk of adverse health effects. Most reports

suggest a toxicity threshold for vitamin D of 10000–40000 IU/day and serum calcidiol levels of 500–600 nmol/L (200–240 ng/mL). While symptoms of toxicity are unlikely at daily intakes below 10000 IU/day, the FNB (Food and Nutrition Board) pointed to emerging science from national survey data, observational studies and clinical trials suggesting that even lower vitamin D intakes and serum calcidiol levels might have adverse health effects over time. The FNB concluded that serum calcidiol levels above approximately 125–150 nmol/L (50–60 ng/mL) should be avoided, as even lower serum levels (approximately 75–120 nmol/L or 30–48 ng/mL) are associated with increases in all-cause mortality, greater risk of cancer at some sites such as the pancreas, greater risk of cardiovascular events, and more falls and fractures among the elderly

4.9 Overdose

Overdosage can lead to hyper-vitaminosis, hypercalciuria and hypercalcaemia. Symptoms of hypercalcaemia may include anorexia, thirst, nausea, vomiting, constipation, abdominal pain, muscle weakness, fatigue, mental disturbances, polydipsia, polyuria, 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.

Treatment of Hypercalcaemia: The treatment with calcium must be discontinued. Treatment with thiazide diuretics, lithium, vitamin A, vitamin D and cardiac glycosides must also be discontinued. Emptying of the stomach should be done in patients with impaired consciousness. Rehydration and, according to severity, isolated or combined treatment with loop diuretics, bisphosphonates, calcitonin and corticosteroids must be initiated. Serum electrolytes, renal function and diuresis must be monitored. In severe cases, electrocardiogram (ECG) and central venous pressure should be followed.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Cholecalciferol, also called as vitamin D3, is produced naturally by ultraviolet irradiation of the pro-vitamin, 7-dehydrocholesterol (a precursor of vitamin D) in the skin. Absorbed cholecalciferol requires metabolic activation. The circulating vitamin undergoes hydroxylation in the liver with the help of the enzyme, vitamin D 25-

hydroxylase to form 25-hydroxycholecalciferol (calcidiol), which is the predominant circulating metabolite. Further hydroxylation in the kidneys (in response to the need for phosphorus and calcium) forms 1,25-dihydroxycholecalciferol (calcitriol) with the help of 1alpha-hydroxylase. Calcidiol possesses some intrinsic activity, but calcitriol is the most active vitamin D metabolite with respect to initiating intestinal transport of calcium and phosphate and mobilizing calcium from bone. Calcitriol may prevent phosphaturia by inhibiting parathyroid hormone secretion. Conversion to calcitriol, as well as decreases in serum inorganic phosphate levels is stimulated by the parathyroid hormone. Reduced renal conversion of calcidiol to calcitriol contributes to altered calcium haemostasis and osteodystrophy in uraemia.

5.2 Pharmacokinetic properties

Absorption

Vitamin D substances are well absorbed from the gastrointestinal tract. The presence of bile is essential for adequate intestinal absorption; absorption may be decreased in patients with decreased fat absorption.

Distribution

Vitamin D and its metabolites circulate in the blood, bound to a specific alpha-globulin. Vitamin D 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 has a slow onset and a long duration of action.

Metabolism

Cholecalciferol is converted in the liver by hydroxylation to the active form 25-hydroxyl-cholecalciferol. It is then further converted in the kidneys to 1,25- dihydroxy-cholecalciferol. 1,25-dihydroxycholecalciferol is the metabolite responsible for increasing calcium absorption. Vitamin D that is not metabolized is stored in adipose and muscle tissues.

Excretion

Vitamin D compounds and their metabolites are excreted mainly in the bile and faeces, with only small amounts appearing in urine. There is some entero-hepatic recycling but it is considered to have a negligible contribution to vitamin D status. Certain vitamin

D substances may be distributed into breast milk.

5.3 Preclinical safety data

Cholecalciferol is a well-known and established product and has been used in clinical practice for many years. No further specific toxicological hazard for humans is expected other than in chronic overdosage where hypercalcaemia could be seen. Cholecalciferol overdosage in animals has been shown to induce malformations in rats, mice and rabbits at doses significantly higher than the human dose. The malformations included skeletal defects, microcephaly and cardiac malformations. At doses equivalent to those used therapeutically, cholecalciferol has no teratogenic activity. Cholecalciferol has no potential mutagenic or carcinogenic activity.

6. Pharmaceutical particulars

6.1 Incompatibilities

None supplied.

6.3 Shelf life

As mentioned on the package material.

6.4 Special precautions for storage

As mentioned on the package material.

Administrative data

7. Marketing authorisation holder

Strides Shasun Limited
Strides House, Bilekahalli,
Bannerghatta Road,
Bengaluru – 560 076, India

8. Toll free number for reporting

1800 4190601

9. Date of text

30th November 2016