SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Ergocalciferol 50 000 IU Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains Ergocalciferol 50 000 IU (equivalent to 1.25mg vitamin D₂).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsule, hard

Orange opaque, unprinted, hard gelatin capsule containing clear, slightly yellow oily liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
The treatment of vitamin D deficiency and the maintenance of vitamin D levels.

Ergocalciferol is indicated in adults and the elderly.

4.2 Posology and method of administration
One capsule contains 50 000 IU Ergocalciferol (vitamin D₂).

- Adult Posology

  - Treatment of vitamin D deficiency: 50 000 IU (1 capsule) once a week for 12 weeks, followed by maintenance therapy of 50 000 IU (1 capsule) every 4 weeks, as directed.
- Maintenance of vitamin D levels: 50 000 IU (1 capsule) every 4 weeks.

Higher doses may be required in certain populations, see below “certain populations”.

Follow-up serum 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 D 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
- Patients being evaluated for osteoporosis
- Obese individuals
- Use of certain concomitant medications (e.g. anticonvulsant medications glucocorticoids, anti-retrovirals)
- Those recently treated for vitamin D deficiency, and requiring maintenance therapy
- Patients with liver or renal disease
- Patients with malabsorption, including inflammatory bowel disease and coeliac disease

**Infants and children**

Not recommended for children under 18 years.

**Pregnancy and breastfeeding**

Ergocalciferol 50 000 IU capsules are not recommended during pregnancy unless the clinical condition of the woman requires treatment.

Ergocalciferol and its metabolites are excreted in breast milk. Overdose in infants induced by nursing mothers has not been observed but allowance for any maternal dose should be made when prescribing vitamin D products to a breast-fed child.

**Method of administration**

This medicine is taken orally.

The capsule should be swallowed whole with water, preferably with the main meal of the day.
4.3 **Contraindications**

Ergocalciferol 50 000 IU Capsules must not be used in patients with:

- hypersensitivity to the active substance (ergocalciferol) or to any of the excipients listed in section 6.1
- hypercalcaemia and/or hypercalciuria
- nephrolithias (Renal calculi)
- hypervitaminosis
- severe renal impairment

4.4 **Special warnings and precautions for use**

Ergocalciferol 50 000 IU Capsules should be administered with caution to patients who may have an increased sensitivity to its effects.

Use with care in patients with mild to moderate renal impairment, renal calculi or a tendency to form calculus, and heart disease or arteriosclerosis that might be at increased risk of organ damage if hypercalcaemia were to occur.

Ergocalciferol 50 000 IU Capsules should be prescribed with caution to patients suffering from sarcoidosis because of the risk of increased metabolism of vitamin D to its active form. These patients should be monitored with regard to the calcium content in serum and urine.

Allowances should be made for vitamin D supplements, other vitamin D containing medicines or from other sources.

The need for additional calcium supplementation should be considered for individual patients. Calcium supplements should be given under close medical supervision.

All patients receiving doses of vitamin D should have their plasma calcium and 25-hydroxycalciferol concentrations checked at initiation of treatment and whenever nausea and vomiting are present.

**Paediatric Population**

Ergocalciferol 50 000 IU Capsules should not be given to infants and children under the age of 18 years.
4.5 Interaction with other medicinal products and other forms of interaction

Phosphate infusions should not be administered to lower hypercalcaemia of hypervitaminosis D because of the dangers of metastatic calcification.

Patients treated with cardiac glycosides may be susceptible to high calcium levels and should have ECG parameters and calcium levels measured to monitor any risk of cardiac arrhythmias. It is recommended to reduce the dose or interrupt treatment if the calcium content in the urine exceeds 7.5 mmol/24 hours (300 mg/24 hours).

Simultaneous administration of benzothiadiazine derivatives (thiazide diuretics) increases the risk of hypercalcaemia because they decrease the calcium excretion in the urine. The calcium levels in plasma and urine should therefore be monitored for patients undergoing long-term treatment.

Adsorption of calcium may be reduced by oral sodium sulphate parenteral magnesium sulphate.

Additional monitoring of serum calcium is recommended when therapy is combined with vitamin D analogue or metabolites.

Anti-convulsants, e.g. carbamazepine, phenobarbital, phenytoin and primidone, may diminish the effect of ergocalciferol due to hepatic enzyme induction.

Rifampicin may reduce the effectiveness of ergocalciferol due to hepatic enzyme induction.

Isoniazid may reduce the effectiveness of ergocalciferol due to inhibition of the metabolic activation of ergocalciferol.

Glucocorticosteroids can reduce the serum 25-hydroxycalciferol levels, requiring dose additional supplementation of ergocalciferol.

Drugs leading to fat malabsorption, e.g. orlistat, liquid paraffin, cholestyramine, may impair the absorption of ergocalciferol.

The cytotoxic agent actinomycin and imidazole antifungal agents interfere with vitamin D activity by inhibiting the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D by the kidney enzyme, 25-hydroxyvitamin D-1-hydroxylase.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data on the use of ergocalciferol in pregnant women. Ergocalciferol 50 000 IU Capsules should not be used in pregnancy unless the clinical
condition of the woman requires treatment with ergocalciferol, where the potential benefit outweighs the potential hazards to the foetus.

Animal studies have shown foetal abnormalities associated with hypervitaminosis D. Vitamin D is teratogenic in animals when given in doses several times the human dose. The offspring of a woman administered 17-144 times the recommended dose of vitamin D during pregnancy manifested mild hypercalcaemia in the first 2 days of life, which returned to normal at day 3.

Breast-feeding

Ergocalciferol and its metabolites are excreted in breast milk in limited amounts. In a mother given large doses of ergocalciferol, 25-hydroxycalciferol appeared in the milk and caused hypercalcaemia in the child. Monitoring of the infants serum calcium and 25-hydroxycalciferol is required in such cases especially when a breast-fed child is prescribed additional 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. Ergocalciferol 50 000 IU Capsules have no known effect on the ability to drive or use machines.

4.8 Undesirable effects
Adverse reactions are listed below, by system organ class and frequency.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>(≥1/10,000; &lt;1/1,000)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hypercalcaemia, hypercalciuria</td>
</tr>
<tr>
<td>Skin and subcutaneous disorders</td>
<td>Pruritus, rash, urticaria</td>
</tr>
</tbody>
</table>

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 (www.mhra.gov.uk/yellowcard).

4.9 Overdose
A single acute overdose is virtually non-toxic and requires supportive treatment with liberal fluids only.

Acute or chronic overdose of ergocalciferol can cause hypercalcaemia, an increase in the serum and urinary concentrations of calcium. The symptoms of hypercalcaemia are not very specific and consist of nausea, vomiting, diarrhoea often in the early stages and later constipation, anorexia, weight loss, fatigue, headache, vertigo, mental disturbances, abdominal pain, muscle and joint pain, muscle weakness, polydipsia, polyuria, formation of renal calculi, nephrocalcinosis, kidney failure, calcification of soft tissues, changes in ECG measurements, arrhythmias and pancreatitis. In rare and isolated cases there are reports that hypercalcaemia is fatal.

Treatment of Overdose
A normalisation of hypercalcaemia due to vitamin D intoxication lasts several weeks. Treatment of chronic overdose with resulting hypercalcaemia requires immediate withdrawal of vitamin D (including supplements), a low calcium or calcium-free diet, avoidance of sunlight and generous fluid intake. Severe cases may require hydration with intravenous saline together with symptomatic and supportive treatment as indicated by the patient’s clinical condition. Plasma calcium, urea and electrolytes should be monitored.

Phosphate infusions should not be administered to lower hypercalcaemia of hypervitaminosis D because of the dangers of metastatic calcification.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Vitamin D and analogues, ATC code: A11CC01

Absorption
Ergocalciferol is a fat-soluble vitamin, usually absorbed from the diet in the small intestine. In its biologically active form, ergocalciferol stimulates intestinal calcium absorption, incorporation of calcium into the osteoid, and release of calcium from bone tissue. In the small intestine it promotes 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 parathyroid glands is inhibited directly by the biologically active form of ergocalciferol. PTH secretion is inhibited additionally by
the increased calcium uptake in the small intestine under the influence of biologically active ergocalciferol.

Elimination
Ergocalciferol and its metabolites are excreted in the bile and faeces.

5.2 Pharmacokinetic properties
The pharmacokinetics of ergocalciferol have been widely studied and are well-known. Ergocalciferol, a pro-vitamin from nutritional sources, is almost completely absorbed from within the gastro-intestinal tract in the presence of dietary lipids and bile acids. The elimination half-life of Ergocalciferol is ca. 2 days however it may be stored in fat deposits for prolonged periods. The half-life of 25-(OH)D₂ in blood is ca. 15 days.

After a single oral dose of 50 000 IU Ergocalciferol in healthy male volunteers, the maximum serum concentrations of the primary storage form (25(OH)D₂) are reached after approximately 3 days and the levels return to baseline after approximately 14 days. In elderly vitamin D deficient females, a single large oral dose of 300 000 IU also results in peak (25(OH)D₂) levels after ca. 3 days but with a slow elimination such that levels are insufficient after about 50 days, although still higher than baseline after 60 days. Ergocalciferol and its metabolites are excreted mainly in the bile and faeces.

After high doses of ergocalciferol, serum concentrations of 25-hydroxycholecalciferol may be increased for months. Overdose-induced hypercalcaemia may persist for weeks (see section 4.9, Overdose).

Ergocalciferol is metabolised by microsomal hydroxylase to form 25-hydroxyergocalciferol (25(OH)D₂), the primary storage form of vitamin D. 25(OH)D₂ undergoes a secondary hydroxylation within the kidney to form the predominant active metabolite 1,25-dihydroxyergocalciferol (1,25(OH)₂D₃ calcitriol). These metabolites are lipophilic and due to their low solubility in the aqueous media of plasma, the metabolites circulate in the blood bound to a specific α-globulin (vitamin D-binding protein). 25(OH)D₂ and 1,25(OH)₂D₃ inactivating the molecule. 24-hydroxylation may also occur in the liver prior to 25-hydroxylation to give 24(OH)D₂ and subsequently 1,24(OH)₂D₃.

5.3 Preclinical safety data
Ergocalciferol 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.
Ergocalciferol 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, ergocalciferol has no teratogenic activity. Ergocalciferol has no potential mutagenic or carcinogenic activity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Capsule contents:
Medium-chain triglycerides (from vegetable sources)
Butylated hydroxytoluene
Colloidal silicon dioxide

Capsule shell:
Gelatin
Red iron oxide (E172)
Titanium dioxide (E171)
Yellow iron oxide (E172)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store below 25°C. Keep the blister in the outer carton in order to protect from light.
6.5 **Nature and contents of container**
Opaque, white PVC/PVDC blister strips with aluminium foil in the following pack sizes:

10, 14, 20, 28, 30, 50, 56, 60, 84, 100 capsules

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements for disposal. Any unused product should be disposed of in accordance with local requirements.

7 **MARKETING AUTHORISATION HOLDER**
Colonis Pharma Limited
Hanover Place
8 Church Road
Royal Tunbridge Wells
Kent
TN1 1JP
United Kingdom

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 41344/0002

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
17/12/2014

10 **DATE OF REVISION OF THE TEXT**
22/11/2016