IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0535/001/001
Case No: 2031455

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Shire Pharmaceuticals Limited

Hampshire International Business, **Chineham**, **Basingstoke, Hampshire RG24 8EP**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

CALCICHEW D3 Chewable Tablets, calcium/colecalciferol equivalent to 500mg calcium/200IU colecalciferol

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **27/07/2007** until **15/08/2008**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Calcichew-D_3 Chewable Tablets, calcium carbonate/colecalciferol equivalent to 500mg Calcium/200IU colecalciferol.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Per tablet:		
Calcium Carbonate (equivalent to 500 mg of elemental calcium)	1250	mg
Colecalciferol (equivalent to 5 micrograms vitamin D_3)	200	IU

Contains sorbitol, 390mg; isomalt, 62mg; aspartame, 1mg; sucrose 0.76mg and soya bean oil, hydrogenated, 0.165mg. For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Chewable Tablet.
Round, white, biconvex, orange-flavoured tablet. May have small specks.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Calcichew-D_3 Chewable Tablets may be used as an adjunct to specific therapy for osteoporosis or as a therapeutic supplement in established osteomalacia. It may also be used in pregnant patients at high risk of needing such a therapeutic supplementation or malnutrition when dietary intake is less than that required.

4.2 Posology and method of administration

Oral

Adjunctive therapy in osteoporosis:
One chewable tablet 2-3 times per day

Calcium and vitamin D deficiency:
Adults One chewable tablet 2-3 times per day
Children One chewable tablet 1-2 times per day
The tablet may be chewed or sucked.
Dosage in hepatic impairment:
No dose adjustment is required.

Dosage in renal impairment:
Calcichew-D_3 Chewable Tablets should not be used in patients with severe renal impairment.

4.3 Contraindications

- Diseases and/or conditions resulting in hypercalcaemia and/or hypercalciuria
- Nephrolithiasis
- Hypervitaminosis D
- Hypersensitivity to soya or peanut
- Hypersensitivity to the active substances or to any of the excipients

4.4 Special warnings and precautions for use

During long-term treatment, serum 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 (see section 4.5) 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.

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. The risk of soft tissue calcification should be taken into account. In patients with severe renal insufficiency, vitamin D in the form of colecalciferol is not metabolised normally and other forms of vitamin D should be used (see section 4.3 Contraindications).

Calcichew-D_3 Chewable Tablets 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.

Calcichew-D_3 Chewable Tablets should be used with caution in immobilised patients with osteoporosis due to the increased risk of hypercalcaemia.

The dose of colecalciferol (200 IU) in Calcichew-D_3 Chewable Tablets 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.

Calcichew-D_3 Chewable Tablets contain aspartame (a source of phenylalanine) which may be harmful for people with phenylketonuria.

Calcichew-D_3 Chewable Tablets contain sorbitol (E420), isomalt (E953) and sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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.

Systemic corticosteroids reduce calcium absorption. During concomitant use, it may be necessary to increase the dose of Calcichew-D_3 Chewable Tablets.

Simultaneous treatment with ion exchange resins such as cholestyramine or laxatives such as paraffin oil may reduce the gastrointestinal absorption of vitamin D.

Calcium carbonate 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.

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.

If a bisphosphonate or sodium fluoride is used concomitantly, this preparation should be administered at least three hours before the intake of Calcichew-D_3 Chewable Tablets since gastrointestinal absorption may be reduced.

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

4.6 Pregnancy and lactation

Pregnancy
During pregnancy the daily intake should not exceed 1500 mg calcium and 600 IU colecalciferol (15µg vitamin D). Studies in animals have shown reproductive toxicity with 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 the developing foetus. There are no indications that vitamin D at therapeutic doses is teratogenic in humans. Calcichew-D_3 Chewable Tablets can be used during pregnancy, in case of a calcium and vitamin D deficiency.

Lactation
Calcichew-D_3 Chewable Tablets can be used during breast-feeding. Calcium and vitamin D_3 pass into breast milk. This should be considered when giving additional vitamin D to the child.

4.7 Effects on ability to drive and use machines

There are no data about the effect of this product on driving capacity. An effect is, however, unlikely.

4.8 Undesirable effects

Adverse reactions are listed below, by system organ class and frequency. Frequencies are defined as: uncommon (>1/1,000, <1/100) or rare (>1/10,000, <1/1,000).

Metabolism and nutrition disorders
Uncommon: Hypercalcaemia and hypercalciuria.

Gastrointestinal disorders
Rare: Constipation, flatulence, nausea, abdominal pain and diarrhoea.

Skin and subcutaneous disorders
Rare: Pruritus, rash and urticaria.

4.9 Overdose

Overdose can lead to hypercalcaemia. Symptoms of hypercalcaemia may include anorexia, thirst, nausea, vomiting, constipation, abdominal pain, muscle weakness, fatigue, mental disturbances, polydipsia, polyuria, bone pain, nephrocalcinosis, nephrolithiasis 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. Treatment: rehydration, and according to severity of hypercalcaemia, isolated or combined treatment with loop diuretics, bisphosphonates, calcitonin and corticosteroids should be considered. Serum electrolytes, renal function and diuresis must be monitored. In severe cases, ECG and CVP should be followed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: mineral supplements

ATC code: A12AX

Vitamin D increases the intestinal absorption of calcium.

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

A clinical study of institutionalised patients suffering from vitamin D deficiency indicated that a daily intake of two tablets of calcium 500mg/vitamin D 400iu for six months normalised the value of the 25-hydroxylated metabolite of vitamin D_3 and reduced secondary hyperparathyroidism and serum alkaline phosphatase.

5.2 Pharmacokinetic properties

Calcium
Absorption: The amount of calcium absorbed through the gastrointestinal tract is approximately 30% of the swallowed dose.

Distribution and metabolism: 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 extracelluar fluids. 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 and metabolism: Colecalciferol and its metabolites circulate in the blood bound to a specific globulin. Colecalciferol is converted in the liver by hydroxylation to the active form 25-hydroxycholecalciferol. It is then further converted in the kidneys to 1,25-hydroxycholecalciferol; 1,25-hydroxycholecalciferol is the metabolite responsible for increasing calcium absorption. Vitamin D, which is not metabolised, is stored in adipose and muscle tissue.

Elimination: Vitamin D is excreted in faeces and urine.

5.3 Preclinical safety data

At doses far higher than the human therapeutic range teratogenicity has been observed in animal studies. There is no further information of relevance to the safety assessment in addition to what is stated in other parts of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E420)
Povidone
Isomalt (E953)
Flavour (orange)
Magnesium stearate
Aspartame (E951)
Mono, di-fatty acid glycerides
Sucrose
Gelatin
Soya-bean oil, hydrogenated
Tocopherol
Maize Starch

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 30°C. Keep the container tightly closed.

6.5 Nature and contents of container

White HDPE containers with a primary tamper proof seal and secondary resealable closure containing 60 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Shire Pharmaceuticals Limited
Hampshire International Business Park
Chineham
Basingstoke
Hampshire RG24 8EP
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 535/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16th August 1993

Date of last renewal: 16th August 2003

10 DATE OF REVISION OF THE TEXT

July 2007