

ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS, ROUTES OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS, PACKAGING AND PACKAGE SIZES OF THE MEDICINAL PRODUCT IN THE MEMBER STATES

Article 30 Referral for Calcichew D₃ (and related names) Chewable tablets (Calcium 500 mg plus cholecalciferol 10 µg)

Member State	MAH	Invented name	Strength	Pharmaceutical form	Route of Administration	Packaging	Package size
Austria	Nycomed Austria GmbH	Cal - D - or	500 mg / 10 µg	Chewable tablet	Oral	Polyethylene (PEHD) bottle	20, 60, 120
Belgium	Christiaens Pharma	SteoVit D ₃ 500mg /400 I.E	500 mg / 10 µg	Chewable tablet	Oral	Polyethylene (PEHD) bottle Unit dose (blister): PVC/PVdC/PE/Al	20, 30, 50, 60, 90, 100, 180 Unit dose (blister): 50
Denmark	Nycomed Danmark A/S	CaviD	500 mg / 10 µg	Chewable tablet	Oral	Polyethylene (PEHD) bottle	100
Finland	Oy Leiras Finland Ab	Calcichew D3 Forte 500 mg/400 IU purutabletti	500 mg / 10 µg	Chewable tablet	Oral	Polyethylene (PEHD) bottle Unit dose (blister): PVC/PVdC/PE/Al	20, 30, 50, 60, 90, 100, 180 Unit dose (blister): 50
Germany	Jenapharm GmbH&Co KG	Calcilac KT	500 mg / 10 µg	Chewable tablet	Oral	Polyethylene (PEHD) bottle Unit dose (blister): PVC/PVdC/PE/Al	20, 30, 50, 60, 90, 100, 180 Unit dose (blister): 50
	Orion Pharma GmbH	Calcimagon-D3	500 mg / 10 µg	Chewable tablet	Oral	Polyethylene (PEHD) bottle	20, 50, 100 and 10 x 20
Greece	Nycomed Hellas S.A	Calcioral D3	500 mg / 10 µg	Chewable tablet	Oral	Polyethylene (PEHD) bottle Unit dose (blister): PVC/PVdC/PE/Al	20, 30, 50, 60, 90, 100, 180 Unit dose (blister): 50
Luxembourg	Christiaens Pharma	SteoVit D ₃ 500 mg/400 I.E	500 mg / 10 µg	Chewable tablet	Oral	Polyethylene (PEHD) bottle Unit dose (blister): PVC/PVdC/PE/Al	20, 30, 50, 60, 90, 100, 180 Unit dose (blister): 50
Netherlands	Christiaens B.V	Calci-Chew-D3 500 mg /400 I.E	500 mg / 10 µg	Chewable tablet	Oral	Polyethylene (PEHD) bottle Unit dose (blister): PVC/PVdC/PE/Al	Bottle: 20, 30, 50, 60, 90, 100, 180 Unit dose (blister): 50

Member State	MAH	Invented name	Strength	Pharmaceutical form	Route of Administration	Packaging	Package size
Norway	Nycomed Pharma AS, Norway	Calcigran Forte	500 mg / 10 µg	Chewable tablet	Oral	Polyethylene (PEHD) bottle	50 60, 100
Portugal	Laboratoires Theramex	Orocal-D3	500 mg / 10 µg	Chewable tablet	Oral	Polyethylene (PEHD) bottle	20, 60
Sweden	Nycomed Pharma AS, Norway	Calcichew D3	500 mg / 10 µg	Chewable tablet	Oral	Polyethylene (PEHD) bottle Unit dose (blister): PVC/PVdC/PE/Al	20, 30, 50, 60, 90, 100, 180 Unit dose (blister): 50
Sweden	Nycomed Pharma AS, Norway	Calcichew-D3 Spearmint	500 mg / 10 µg	Chewable tablet	Oral	Polyethylene (PEHD) bottle	20, 30, 60, 100, 120, 180

ANNEX II

**SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY
OF PRODUCT CHARACTERISTICS PRESENTED BY THE EMEA**

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF CALCICHEW D3 AND ASSOCIATED NAMES (see Annex I)

- Quality issues

The pharmaceutical documentation (module 3) as well as the pharmaceutical particulars of the SPC were harmonised, except the sections, which need to be introduced nationally by the Member States when implementing the harmonised SPC.

- Efficacy issues

Section 4.1. Therapeutic indications

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Calcium carbonate and cholecalciferol, the following was considered to be the most suitable harmonised Section 4.1 indications text:

4.1 Therapeutic indications

Prevention and treatment of vitamin D and calcium deficiency in the elderly.

Vitamin D and calcium supplement as an adjunct to specific osteoporosis treatment of patients who are at risk of vitamin D and calcium deficiency.

Section 4.2. Posology and method of administration

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Calcium carbonate and cholecalciferol, the following was considered to be the most suitable harmonised Section 4.2 Posology text:

4.2 Posology and method of administration

Adults and elderly

One chewable tablet twice daily. The tablet may be chewed or sucked.

Dosage in hepatic impairment

No dose adjustment is required

Dosage in renal impairment

Calcichew-D3 (and associated names) should not be used in patients with severe renal impairment.

- Safety issues

Section 4.3. Contra-indications

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Calcium carbonate and cholecalciferol, the most suitable harmonised Section 4.3 Contraindications text was approved (See Annex III). The text in the harmonised SPC is not so dissimilar to the currently approved SPCs that it will significantly change clinical practices

Section 4.4. Special warnings and precautions for use

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Calcium carbonate and cholecalciferol, the most suitable harmonised Section 4.4 Special Warnings and Precautions for Use text was approved (See Annex III).

The text in the harmonised SPC is not so dissimilar to the currently approved SPCs that it will significantly change clinical practices

Section 4.6. Pregnancy and lactation

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Calcium carbonate and cholecalciferol, the most suitable harmonised Section 4.6 Pregnancy was approved (See Annex III).

Section 4.8 Undesirable effects

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Calcium carbonate and cholecalciferol, the most suitable harmonised Section 4.8 Undesirable effects was approved (See Annex III).

All other sections of the SPC were harmonised as a result of the referral procedure (except See Below; Administrative Issues).

- Administrative issues

Other sections of the SPC which were not harmonised and which need to be introduced nationally by the Member States when implementing the harmonised SPC are the following: Product name, MAH, MA number, date of first authorisation/renewal of authorisation, Date of revision of the text.

Benefit/Risk considerations

Based on the documentation submitted by the MAH and the scientific discussion within the Committee, the CPMP considered that the benefit/risk ratio of Calcichew-D3 is favourable for use relating to prevention and treatment of vitamin D and calcium deficiency in the elderly and for use as vitamin D and Calcium supplement as an adjunct to specific osteoporosis treatment of patients who are at risk of vitamin D and calcium deficiency.

GROUNDINGS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS

Whereas,

- the scope of the referral was the harmonisation of the Summaries of Products Characteristics and additionally the harmonisation of the technical document – module 3 (quality),
- the Summary of Products Characteristic proposed by the Marketing Authorisation Holder(s) has been assessed based on the documentation submitted and the scientific discussion within the Committee,

the CPMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics is set out in Annex III of the Opinion.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS

**NOTE: THIS SPC IS THE ONE THAT WAS ANNEXED TO THE COMMISSION
DECISION CONCERNING THIS REFERRAL FOR ARBITRATION; THE TEXT
WAS VALID AT THAT TIME**

**IT IS NOT SUBSEQUENTLY MAINTAINED OR UPDATED BY THE EMEA, AND
THEREFORE MAY NOT NECESSARILY REPRESENT THE CURRENT TEXT**

1. NAME OF THE MEDICINAL PRODUCT

Calcichew-D3 and associated names (see Annex I) 500 mg / 10 µg chewable tablets

[To be implemented nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains:

Elemental calcium	500 mg
<i>as</i>	
Calcium carbonate	
Cholecalciferol (vitamin D3)	10 microgram (400 IU)
<i>as</i>	
Cholecalciferol concentrate (powder form)	

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Chewable tablet

Round, white, uncoated and convex tablets. May have small specks.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention and treatment of vitamin D and calcium deficiency in the elderly.

Vitamin D and calcium supplement as an adjunct to specific osteoporosis treatment of patients who are at risk of vitamin D and calcium deficiency.

4.2 Posology and method of administration

Adults and elderly

One chewable tablet twice daily. The tablet may be chewed or sucked.

Dosage in hepatic impairment

No dose adjustment is required

Dosage in renal impairment

Calcichew-D3 (and associated names) 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 the active substances or to any of the excipients

4.4 Special warnings and special precautions for use

Calcichew-D3 (and associated names) tablets contain aspartame and should be avoided by patients with phenylketonuria.

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 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 cholecalciferol is not metabolised normally and other forms of vitamin D should be used (see section 4.3, contraindications).

Calcichew-D3 (and associated names) tablets 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.

Calcichew-D3 (and associated names) tablets should be used cautiously in immobilised patients with osteoporosis due to increased risk of hypercalcaemia.

The content of vitamin D (400 IU) in Calcichew-D3 (and associated names) tablets 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.

Calcichew-D3 (and associated names) tablets are not intended for use in children.

4.5 Interactions 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-D3 (and associated names).

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-D3 (and associated names) 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 compounds with calcium ions. 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 1,500 mg calcium and 600 IU vitamin D. 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 the developing foetus. There are no indications that vitamin D at therapeutic doses is teratogenic in humans. Calcichew D3 can be used during pregnancy, in case of a calcium and vitamin D deficiency.

Breast-feeding

Calcichew D3 can be used during breast-feeding. Calcium and vitamin D₃ 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 hypervitaminosis 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 and vitamin D must be discontinued. Treatment with thiazide diuretics, lithium, vitamin A, vitamin D and cardiac glycosides must also be discontinued. Emptying of the stomach in patients with impaired consciousness. Rehydration, and, according to severity, isolated or combined treatment with loop diuretics, bisphosphonates, calcitonin and corticosteroids. 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 D₃ 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 Calcichew-D3 (and associated names) for six months normalised the value of the 25-hydroxylated metabolite of vitamin D₃ and reduced secondary hyperparathyroidism and alkaline phosphatases.

An 18 month double-blind, placebo controlled study including 3270 institutionalised women aged 84+/- 6 years who received supplementation of vitamin D (800 IU/day) and calcium phosphate (corresponding to 1200 mg/day of elemental calcium), showed a significant decrease of PTH secretion. After 18 months, an "intent-to treat" analysis showed 80 hip fractures in the calcium-vitamin D group and 110 hip fractures in the placebo group (p=0,004). A follow-up study after 36 months showed 137 women with at least one hip fracture in the calcium-vitamin D group (n=1176) and 178 in the placebo group (n=1127) (p≤0,02).

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 extracellular 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: Cholecalciferol and its metabolites circulate in the blood bound to a specific globulin. 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 hydroxycholecalciferol. 1,25 hydroxycholecalciferol is the metabolite responsible for increasing calcium absorption. Vitamin D which is not metabolised is stored in adipose and muscle tissues.

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 further no information of relevance to the safety assessment in addition to what is stated in other parts of the SPC

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol
Povidone
Isomalt
Flavouring (lemon or spearmint)
Magnesium Stearate
Aspartame
Mono- and diglycerides of fatty acids
Tocopherol
Vegetable fat
Sucrose
Gelatin
Maize starch

6.2 Incompatibilities

Not applicable

6.3 Shelf life

High Density Polyethylene tablet container: 3 years
Blister pack: 2 years

6.4 Special precautions for storage

High Density Polyethylene tablet container: Do not store above 30°C. Keep the container tightly closed in order to protect from moisture.
Blister pack: Do not store above 25°C. Store in the original package.

6.5 Nature and content of container

The chewable tablets are packed in:
High Density Polyethylene tablet containers
Pack sizes: 20, 30, 50, 60, 90, 100, 120 and 180 tablets
Blister pack (PVC/PE/PVdC/AI) (Lemon flavoured tablets)
Package size: 50 x 1 tablets (unit dose)

Not all pack sizes may be marketed

6.6 Instructions for use and handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

(See Annex I – To be implemented nationally)

8. MARKETING AUTHORISATION NUMBERS

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF THE REVISION OF THE TEXT