



Medicines & Healthcare products  
Regulatory Agency



## **Public Assessment Report**

**UKPAR**

**Calcium Carbonate/Colecalciferol 1500mg/400IU  
chewable tablets**

**(calcium carbonate and colecalciferol)**

**UK Licence No: PL 33831/0027**

**Blue Bio Pharmaceuticals Limited**

## LAY SUMMARY

### Calcium Carbonate/Colecalciferol 1500mg/400IU chewable tablets (calcium carbonate and colecalciferol)

This is a summary of the Public Assessment Report (PAR) for Calcium Carbonate/Colecalciferol 1500mg/400IU chewable tablets (PL 33831/0027). It explains how Calcium Carbonate/Colecalciferol 1500mg/400IU chewable tablets were assessed and their authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Calcium Carbonate/Colecalciferol 1500 mg/400IU chewable tablets.

This product will be referred to as Calcium Carbonate/Colecalciferol tablets throughout the remainder of this summary.

For practical information about using Calcium Carbonate/Colecalciferol tablets, patients should read the package leaflet or contact their doctor or pharmacist.

#### **What are Calcium Carbonate/Colecalciferol tablets and what are they used for?**

Calcium Carbonate/Colecalciferol tablets is a medicine with ‘well established use’. This means that the medicinal use of the active substances calcium carbonate and colecalciferol are well established in the European Union for at least ten years, with recognised efficacy and an acceptable level of safety.

Calcium Carbonate/Colecalciferol chewable tablets provide extra calcium and vitamin D<sub>3</sub> to the diet. The tablets are therefore used in conditions where the body’s calcium and vitamin D levels need to be increased.

This medicine can also be recommended by a pharmacist for certain bone conditions, for example, osteoporosis. Studies show that taking calcium and vitamin D<sub>3</sub> over a long time can prevent hip and other non vertebral bone fractures in later life.

#### **How do Calcium Carbonate/Colecalciferol tablets work?**

This medicinal product is a chewable tablet which contains the active substances calcium carbonate and colecalciferol (Vitamin D<sub>3</sub>). A combination of these two actives helps increase the level of calcium and vitamin D in the body that are essential for healthy bones and teeth.

#### **How are Calcium Carbonate/Colecalciferol tablets used?**

Calcium Carbonate/Colecalciferol tablets are taken by mouth. A whole tablet should be chewed.

The patient should always take this medicine exactly as the patient’s doctor has told them to. The patient must check with their doctor or pharmacist if they are not sure.

The recommended dose in adults, elderly and children over 12 years of age is 2 tablets daily, ideally one taken in the morning and one tablet in the evening.

Calcium Carbonate/Colecalciferol tablets are not recommended in children under the age of 12.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

Calcium Carbonate/Colecalciferol tablets can be obtained from a pharmacy.

#### **What benefits of Calcium Carbonate/Colecalciferol tablets have been shown in studies?**

As calcium carbonate and colecalciferol are well-known substances, and their use for certain bone conditions, for example, osteoporosis is well established, the applicant (Blue Bio Pharmaceuticals Limited) presented data from the scientific literature. The literature provided confirmed the efficacy and safety of these active substances in the prevention and treatment of calcium/vitamin D deficiencies.

**What are the possible side effects of Calcium Carbonate/Colecalciferol tablets?**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Calcium Carbonate/Colecalciferol tablets, see section 4 of the package leaflet or the Summary of Product Characteristics (SmPC) available on the MHRA website.

**Why were Calcium Carbonate/Colecalciferol tablets approved?**

The use of Calcium Carbonate/Colecalciferol tablets for the approved indications is well-established. Literature data have been submitted to support this application. No new or unexpected safety concerns arose from this application. It was, therefore, considered that the benefits of Calcium Carbonate/Colecalciferol tablets outweigh the risks and the grant of a Marketing Authorisation was recommended.

**What measures are being taken to ensure the safe and effective use of Calcium Carbonate/Colecalciferol tablets?**

A Risk Management Plan has been developed to ensure that Calcium Carbonate/Colecalciferol tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Calcium Carbonate/Colecalciferol tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

**Other information about Calcium Carbonate/Colecalciferol tablets**

A Marketing Authorisation was granted in the UK on 25 January 2016.

The full PAR for Calcium Carbonate/Colecalciferol tablets follows this summary.

For more information about treatment with Calcium Carbonate/Colecalciferol tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in March 2016.

## TABLE OF CONTENTS

I	Introduction	Page 5
II	Quality aspects	Page 6
III	Non-clinical aspects	Page 8
IV	Clinical aspects	Page 9
V	User consultation	Page 18
VI	Overall conclusion, benefit/risk assessment and recommendation	Page 18
	Table of content of the PAR update	Page 22

## I Introduction

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Blue Bio Pharmaceuticals Limited a Marketing Authorisation for the medicinal product Calcium Carbonate/Colecalciferol 1500mg/400IU chewable tablets (PL 33831/0027). This Pharmacy (P) medicine is used for the following indications:

- As an adjunct to specific therapy for osteoporosis and in situations requiring therapeutic supplementation of malnutrition e.g. in pregnancy and established vitamin D dependent osteomalacia.
- The prevention and treatment of calcium deficiency/vitamin D deficiency especially in the housebound and institutionalised elderly subjects. Deficiency of the active moieties is indicated by raised levels of parathyroid hormone (PTH), lowered 25-hydroxy vitamin D and raised alkaline phosphatase levels which are associated with increased bone loss.

This application was submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing active substances of well-established use.

Calcium Carbonate/Colecalciferol 1500mg/400IU chewable tablets contain the active substances calcium carbonate and colecalciferol. Calcium plays a critical structural role, comprising a substantial proportion of the skeleton. However, although calcium supplementation improves calcium balance, the literature suggests that fracture risk is not significantly reduced by calcium alone. With respect to vitamin D, a meta analysis demonstrated that 700 – 800 IU/d vitamin D reduced risk of hip (or other non-vertebral) fracture.

Vitamin D insufficiency and low calcium intake contribute to increase parathyroid function and bone fragility in elderly people. Calcium and vitamin D supplements can reverse secondary hyperparathyroidism thus preventing hip fractures.

No new non-clinical or clinical studies were necessary for this application, which is acceptable given that this is a bibliographic application for a product containing actives of well-established use. Bioequivalence studies are not necessary to support this application.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacturing and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

A summary of the pharmacovigilance system and a detailed risk management plan have been provided with this application and these are satisfactory.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Calcium Carbonate/Colecalciferol 1500mg/400IU chewable tablets outweigh the risks and a Marketing Authorisation was granted.

## II Quality Aspects

### II.1 Introduction

Each chewable tablet contains 1500 mg calcium carbonate (equivalent to 600 mg calcium) and 400IU colecalciferol as colecalciferol concentrate (powder form) (equivalent to Vitamin D<sub>3</sub> 10 micrograms), as the active ingredients.

Other ingredients consist of the following pharmaceutical excipients starch pregelatinized, povidone K30, aspartame (E951), xylitol, mannitol (E421), sorbitol (E420), magnesium stearate, DL- $\alpha$ -tocopherol, modified food starch, triglycerides of medium chain fatty acids, sodium ascorbate crystalline, sucrose, colloidal anhydrous silica, tutti frutti flavor as powder, tutti frutti premium (contains maize maltodextrin, propylene glycol, alpha tocopherol).

All excipients comply with their respective European Pharmacopoeia monographs with the exception of tutti frutti flavor which complies with an in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient. All primary packaging complies with the current European regulations (Regulation (EU) No. 10/2011). Confirmation has also been given that the magnesium stearate used in the tablets is of vegetable origin.

A Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE) statement has been issued by the supplier to confirm that Vitamin D<sub>3</sub> is prepared synthetically in a process that includes wool grease (lanolin) from healthy live sheep from category A and B countries that does not present a risk of BSE/TSE contamination.

No genetically modified organisms (GMO) have been used in the preparation of this product.

The finished product is packed in a clear polyvinylchloride (PVC), polyvinylidenechloride (PVdC) aluminium blister packs containing 56 and 112 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

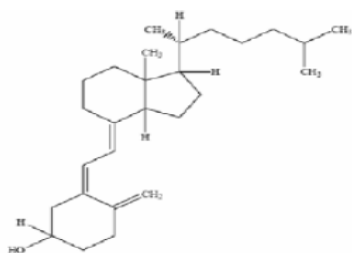
### II.2. Drug Substance

INN	<b>Calcium carbonate</b>
Molecular formula:	CaCO <sub>3</sub>
Molecular Mass:	100.1 g/mol
Appearance:	White or almost white powder.
Solubility:	Calcium carbonate is practically insoluble in water.

Calcium carbonate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, calcium carbonate, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

INN	<b>Colecalciferol</b>
Chemical name:	(3 $\beta$ ,5Z,7E)-9,10-secocholesta- 5,7,10(19)-trien-3-ol
Structural formula:	



Molecular formula:  $C_{27}H_{44}O$   
Molecular Mass: 384.6 g/mol  
Appearance: White or almost white crystals.  
Solubility: Colecalciferol is practically insoluble in water, freely soluble in ethanol (96 per cent), soluble in trimethylpentane and in fatty oils.

Colecalciferol is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, colecalciferol, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

### II.3. Medicinal Product

#### Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, chewable tablets containing 1500 mg of calcium carbonate and 400IU of colecalciferol per tablet.

A satisfactory account of the pharmaceutical development has been provided.

#### Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. A validation report for commercial scale batches has been provided. The process validation data provided is satisfactory.

#### Finished Product Specification

The finished product specification proposed is acceptable. The test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

#### Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months with the storage conditions "Do not store above 25°C" and "Store in the original package in order to protect from moisture".

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

### II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of this application from a pharmaceutical viewpoint.

### III Non-Clinical Aspects

#### III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of calcium carbonate and colecalciferol are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

#### III.2 Pharmacology

Calcium reduces bone loss and decreases the risk of fracturing the vertebrae. Calcium also has benefits in other body systems by reducing blood pressure and cholesterol levels. Calcium carbonate was the most effective  $\text{Ca}^{2+}$  salt to bind haem *in vitro* and decrease faecal biomarkers previously associated with increased carcinogenesis in *in vivo* studies in rats. Calcium has also been shown to enhance the intestinal resistance to *Salmonella* in rats. Calcium carbonate has also been used therapeutically as an antacid, for the treatment of peptic ulcer or for restriction of phosphate absorption.

Colecalciferol is the naturally occurring form of vitamin D. It is produced from 7-dehydrocholesterol, a sterol present in mammalian skin, by ultraviolet irradiation. Vitamin D is essential for the regulation of calcium and phosphate homeostasis and for mineralisation of the organic matrix of bone. Vitamin D increases the intestinal absorption of calcium and phosphate and allows the proper functioning of parathyroid hormone (PTH) so that plasma calcium levels are maintained. It is also essential for neuromuscular function, and may play important roles in guarding against cardiovascular disease, depression and colon cancer.

#### III.3 Pharmacokinetics

Calcium carbonate is converted to calcium chloride by gastric acid. Calcium is absorbed to the extent of about 15 – 25% from the gastrointestinal tract while the remainder reverts to insoluble calcium carbonate and calcium stearate and is excreted in the faeces.

Vitamin D is well absorbed from the gastrointestinal tract in the presence of bile. It is hydroxylated in the liver to form 25-hydroxycholecalciferol and then undergoes further hydroxylation in the kidney to form the active metabolite 1, 25 dihydroxycholecalciferol. The metabolites circulate in the blood bound to a specific  $\alpha$ -globulin known as vitamin D-binding protein. Because of its lipophilic nature, vitamin D can be stored in adipose and muscle tissue for prolonged periods. It is slowly released from these storage sites and from the skin. Vitamin D and its metabolites are excreted mainly in the bile and faeces. Small quantities are excreted in the urine.

#### III.4 Toxicology

Calcium carbonate and vitamin D are well known and widely used substances and have been used in clinical practice for many years. As such toxicity is only likely to occur in chronic overdosage where hypercalcaemia could result.

The  $\text{LD}_{50}$  of calcium carbonate in rats was determined as 6450 mg/kg body weight, indicating very low acute toxicity of calcium carbonate.

Very high doses of vitamin D can induce acute toxicity. The lethal dose in dogs is said to be about 13 mg/kg; immediate effects are bloody diarrhoea, anorexia, thirst, polyuria and prostration. In surviving animals calcium is deposited as in chronic hypervitaminosis-D.

No evidence of mutagenic or carcinogenic potential has been reported in tests performed to date with calcium carbonate and colecalciferol.

Vitamin D<sub>3</sub> was negative for mutagenicity in *Salmonella typhimurium* strains TA1535, TA1537, TA97, TA98 and TA100, in the presence and absence of rat or hamster liver S-9, at concentrations up to 10-mg/plate.

Tumour inhibition studies performed with each substance separately showed positive results in some tests, i.e. an inhibition of tumour growth.

Rats fed up to 1.25% dietary calcium carbonate for 6 weeks prior to mating and during gestation and found no adverse effects. There is no evidence that normal levels of calcium will interfere with reproduction.

Offspring of pregnant rabbits that have been treated with large doses of vitamin D have lesions anatomically similar to those of supravalvular aortic stenosis. In addition, offspring with no aortic narrowing show vasculotoxicity similar to adults following acute vitamin D toxicity.

### **III.5 Ecotoxicity/environmental risk assessment (ERA)**

The Marketing Authorisation holder has provided adequate justification for not submitting an Environmental Risk Assessment ERA). This is acceptable as vitamins are unlikely to result in significant risk to the environment.

### **III.6 Discussion on the non-clinical aspects**

No new non-clinical studies were conducted, which is acceptable given that this is a bibliographic application for a product containing active ingredients of well-established use.

There are no objections to the approval of this application from a non-clinical viewpoint.

## **IV Clinical Aspects**

### **IV.1 Introduction**

This application is submitted under Article 10a of Directive 2001/83/EC, as amended, for Calcium Carbonate/Colecalciferol 1500mg/400IU chewable tablets.

No new clinical pharmacology, efficacy or safety data have been submitted and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of calcium carbonate and colecalciferol.

The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

### **IV.2 Pharmacokinetics**

The pharmacokinetics of both calcium carbonate and colecalciferol are well known. Both are endogenously occurring substances.

#### **Absorption**

**Colecalciferol:** Absolute bioavailability data for colecalciferol (oral) is unavailable. The vitamin appears to be well-absorbed after oral doses, possibly more efficiently than ergocalciferol. Colecalciferol is absorbed from the small intestine, and bile is essential for the absorption process (primarily deoxycholic acid). Absorption is impaired in the presence of biliary or hepatic dysfunction or fat malabsorption syndromes.

**Calcium:** Oral bioavailability of calcium is about 4% to 45%. Percent of absorption depends on the calcium salt, dose, presence of gastric hydrochloric acid, and presence of activated vitamin D. In achlorhydric patients, absorption from calcium carbonate was 4% and in normal subjects, absorption was 22%. Active vitamin-D dependent absorption of calcium occurs in the proximal duodenum; facilitated diffusion occurs throughout the small intestine.

The absorption of both actives is well understood. The specific role of vitamin D in the absorption of calcium is also known.

### **Distribution**

**Colecalciferol:** It is bound to vitamin D-binding protein (an alpha-globulin) and is transported to and stored in liver, adipose and muscle tissue.

**Calcium:** It is 45% protein bound. Bone contains 99% of the body's calcium, with the remainder in the intra- and extracellular fluids.

The distribution of both actives is well established.

### **Metabolism**

**Colecalciferol:** Colecalciferol is inactive until metabolic conversion. It is first hydroxylated in the liver via vitamin D 25-hydroxylase to 25-hydroxycholecalciferol (calcifediol); subsequent metabolism of calcifediol occurs in the kidney. Following enterohepatic circulation, calcifediol (formed from vitamin D in the liver) undergoes renal 1-alpha hydroxylation to 1, 25-dihydroxycholecalciferol (calcitriol). This is mediated via a calcifediol-1-alpha hydroxylase system associated with mitochondria in the proximal tubules. 1-alpha hydroxylase activity is enhanced in the presence of dietary deficiency of calcium, vitamin D and phosphate, and is stimulated by parathyroid hormone and estrogen. Additional renal hydroxylations of calcitriol to 1, 24, 25- trihydroxycholecalciferol and 24, 25-dihydroxycholecalciferol occur. Calcitriol also undergoes additional side-chain oxidation. Metabolites are 25-hydroxycholecalciferol (calcifediol) (active), 1, 25-dihydroxycholecalciferol (calcitriol), 1, 24, 25 trihydroxycholecalciferol (active), 24, 25-dihydroxycholecalciferol (active).

The metabolism of vitamin D is well established. As an element there is no metabolism of calcium.

### **Excretion**

**Colecalciferol:** Only a small percentage of a dose of colecalciferol is excreted in the urine. Most of the dose is excreted in the bile. Colecalciferol and its metabolites undergo extensive enterohepatic recirculation.

**Calcium:** Renal clearance rate is 50 to 300 mg/day. In chronic renal failure, calcium excretion decreases as filtration rate decreases. However, in renal acidosis, calcium excretion may be enhanced. Urinary calcium excretion is higher with a high protein diet than with a low protein diet. Calcium is excreted in the faeces as unabsorbed calcium and endogenous calcium in sloughed intestinal cells and mucosal and biliary secretions.

The excretion of both actives is well established.

### **Special populations**

The applicant adequately discussed the pharmacokinetics in the appropriate special populations.

### **IV.3 Pharmacodynamics**

No new pharmacodynamic data were submitted and none were required for an application of this type.

For all those who are treated for loss of bone mass, the aim is not only to ensure an adequate intake of calcium but also of vitamin D and other nutrients which are indispensable for bone health. The best way, from the pharmacological point of view, of supplementing calcium is in its carbonate form. Most patients do not meet the adequate intake for calcium and vitamin D; supplementation of both can help to meet requirements. Inappropriate intake can lead to reduced calcium absorption, higher bone remodeling rates and increased bone mass loss. Also, vitamin D deficit has been linked to reduced muscle function and increased risk of falling.

Calcium from carbonate is the most common form, due to its cost-effectiveness profile, of calcium supplement for choice. Calcium carbonate is the most prevalent calcium supplements in the market. It provides more elemental calcium than calcium citrate hence patients may not need to take as many pills. Calcium lactate and gluconate are less concentrated forms of calcium and are not practical oral supplements. On the other hand, calcium citrate decreased markers of bone resorption significantly more than calcium carbonate in postmenopausal women, although no differences in their effects in calcium excretion or PTH were detected.

Calcium and vitamin D<sub>3</sub> can reduce the incidence of hip and other non-vertebral fractures. It has a positive effect on bone mineral density. Vitamin D decreases bone loss and lowers the risk of fracture, especially in older men and women. Along with calcium, vitamin D also helps to prevent and treat osteoporosis. To absorb calcium efficiently, an adequate amount of vitamin D must be present. Vitamin D is normally made in the skin after exposure to sunlight.

In an 18 month randomized placebo controlled study conducted in 3270 healthy elderly women living in nursing homes or apartments for elderly people, it is concluded that calcium and vitamin D<sub>3</sub> supplementation can reduce the incidence of hip and other non-vertebral fractures. A positive effect on bone mineral density was also observed. In patients treated with 1200 mg elemental calcium and 800IU vitamin D<sub>3</sub> daily, the number of hip fractures was 43% lower (p=0.043) and the total number of non-vertebral fractures was 32% lower than among those who received placebo. Proximal femur bone mineral density after 18 months of treatment increased 2.7% in the calcium/vitamin D<sub>3</sub> group and decreased 4.6% in the placebo group (p < 0.001). In the calcium/vitamin D<sub>3</sub> group, the mean serum PTH concentration decreased by 44% from baseline at 18 months and serum 25-hydroxy-vitamin D concentration had increased by 162% over baseline. Analysis of the intention-to-treat results showed a decreased probability of both hip fractures (p = 0.004) and other fractures (p < 0.001) in the calcium/vitamin D<sub>3</sub> treatment group. Analysis of the other two populations (active treatment and those treated and followed for 18 months) revealed comparable results to the intention-to-treat analysis. The odds ratio for hip fractures among women in the placebo group compared with those in the calcium/vitamin D<sub>3</sub> group was 1.7 (95% confidence interval (CI) 1.0 to 2.8) and that for other non-vertebral fractures was 1.4 (95% CI 1.4 to 2.1). In the placebo group, there was a marked increase in the incidence of hip fractures over time whereas the incidence in the calcium/vitamin D<sub>3</sub> group was stable. Thus treatment reduced the age-related risk of fracture at 18 months (p = 0.007 for hip fractures and p=0.009 for all non-vertebral fractures). At 3 years follow-up, the decrease in fracture risk was maintained in the calcium/vitamin D<sub>3</sub> group.

### **Interactions**

**Thiazide diuretics:** The risk of hypercalcaemia should be considered in patients taking thiazide diuretics since these drugs can reduce urinary calcium excretion. Hypercalcaemia must be avoided in digitalized patients.

**Phenytoin:** Concomitant treatment with phenytoin or barbiturates can decrease the effect of vitamin D because of metabolic activation.

**Glucocorticoids:** Concomitant use of glucocorticoids can decrease the effect of vitamin D.

**Digitalis and other cardiac glycosides:** These drugs may be accentuated with the oral administration of calcium combined with Vitamin D. Strict medical supervision is needed and, if necessary monitoring of ECG and calcium.

**Thyroxine, bisphosphonates, sodium fluoride, quinolone or tetracycline antibiotics or iron:**

Calcium salts may reduce the absorption of these drugs. It is advisable to allow a minimum period of four hours before taking the calcium.

**Certain foods:** Foods containing oxalic acid, phosphate or phytinic acid may reduce the absorption of calcium.

The pharmacodynamic interactions of both actives are well understood. The applicant's summary of the pharmacodynamic of both actives is adequate. Both can be considered well established.

#### IV.4 Clinical efficacy

The combination of actives has been licenced in the UK for many years and their efficacy is well established.

##### **Combination:**

In a subject-blind, sequential study in 24 healthy postmenopausal women, each subject received two placebo tablets once daily for 3 days (days -3 to -1) immediately followed by two calcium-vitamin D tablets (600 mg of calcium + 400 IU of vitamin D) during the subsequent 3 days (days 1-3). Serial blood sampling and 24 hours (h) urine collection took place on days 1 and 3. The subjects fasted until 6 hours post-dosing. Total urinary calcium excretion  $A_e$  (0-24 h) increased by 42% (uncorrected,  $p = 0.0001$ ) and 30% (creatinine-corrected,  $p = 0.0001$ ), after intake, compared with the placebo; serum calcium exposure AUC (0-6 h) was also, statistically, significantly greater. PTH, in serum, decreased by 28% (AUC (0-6 h),  $p = 0.0001$ ) and 14% (AUC (0-24 h),  $p = 0.0009$ ) when compared with the placebo.

In a study 36,282 postmenopausal women (50-79 years), who had already enrolled in a Women's Health Initiative (WHI) clinical trial, were randomly assigned to receive 1000 mg of elemental calcium as calcium carbonate with 400 IU of vitamin D<sub>3</sub> daily or placebo. Fractures were ascertained for an average follow-up period of seven years. Hip bone density was 1.06 percent higher in the calcium plus vitamin D group than in the placebo group ( $P < 0.01$ ). Intention-to-treat analysis indicated that participants receiving calcium plus vitamin D supplementation had a hazard ratio of 0.88 for hip fracture (95 percent confidence interval, 0.72 to 1.08), 0.90 for clinical spine fracture (0.74 to 1.10), and 0.96 for total fractures (0.91 to 1.02). The risk of renal calculi increased with calcium plus vitamin D (hazard ratio, 1.17; 95 percent confidence interval, 1.02 to 1.34). Censoring data from women when they ceased to adhere to the study medication reduced the hazard ratio for hip fracture to 0.71 (95 percent confidence interval, 0.52 to 0.97). Effects did not vary significantly according to pre randomisation serum vitamin D levels.

In a double-blind randomized controlled trial, we studied 122 elderly women (mean age, 85.3 years; range, 63-99 years) in long-stay geriatric care. Participants received 1200 mg calcium plus 800 IU colecalciferol (Calcium + vitamin D group;  $n = 62$ ) or 1200 mg calcium (Calcium group;  $n = 60$ ) per day over a 12-week treatment period. The number of falls per person (0, 1, 2-5, 6-7, >7 falls) was compared between the treatment groups. In an intention to treat analysis, a Poisson regression model was used to compare falls after controlling for age, number of falls in a 6-week pre-treatment period, and baseline 25-hydroxyvitamin D and 1, 25-dihydroxyvitamin D serum concentrations. Among fallers in the treatment period, crude excessive fall rate was compared between treatment groups. Change in musculoskeletal function was measured as a secondary outcome. Among subjects in the calcium + vitamin D-group, there were significant increases in median serum 25-hydroxyvitamin D (+71%) and 1,

25-dihydroxyvitamin D (+8%). Before treatment, mean observed number of falls per person per week was 0.059 in the Ca<sup>1+</sup>D-group and 0.056 in the Cal-group. In the 12-week treatment period, mean number of falls per person per week was 0.034 in the Ca<sup>1+</sup>D-group and 0.076 in the Cal-group. After adjustment, Ca<sup>1+</sup>D-treatment accounted for a 49% reduction of falls (95% CI, 14-71%;  $p < 0.01$ ) based on the fall categories stated above. Among fallers of the treatment period, the crude average number of excessive falls was significantly higher in the Cal-group ( $p = 0.045$ ). Musculoskeletal function improved significantly in the Ca<sup>1+</sup>D-group ( $p = 0.0094$ ). A single intervention with vitamin D plus calcium over a 3-month period reduced the risk of falling by 49% compared with calcium alone. Over this short-term intervention, recurrent fallers seem to benefit most by the treatment. The impact of vitamin D on falls might be explained by the observed improvement in musculoskeletal function.

A two-year, multicenter, randomized, double-masked, placebo-controlled confirmatory study was conducted. The intention-to-treat population consisted of 583 ambulatory institutionalized women (mean age 85.2 years, SD = 7.1) randomised to the calcium vitamin D<sub>3</sub> fixed combination group (n = 199); separate calcium plus vitamin D<sub>3</sub> supplement group (n = 190) and the placebo group (n = 194). Fixed and separate combination groups received the same daily amount of calcium (1200 mg) and vitamin D<sub>3</sub> (800 IU), which had similar pharmacodynamic effects. Both types of calcium-vitamin D<sub>3</sub> regimens increased serum 25-hydroxyvitamin D and decreased serum intact parathyroid hormone to a similar extent, with levels returning within the normal range after 6 months. In a subgroup of 114 patients, femoral neck bone mineral density (BMD) decreased in the placebo group (mean = -2.36% per year, SD = 4.92), while remaining unchanged in women treated with calcium-vitamin D<sub>3</sub> (mean = 0.29% per year, SD = 8.63). The difference between the two groups was 2.65% (95% CI = -0.44, 5.75%) with a trend in favour of the active treatment group. No significant difference between groups was found for changes in distal radius BMD and quantitative ultrasonic parameters at the ocalcis. The relative risk (RR) of hip fracture (HF) in the placebo group compared with the active treatment group was 1.69 (95% CI = 0.96, 3.0), which is similar to that found in another study (RR = 1.7; 95% CI = 1.0, 2.8).

## Separate actives

### Vitamin D:

A meta-analysis was conducted using various data bases. Older adults (aged  $\geq 60$ ) who participated in randomised controlled trials were investigated both the effectiveness of vitamin D therapy in the prevention of falls and used an explicit fall definition. Two author's independently extracted data, including study characteristics, quality assessment, and outcomes. The I (2) statistic was used to assess heterogeneity in a random-effects model. Of 1,679 potentially relevant articles, 10 met inclusion criteria. In pooled analysis, vitamin D therapy (200-1,000 IU) resulted in 14% (RR=0.86, 95% CI=0.79-0.93; I(2)=7%) fewer falls than calcium or placebo (number needed to treat=15). The following subgroups had significantly fewer falls: community-dwelling (aged <80), adjunctive calcium supplementation, no history of fractures or falls, duration longer than 6 months, colecalciferol, and dose of 800 IU or greater. Meta-regression demonstrated no linear association between vitamin D dose or duration and treatment effect. Post hoc analysis including seven additional studies (17 total) without explicit fall definitions yielded smaller benefit (RR=0.92, 95% CI=0.87-0.98) and more heterogeneity (I(2)=36%) but found significant intergroup differences favouring adjunctive calcium over none (P=.001).

Epidemiological and prospective studies have related vitamin D deficiency with not only osteoporosis but also cardiovascular disease, diabetes, cancer, infections and neurodegenerative disease. However the evidence is robust for skeletal but not non skeletal outcomes where data from large prospective studies are lacking. The major natural source of vitamin D is cutaneous synthesis through exposure to sunlight with a small amount from the diet in animal-based foods such as fatty fish, eggs and milk.

Vitamin D status is determined by measuring serum 25-hydroxyvitamin D [25(OH) D] levels. Optimal serum 25(OH) D levels are in the region of 30-90 ng/mL (75-225 nmol/L) though there is no

international consensus. Levels vary according to time of the year (lower in the winter), latitude, altitude, air pollution, skin pigmentation, use of sunscreens and clothing coverage. Risk factors for low serum 25(OH) D levels include: obesity, malabsorption syndromes, medication use (e.g. anticonvulsants, antiretrovirals), skin aging, low sun exposure and those in residential care. Fortified foods do not necessarily provide sufficient amounts of vitamin D. Regular sunlight exposure (without sunscreens) for 15 minutes, 3-4 times a week, in the middle of the day in summer generate healthy levels.

In a prospective drug-intervention study seven individuals with chronic spinal cord injury (SCI) and vitamin D deficiency had administered 3 months of oral vitamin D<sub>3</sub> supplementation. At screening, baseline, and months 1 and 3, blood was collected for serum calcium, 25 hydroxyvitamin D [25(OH) D], intact parathyroid hormone (iPTH), and N-telopeptide (NTx); 24-hour urine for calcium, creatinine, and NTx was performed. Oral vitamin D<sub>3</sub> (2000 IU daily) and elemental calcium (1.3 g daily) were prescribed for 90 days. Analysis of variance with a Fisher's post-hoc analysis was performed to test for differences between study visits. Subjects were classified as deficient (<20 ng/ml), relatively deficient (20-30 ng/ml), or not deficient (>30 ng/ml) in 25(OH) D. Serum 25(OH) D levels were greater at months 1 and 3 than at baseline ( $26 \pm 6$  and  $48 \pm 17$  vs.  $14 \pm 2$  ng/ml;  $P = 0.005$ ). Six of seven subjects were no longer deficient [25(OH) D >30 ng/ml] by month 3. Serum iPTH levels were significantly decreased at month 1 and month 3; serum NTx levels were significantly lower at month 3 than at baseline. Serum and urinary calcium levels remained within the normal range.

#### Calcium:

A review of large-scale clinical studies was undertaken to evaluate the effects of calcium supplementation for prevention of osteoporosis-related fractures in postmenopausal women. Five large-scale, randomised, controlled trials have called into question the benefits of calcium in reducing fracture risk, and four of the studies indicated that calcium users may be at increased risk for renal stones and gastrointestinal problems. However, all five studies had one or more important limitations, including possible selection bias and study participants' relatively high baseline calcium intake and generally low adherence to treatment regimens. Moreover, in some of the studies, vitamin D was not included in the treatment protocol or was not used at levels sufficient to optimize calcium absorption. In three of the five trials, subgroup analysis of the most treatment-adherent participants indicated significant reductions in osteoporotic fracture risk with calcium supplement use. In conclusion, results of recent clinical trials included in this meta analysis indicate that calcium supplementation alone does not significantly reduce fracture risk in postmenopausal women. However, evidence from the same studies suggests that beneficial effects on fracture risk may be seen in women who are adherent to therapy. Hence postmenopausal women should continue calcium supplementation to reduce osteoporosis risk.

The efficacy of this combination is well established. The overview demonstrates the efficacy of the requested formulation.

## IV.5 Clinical safety

The combination of these actives has been licenced in the UK for many years and their safety is well established.

Calcium and vitamin D combination is contraindicated in patients with hypercalcaemia, hypercalciuria, hyperparathyroidism, nephrolithiasis, Zollinger-Ellison syndrome, hypervitaminosis D or hypersensitivity to any of the ingredients.

Adverse reactions of a generally mild nature have been observed with calcium carbonate treatment, especially constipation and flatulence. A possible effect of high calcium intake is that the absorption of other minerals, e.g. iron, may be reduced. The main symptomatic effects of a calcium overdose are related to hypercalcaemia and include thirst, polyuria, anorexia, constipation, muscular weakness, fatigue and confusion. In severe cases nausea, vomiting and, rarely, cardiac arrhythmias may occur.

Serious adverse effects of calcium carbonate result from hypercalcaemia. A few such cases are reported in the literature, particularly in haemodialysis patients. Persistent high serum calcium levels may lead to irreversible renal damage and soft tissue calcification and extreme hypercalcaemia may result in coma and death. Reports on severe hypercalcaemia under vitamin D/calcium treatment have occurred with doses of vitamin D exceeding 10.000 IU per day.

With respect to vitamin D, very large amounts over a long time period can induce hypercalcaemia or toxic symptoms (more than 60.000 IU daily). In infants, vitamin D intoxication can occur after long-term doses of 2.5 - 5 times the recommended daily intake and cause hypercalcaemia, hypercalciuria and calcification of soft tissues.

### **Adverse Events**

In a study conducted 583 ambulatory institutionalised women (mean age 85.2 years, SD=7.1) were randomised to the calcium–vitamin D<sub>3</sub> fixed combination group (n=199); the calcium plus vitamin D<sub>3</sub> separate combination group (n=190) and the placebo group (n = 194). Fixed and separate combination groups received the same daily amount of calcium (1200 mg) and vitamin D<sub>3</sub> (800 IU), which had similar pharmacodynamic effects. Only 40 patients (24 in the active treatment group and 16 in the placebo) reported gastrointestinal disorders (nausea, diarrhea, epigastric pains). These gastrointestinal symptoms led to discontinuation of the study only in 3 cases. Three patients developed hypercalcaemia in the active treatment group: one resulting from recent myeloma, the two others from hyperparathyroidism which was masked at baseline by the very low serum vitamin D level and was revealed under therapy.

In a randomised population-based trial, the supplementation group (n=287) received daily colecalciferol 800 IU + calcium 1,000 mg for 3 years while the control group (n=306) received neither supplementation nor placebo. In the intention-to-treat analysis, total body BMD (n=362) increased significantly more in the intervention group than in the control group (0.84% vs. 0.19%, p=0.011). The analyses in compliant women ( $\geq 80\%$  of use) resulted in stronger and statistically significant effects at the total body and femoral regions. In total, 17 out of 290 women discontinued the intervention due to adverse effects. The adverse effects responsible for discontinuation were gastrointestinal symptoms (nine), exacerbation of diseases (two), and mouth irritation (one), skin symptoms (one), nausea (one), cough (one), backache (one), and weight increase (one).

### **Laboratory Findings**

Patients with mild to moderate renal failure or mild hypercalciuria should be supervised carefully including periodic checks of plasma calcium levels and urinary calcium excretion. With long-term treatment it is advisable to monitor serum and urinary calcium levels and kidney function, and reduce or stop treatment temporarily if urinary calcium exceeds 7.5 mmol/24 hours (300 mg/24 hours).

The safety of this combination is well established. The overview demonstrates the safety of the requested formulation.

## **IV.6 Risk Management Plan (RMP) and Pharmacovigilance system**

The Marketing Authorisation Holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Calcium Carbonate/Colecalciferol 1500mg/400IU chewable tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

<b>Safety concern</b>	<b>Routine risk minimisation measures</b>	<b>Additional risk minimisation measures</b>
Hypercalcaemia	SmPC includes: Contraindication in section 4.3 for patient with hypercalcaemia. Warning in section 4.4 for patient with increased risk for hypercalcaemia. ADRs listed in section 4.8	None
Hypercalciuria	SmPC includes: Contraindication in section 4.3 for patient with severe hypercalciuria. Warning in section 4.4 for patient with mild hypercalciuria ADRs listed in section 4.8	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Use in patients with conditions that modify vitamin D metabolism including sarcoidosis	SmPC includes: Contraindication in section 4.3 for patient with sarcoidosis. Cautions in section 4.4 for patients with increased risk of hypercalcaemia e.g. patients with sarcoidosis or those suffering from malignancies. ADRs listed in section 4.8	None
Interaction with thiazide diuretics	SmPC includes: Warning in section 4.4 for patients receiving treatment for cardiovascular disease.	None
Interaction with cardiac glycosides	SmPC includes: Warning in section 4.4 for patients receiving treatment for cardiovascular disease.	None
Use in patients with hypervitaminosis D	SmPC includes: Contraindication in section 4.3 for patients with vitamin D overdose. Cautions in section 4.4: Allowances should be made for calcium and vitamin D supplements from other sources.	None
Hypersensitivity	SmPC includes: Contraindication in section 4.3 for patients with hypersensitivity to any of the ingredients in the tablet.	None
Use in patients with renal impairment (including nephrolithiasis or nephrocalcinosis)	SmPC includes: Contraindications in section 4.3 for patients with severe renal failure and patients with renal stones. Warning in section 4.4 for patients with mild to moderate renal failure and in patients with a story of renal stones.	None
Pregnancy and lactation	SmPC includes: Pregnancy and lactation in section 4.6 where patients are advised to always be under the direction of a physician when taking the Product. Also be aware to take the Product and iron supplements at different	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	times.	
Overdose	SmPC includes: Overdose section 4.9 where patients should be aware of symptoms related to overdose.	None

#### IV.7 Discussion on the clinical aspects

The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

The bibliographic data submitted for this application does support the claim of well-established use for the sought indications.

The grant of a Marketing Authorisation is recommended for this application.

#### V User consultation

The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability, as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

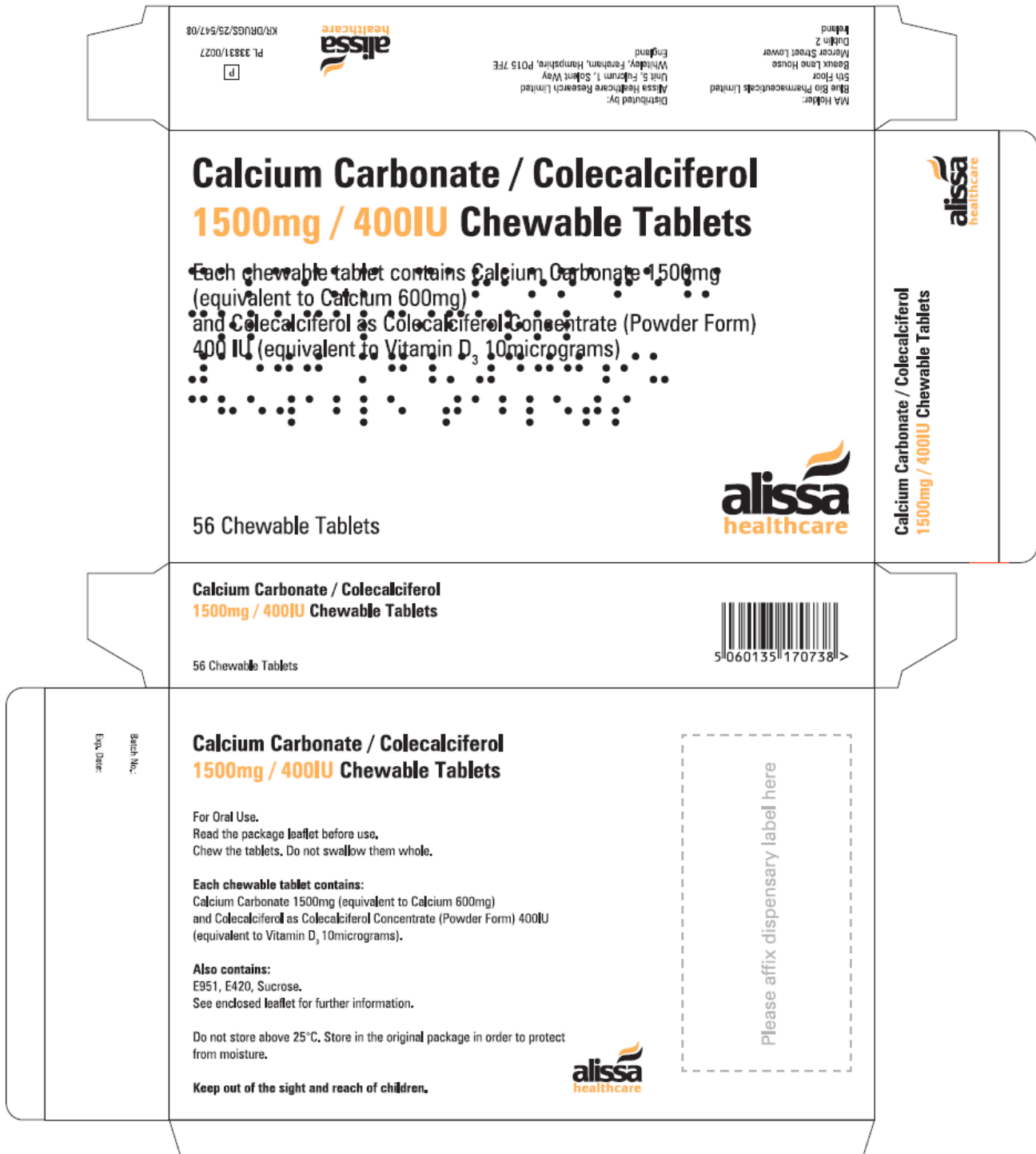
#### VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with calcium carbonate and colecalciferol is considered to have demonstrated the therapeutic value of the compounds. The benefit-risk is, therefore, considered to be positive.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Calcium Carbonate/Colecalciferol 1500mg/400IU chewable tablets is presented below:







## Table of content of the PAR update

### Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitment

<b>Date submitted</b>	<b>Application type</b>	<b>Scope</b>	<b>Outcome</b>