VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Calcium and vitamin D deficiency are common world-wide and can give rise to osteoporosis which can result in considerable morbidity and mortality. Overall deficiency of calcium and vitamin D is more important in susceptible conditions where there is a greater need for supplementation. Over the long term, inadequate calcium intake causes low bone mineral density which if untreated can lead to osteoporosis. The risk of bone fractures also increases, especially in older individuals Calcium deficiency can also cause rickets, though it is more commonly associated with vitamin D deficiency

The main risk groups for inadequate intake of calcium include postmenopausal women as menopause leads to bone loss because of decrease in female hormone production and decrease in calcium absorption. Other risk groups include people with lactose intolerance or cow's milk allergy who avoid milk, people on weight loss regimens, also pregnant and lactating women may be at risk of inadequate calcium intake because of increased needs during the 2nd and 3rd trimester of pregnancy and during lactation, amenorrheic women, people with malabsorption syndrome and strict vegetarians.

Calcium and vitamin D deficiency can lead to osteoporosis which is characterised by loss of bone mass and results in fragility fractures that can lead to acute and chronic pain as well as loss of function and early mortality. Fractures of the hip and the bones in the back are two of the most common osteoporotic fractures. Such fractures attributable to osteoporosis have a considerable associated co-morbidity and pose a considerable healthcare cost. Hip fractures can lead to additional risks of complications such as deep venous thrombosis and/or pulmonary embolism, and pneumonia as well as decreased mobility. The six-month mortality rate following hip fracture is around 10-20%, and almost 25% of people who have suffered a hip fracture need long term assistance.

VI.2.2 Summary of treatment benefits

Calcium and vitamin D3 are essential elements required for the correct functioning of the body. Prolonged states of deficiency of calcium and vitamin D3 can lead to low bone mineral density, osteoporosis and bone fractures.

In a randomized population-based open trial in ambulatory postmenopausal women (3,432 women (aged 66 to 71 years). A randomly selected subsample of 593 subjects underwent bone mineral

density measurements (BMD). The supplementation group (n = 287) received daily cholecalciferol 800 IU + calcium 1,000 mg for 3 years while the control group (n = 306) received neither supplementation nor placebo. In the supplementation group BMD increased significantly than in the control group. The study results indicated that daily vitamin D and calcium supplementation has a positive effect on the skeleton in ambulatory postmenopausal women with adequate nutritional calcium intake.

VI.2.3 Unknowns relating to treatment benefits

Calcium carbonate and cholecalciferol combination product has been clinically available for decades. It is used worldwide for the prevention and treatment of calcium and vitamin D deficiency and 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. As such the treatment benefits for calcium carbonate and cholecalciferol are well established and there are no unknown factors requiring further investigation.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Aggravation of Hypervitaminosis D	In hypervitaminosis D there is an excess of vitamin D leading to toxicity. The toxicity is usually associated with increased levels of calcium.	Patients requiring the medication will have low level of vitamin D. Those requiring long term treatment, or who are at risk of high calcium levels are not suitable for this product, or require regular monitoring of calcium levels.
Diseases or conditions resulting in or from hypercalcaemia and/or hypercalciuria such as renal stones (Nephrolithiasis).	Hypercalcaemia (high calcium levels) and hypercalciuria (high calcium levels in the urine) may be caused by a number of conditions including cancer and hormone imbalances (such as primary hyperparathyroidism), and chronic conditions, such as sarcoidosis. It is important that calcium levels are monitored in these patients to ensure additional calcium and vitamin D continues to be appropriate and does not lead to higher levels of calcium than is required.	Patients requiring the medication will have low level of calcium, or low reserves of calcium. Those requiring long term treatment, or who are at risk of high calcium levels are not suitable for this product, or require regular monitoring of calcium levels.

Risk	What is known	Preventability
Use in renal impairment	Severe kidney disease alters the phosphate and calcium balance in the body leading to high levels of both in the blood. The increased calcium and phosphate levels can lead to soft tissue calcification in the body and are implicated in cardiovascular disease. Therefore calcium carbonate/cholecalciferol should be used with caution in patients with kidney disease.	Patients with mild to moderate kidney disease should be monitored for calcium and phosphate levels. Patients with severe renal impairment should not use this product.
Interaction with cardiac glycosides	Cardiac glycosides such as digoxin are used in the treatment of heart failure and arrhythmias (irregular heart rate). If patients receive too much cardiac glycoside this leads to toxicity, which can lead to additional heart rate abnormalities, which can be life threatening. With these cardiac glycoside medications toxicity can occur at doses only slightly higher doses than the intended dose. High levels of calcium can increase the likelihood of this toxicity so calcium levels need to be monitored.	Patients receiving cardiac glycosides and calcium supplements require regular monitoring of their calcium levels and regular ECGs to evaluate the heart rate.
Hypersensitivity reaction to the active substance or any excipients	Hypersensitivity reactions or allergic reactions can occur when the body's immune system over reacts to a 'foreign body' such as a medicine. The patient may have taken the medicine previously or have risk factors for developing hypersensitivity such as old age, female sex, and use of medicines such as ACE inhibitors that affect kidney function. Hypersensitivity reactions can be mild such as a rash to serious such as anaphylaxis which requires immediate medical attention..	Calcium carbonate/cholecalciferol should be avoided if a patient previously experienced a hypersensitivity reaction to the medicine.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)	
In patients suffering from sarcoidosis there is a risk of increased metabolism of vitamin D to its active form.	Sarcoidosis is a rare condition that causes small patches of red and swollen tissue, called granulomas, to develop in the organs of the body. It most often affects the lungs and skin. Patient with sarcoidosis can also experience high levels of calcium.	Patients requiring the medication will have low level of calcium, or low reserves of calcium, despite having sarcoidosis. Those patients with raised calcium or at risk of higher calcium levels should not take this product. Those patients with sarcoidosis who require this product, will require regular monitoring of their calcium levels.
Concomitant treatment with other sources of vitamin D and/or medications and nutrients containing calcium	Concomitant treatment with other sources of vitamin D and/or medications and nutrients containing calcium can lead to hypercalcaemia (high calcium levels). This especially important in patients who are predisposed to hypercalcaemia due to conditions including cancer and hormone imbalances (such as primary hyperparathyroidism), and chronic conditions, such as sarcoidosis. It is important that calcium levels are monitored in these patients to ensure additional calcium and vitamin D continues to be appropriate and does not lead to higher levels of calcium than is required.	Those requiring long term treatment, or who are at risk of high calcium levels are not suitable for this product, or require regular monitoring of calcium levels.

Missing information

Risk	What is known
None	Not applicable

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a 'Summary of Product Characteristics' (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the 'Patient Information Leaflet' (PIL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Calcium carbonate and cholecalciferol have been on the market for many decades therefore their efficacy and safety profile is well established. There is no planned post authorisation development program.

VI.2.7 Summary of changes to the Risk Management Plan over time

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
Version 2.0.	12 DEC 2014	Addition of the following risks: Important Identified Risks: Use in Renal Impairment Hypersensitivity Reactions Important Potential Risks: Concomitant treatment with other sources of vitamin D and/or medications and nutrients containing calcium.	Risks were updated as per the FAR for PSUR 14 (02-Oct-2010 to 31-Oct-2013) for Calcium Carbonate + Cholecalciferol (Vitamin D3) (AT/H/PSUR/0040/001) .