VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Vitamin D deficiency

The prevalence rate of vitamin D deficiency does not differ significantly between males and females, or among age groups. The overall prevalence rate of vitamin D deficiency is 41.6%, with the highest rate observed in blacks (82.1%) and Hispanics (69.2%). Individuals with poor overall health, low high-density lipoprotein cholesterol, hypertension, obesity, and non- daily use of milk (all $p<0.05$) were at increased risk of vitamin D deficiency.[1,2,3]

Osteoporosis

Insufficient vitamin D can result in osteoporosis, a bone disease in which the risk of fracture is increased due to reductions in bone mass and bone density. It is estimated that 50% of women and 20% of men over the age of 50 years in the UK (National Osteoporotic Society, UK) and an estimated 44 million Americans (National Osteoporotic Society, USA) are at risk of bone fracture due to osteoporosis. It is responsible for more than 1.5 million fractures annually, including 300,000 hip fractures, approximately 700,000 vertebral fractures, 250,000 wrist fractures, and more than 300,000 other fractures. The lifetime risk for any fractures due to osteoporosis in white people aged 50 years is around 40% in women and 13% in men. Hip fractures have an overall mortality of 15-30%. Post-menopausal osteoporosis is the most common bone disease and is a major cause of death and injury. [4,5,6]

VI.2.2 Summary of treatment benefits

Colecalciferol 800 IU and 20,000 IU Capsules, Soft

The available medical literature is considered sufficient to evaluate the efficacy of Colecalciferol 800 IU capsules, soft in approved indications and 20,000 Capsules, Soft in the proposed therapeutic indications. Based on literature data, the proposed products may be prescribed to treat or prevent vitamin D deficiency. Deficiency of vitamin D may occur when diet or lifestyle does

not provide enough vitamin D or when the body requires more vitamin D (for instance during pregnancy). Colecalciferol 800 IU and 20,000 IU Capsules, Soft may also be prescribed for certain bone conditions, such as thinning of the bone (osteoporosis), when it will be prescribed along with other medicines.

Colecalciferol 3,200 IU Capsules, Soft

The available medical literature is considered sufficient to evaluate the efficacy of Colecalciferol 3,200 IU Capsules, Soft in the proposed therapeutic indications. Based on literature data, the proposed product may be prescribed to treat or prevent vitamin D deficiency. Deficiency of vitamin D may occur when diet or lifestyle does not provide enough vitamin D or when the body requires more vitamin D (for instance during pregnancy).

VI.2.3 Unknowns relating to treatment benefits

Not applicable.

VI.2.4 Summary of safety concerns

Important identified risks:

Risk	What is known	Preventability
Abnormal high levels of calcium in the blood (Hypercalcaemia)	Colecalciferol must not be used in patients with diseases or conditions resulting in abnormal high levels of calcium in the blood (hypercalcaemia). This concern applies especially to patients: • Who suffer from sarcoidosis (a rare condition that causes small patches of red and	Yes. Medical supervision is required during treatment to prevent abnormal high levels of calcium in the blood (hypercalcaemia). Patients are instructed not to take Colecalciferol if they have high levels of calcium in their blood. If the patient is already taking additional doses of calcium or vitamin D, their doctor will monitor the levels of calcium in

Risk	What is known	Preventability
	swollen tissue, called granulomas, to develop in the organs of the body. It most often affects the lungs and skin) because of the risk of higher breakdown of vitamin D to its active form. • Who take medicines used to treat high blood pressure called thiazide diuretics as they reduce the excretion of calcium through urine. • Who suffer from hypervitaminosis D (excess of vitamin D leading to toxicity).	their blood to make sure they are not too high. Patients suffering from sarcoidosis should be monitored with regard to the calcium content in their blood and urine. Colecalciferol should not be prescribed to patients taking medicines used to treat high blood pressure called thiazide diuretics. Due to the increased risk of developing abnormal high levels of calcium in the blood (hypercalcaemia), blood calcium should be regularly monitored. Patients suffering from excess of vitamin D leading to toxicity (hypervitaminosis D) should not take Colecalciferol.
Abnormal high levels of calcium in urine (Hypercalciuria)	Colecalciferol must not be used in patients with diseases or conditions resulting in abnormal high levels of calcium in urine (hypercalciuria).	Yes. The patient is instructed not to take Colecalciferol if they have abnormal high levels of calcium in urine (hypercalciuria).
Severe allergic reactions (Hypersensitivity)	Colecalciferol must not be used in patients who suffer from severe allergic reactions (hypersensitivity) to vitamin D or to any substance contained in the	Yes. Patients are instructed not to take Colecalciferol if they are allergic to vitamin D or to any substance contained in the drug (excipients).

Risk	What is known	Preventability
	drug (excipients).	
Kidney stones (Nephrolithiasis)	Colecalciferol use is contraindicated in patients suffering from kidney stones (nephrolithiasis).	Yes. Vitamin D should be used with caution in patients with reduced kidney function and the effect on calcium and phosphate levels should be monitored. In patients with severely reduced kidney function, vitamin D in the form of colecalciferol is not metabolised normally and other forms of vitamin D should be used.
Abnormal accumulation of calcium in the kidney (Nephrocalcinosis)	Abnormal high levels of calcium in urine (hypercalciuria) can lead to abnormal accumulation of calcium in the kidney (nephrocalcinosis).	Yes. Colecalciferol must not be used in patients suffering from abnormal accumulation of calcium in the kidney (nephrocalcinosis).

Important potential risks:

Risk	What is known

Excessive dosage (Overdose)	The most serious consequence of acute or chronic excessive dosage (overdose) is abnormally high levels of calcium in the blood (hypercalcaemia). Other vitamin D toxicity symptoms may include nausea, vomiting, excessive production of urine (polyuria), eating disorder characterized by weight loss (anorexia), weakness, apathy, thirst and constipation. Chronic excessive dosages (overdoses) can lead to abnormal accumulation of calcium in vessels and organs (vascular and organ calcification) as a result of abnormally high levels of calcium in the blood (hypercalcaemia). Treatment should consist in stopping all intake of vitamin D and rehydration.

Missing information:

None

VI.2.5 Summary of additional risk minimisation measures by safety concern

The Summary of Product Characteristics (SmPC) of Colecalciferol 800 IU, 3,200 IU and 20,000 IU Capsules, Soft 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 package leaflet (PL). All these risk minimisation measures are given in SmPCs and PLs of Colecalciferol 800 IU, 3,200 IU and 20,000 Capsules, Soft.

These medicinal products have no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No post authorisation study is planned for this product.

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

Version	Date of sign-off	Safety Concerns	Comment

01	08-Aug-2014	**Important identified risks:** • Metabolism and nutrition disorders • Skin and subcutaneous disorders • Sarcoidosis • Kidney disorders • Cardiovascular disease **Important potential risks:** • Use during pregnancy • Use in lactating women **Missing information:** • None	Safety concerns submitted with initial submission for new MA (procedure number: UK/H/5835/01/DC).
02	01-Feb-2015	**Important identified risks:** • Hypercalcaemia • Hypercalciuria • Use in patients with conditions that modify vitamin D metabolism, including sarcoidosis • Interaction with thiazide diuretics • Interaction with cardiac	The list of safety concerns was updated following request by RMS- UK during Day 70 comments and approved at the end of UK/H/5835/01/DC procedure).

		glycosides • Hypersensitivity • Use in patients with hypervitaminosis D • Use in patients with renal impairment (including nephrolithiasis or nephrocalcinosis) **Important potential risks:** • Use during pregnancy and lactation • Overdose **Missing information:** • None	
03	10-Apr-2017	**Important identified risks:** • Hypercalcaemia • Hypercalciuria • Hypersensitivity • Nephrolithiasis • Nephrocalcinosis)	MAH filed a type II variation in order to implement changes in the summary of safety concerns and update information in SPC sections: 4.2, 4.3, 4.4, 4.6, 4.8 and 5.3 (procedure number: UK/H/5835/01/E/01).

		Important potential risks: • Overdose **Missing information:** None	
04	07/12/2017	**Important identified risks:** • Hypercalcaemia • Hypercalciuria • Hypersensitivity • Nephrolithiasis • Nephrocalcinosis) **Important potential risks:** • Overdose **Missing information:** None	No changes in the list of safety concerns. This new version has been prepared in order to include two additional strengths: Colecalciferol 3,200 IU and 20,000 IU. This version is submitted within procedure number: UK/H/5835/002-003/DC (line-extension)