III.1. Elements for a Public Summary

III.1.1. Overview of disease epidemiology

Vitamin D insufficiency is widespread and is present in every region of the world. In elderly populations in Europe, vitamin D insufficiency is more common in the south than in the north, and more likely in women than men. It may be present in as many as half of women suffering from osteoporosis. A number of factors influence the ability to produce vitamin D in the skin and may contribute to the risk of low levels of vitamin D. These factors include variation in sun exposure due to latitude, season, time of day, air pollution, clothing, sunscreen use and skin pigmentation, as well as age, obesity and the incidence of several chronic illnesses. Approximately 30% of all postmenopausal women have osteoporosis in Europe. At least 40% of these women and 15-30% of men will suffer one or more fractures due to osteoporosis in their remaining lifetime. The most common fractures associated with osteoporosis occur at the hip, spine and wrist. Of particular concern are vertebral (spinal) and hip fractures. Vertebral fractures can result in serious consequences, including intense back pain and deformity (sometimes called Dowager's Hump). A hip fracture often requires surgery and may result in loss of independence or death.

III.1.2. Summary of treatment benefits

Treatment with vitamin D (colecalciferol) cures osteomalacia (softening of bones) in adults and rickets in children. Combined calcium and vitamin D may reduce the risk of spinal fractures in patients with osteoporosis and, vitamin D plus calcium decrease the risk of hip fractures particularly among institutionalised persons. Vitamin D in combination with calcium may improve balance and muscle function, and reduce the risk of falls in elderly people.

III.1.3. Unknowns relating to treatment benefits

It seems likely that vitamin D substitution improves muscle function and physical performance, particularly in elderly individuals, and among those with severe vitamin D deficiency. However, little is known if vitamin D substitution can provide additional benefits on physical performance among younger people or people with adequate vitamin D levels.

The active form of vitamin D (calcitriol) is known to regulate more than a hundred genes in many different tissues. Calcitriol is known to modulate the immune system. The consequences of this in relation to autoimmune disease, cancer and cardiovascular function etc are not yet fully understood.

III.1.4. Summary of safety concerns

Important identified risks		
Risk	What is known	Preventability
Hypercalcaemia (increased levels of calcium in the blood), hypercalciuria (increased levels of calcium in the urine).	Vitamin D increases the gastrointestinal uptake of calcium. Vitamin D should therefore be used with caution in patients with conditions known to have an increased risk of metabolism of vitamin D into its active form. Vitamin D should be used with caution in patients with impairment of renal function.	Follow the recommendation provided in the product information which states that Vitamin D_3 should not be used in patients with kidney problems or a history of kidney stones.
Allergic (hypersensitive) reactions	The frequency of hypersensitivity reactions	Follow the recommendations given in the product information

Important identified risks		
Risk	What is known	Preventability
	cannot be estimated.	that colecalciferol should not be used by patients allergic to colecalciferol or any of the other ingredients of Divisun/Colecalciferol Meda.

Important potential risks	
Risk	What is known
Vitamin D toxicity	Excessive dosing over long periods of time may constitute a risk. In man toxicity has not been reported at doses lower than 10.000 IU per day. With the maximum daily dosage 4000 IU there is a great safety margin to doses with a potential to cause toxicity.
Missing information	Use in children has not been studied. Use in patients with severe renal impairment has not been studied.

III.1.5. Summary of additional risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SPC) 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 package leaflet (PL). The measures in these documents are known as routine risk minimisation measures. The Summary of Product Characteristics and the Patient Information Leaflet can be found on the competent authorities´web pages. This medicine has no additional risk minimisation measures.

Not applicable. No additional risk minimisation measures are planned.

III.1.6. Planned post authorisation development plan

No post authorization studies are planned.

Studies which are a condition of the marketing authorisation

There are no studies that constitute conditions of the marketing authorisation.

III.1.7. Summary of changes to the Risk Management Plan over time

Table 1: Major changes to the Risk Management Plan over time			
Version	Date	Safety Concerns	Comment
1.0	2014-04-11		RMP requested by MPA (RMS, SE) during assessment of MA for Colecalciferol Meda 800 IU tablet.
2.0	2014-05-16	MPA (RMS, SE) requested adding hypersensitivity as an	

Table 1: Major changes to the Risk Management Plan over time			
Version	Date	Safety Concerns	Comment
		identified risk and that use in children and use in patients with severe renal impairment currently constitute missing information.	
2.1	2014-05-26		Further revision requested by MPA (RMS, SE).
3.0	2014-09-11		Higher strengths 1000 IU, 2000 IU and 4000 IU were included. RMP was submitted with the line extension applications.
3.1	2015-05-04		With the day 70 questions in the assessment of the line extension applications RMS requested that the RMP be updated with the revised indications and posology.
3.2	2015-08-24		With the day 120 DAR and day 145 comments in the line extension application procedure RMS requested update of the posology and CMS NL of the indications. RMS requested a corresponding update of the RMP.
3.3	2015-10-12		MA application for Divisun 2000 IU withdrawn in Spain Aug 2015 for marketing reasons. With day 180 RMS and day 195 CMS comments in the line extension application procedures CMS NL requested a rewording of the indication for 1000 IU. RMS requested a corresponding update of the RMP.