Part VI: Summary of the risk management plan

Summary of risk management plan for DIBASE, DIBASA and DIBASELAB (cholecalciferol)

This is a summary of the risk management plan (RMP) for DIBASE. The RMP details important risks of DIBASE, how these risks can be minimised, and how more information will be obtained about DIBASE's risks and uncertainties (missing information).

DIBASE's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how DIBASE should be used.

Important new concerns or changes to the current ones will be included in updates of DIBASE's RMP.

I. The medicine and what it is used for

DIBASE is authorised for the prevention and treatment of vitamin D deficiency (see SmPC for the full indication). It contains cholecalciferol (Vitamin D3) as the active substance and it is given by oral or intramuscular administration.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of DIBASE, together with measures to minimise such risks and the proposed studies for learning more about DIBASE's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of DIBASE are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of DIBASE. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	- Hypersensitivity reaction - Confusional state - Use in renal failure - Hypercalcaemia (including nephrolitiasis and nephrocalcinosis) - Hypercalciuria (including nephrolitiasis and nephrocalcinosis) - Overdose (including patient with sarcoidosis and overdose for concomitant administration of medicinal products or integrators which contain Vitamin D) - Drug interaction with Thiazide diuretics; - Drug interaction with Digitalis-containing medications
Important potential risks	- Suspected drug interaction between Cholecalciferol – Warfarin: INR alteration - Potential for medication errors - Hypercalcaemia foetal and neonatal during use in pregnancy and lactation. - Interaction between actinomiycina and imidazole antifungal agents.
Missing information	None

II.B Summary of important risks

Important Identified Risk
Hypersensitivity reaction

Evidence for linking the risk to the medicine	Scientific/Medical literature; Drugdex, 2007; DIBASE/XARENEL SmPC; Module 2.5 Case reports collected in RNF during post marketing phase.
Risk factors and risk groups	The following categories of patients are at higher risk to develop hypersensitivity reactions to vitamin D3: • infants/children, which may be hypersensitive to even small doses with resultant hypercalcemia (Drugdex, 2007); • patient affected by sarcoidosis/other granulomatous disease, which are clinical conditions that are potential for enhanced sensitivity to vitamin D (Drugdex, 2007). Cholecalciferol should be administered with caution in these patients. A very serious allergic reaction to this drug is rare.
Risk minimisation measures	*Routine risk communication:* – Contraindications in section 4.3 of SmPC – Listed in section 4.8 of SmPC *Other routine risk minimisation measures beyond the Product Information:* Prescription only medicine

Important Identified Risk Confusional state	
Evidence for linking the risk to the medicine	FDA AERS Reports; FDA Report 2017; DIBASE/XARENEL SmPC; Case reports collected in RNF during post marketing phase.
Risk factors and risk groups	Confusional state is found among people who take Vitamin D, especially for the following classes of patients: – female, – more than 60 years old, – taking vitamin D from less than 1 month, – taking also Calcium as medication, suffering from multiple sclerosis (FDA report, 2017).
Risk minimisation measures	*Routine risk communication:* – Listed in section 4.8 of SmPC *Other routine risk minimisation measures beyond the Product Information:* Prescription only medicine

Important Identified Risk Use in renal failure	
Evidence for linking the risk to the medicine	FDA AERS Reports; FDA Report 2017; DIBASE/XARENEL SmPC; Case reports collected in RNF during post marketing phase.
Risk factors and risk groups	Vitamin D deficiency has a very high prevalence in subjects suffering from renal insufficiency in which to the traditional causes of deficit (poor exposure to sunlight, reduced dietary intake) are added those proper to the pathology (reduction of skin synthesis, loss of renal mass and reduction of GFR)
Risk minimisation measures	*Routine risk communication:* – The following indication for patients with renal failure is proposed in section 4.2. "Dose and mode of administration" and section 4.4 "Special warnings and precautions for use" of SmPCs Dibase limited to capsules 2.000 I.U. and 6.000 I.U. : "In chronic kidney failure , vitamin D in the form of colecalciferol is not normally metabolised. Therefore, the nephropathic patients needs to a special management to the evaluation of the most appropriate dose of vitamin D3 that, depending on the severity of the insufficiency and condition of the patient, may require partial or total replacement with other forms of vitamin D". - "Patients suffering from chronic renal insufficiency have an altered mineral and vitamin D metabolism in the form of colecalciferol; therefore, treatment with cholecalciferol may not be completely sufficient to maintain calcium and phosphate homeostasis and parathyroid hormone control. The nephropathic patient needs specialized management for the assessment of the most suitable vitamin D3 dosage, which, depending on the severity of the renal insufficiency and the patient's condition, may require the integration with other forms of vitamin D (see section 4.3) ." – Contraindications in section 4.3 of SmPC – Warning in section 4.4 of SmPC *Routine risk minimisation activities recommending specific clinical measures to address the risk:*

	– Recommendation for calcium and phosphate homeostasis monitoring in section 4.4 of SmPC *Other routine risk minimisation measures beyond the Product Information:* Prescription only medicine

Important Identified Risk Hypercalcaemia (including nephrolithiasis and nephrocalcinosis)	
Evidence for linking the risk to the medicine	Scientific/Medical literature; AHFS, 2007; DIBASE/XARENEL SmPC; Module 2,5; Case reports collected in RNF during post marketing phase.
Risk factors and risk groups	Acute or chronic administration of excessive doses of vitamin D analogs (including situations such as overdose and medication error) or enhanced responsiveness to physiologic amounts of cholecalciferol, may lead to hypervitaminosis D manifested by hypercalcemia (AHFS, 2007). Hypervitaminosis D is reversible upon discontinuation of treatment unless renal damage is severe (Drugdex, 2007). Vitamin D-associated hypercalcemia is a reported complication of acute or long-term administration of cholecalciferol: hypercalcemia is solely related to circulating levels of calcifediol. Initial symptoms related to hypercalcemia include diarrhoea, constipation (primarily in children/adolescents), nausea, vomiting, anorexia, polyuria, polydipsia, nocturia, weakness/fatigue, headache, and mental changes. More chronic manifestations include proteinuria and renal impairment; soft tissue calcification in kidneys (with nephrolithiasis and/or nephrocalcinosis), heart, vessels and skin; hypertension and possibly arrhythmias; worsening of gastrointestinal symptoms; pancreatitis, and psychotic symptomatology. Renal failure and death may occur after prolonged use of high doses (Drugdex, 2007).
Risk minimisation measures	*Routine risk communication:* – Proposed wording in section 4.2 of SmPCs Dibase capsules 2.000 I.U. and 6.000 I.U.: "In elderly patients already in treatment with cardiac glycosides or diuretics, it is important to monitor serum calcium. In case of hypercalcemia or renal failure, reduce the dosage or discontinue the treatment"

	– Contraindications in section 4.3 of SmPC – Warning in section 4.4 of SmPC – Listed in section 4.8 of SmPC – Warning in section 4.9 of SmPC – Warning in section 5.3 of SmPC *Routine risk minimisation activities recommending specific clinical measures to address the risk:* – Recommendation for monitor serum calcium levels and urinary calcium for elderly patients already being treated with cardiac glycosides or diuretics in section 4.4 of SmPC – Recommendation for monitoring the level of calcium in serum and urine in patients with sarcoidosis in section 4.4 of SmPC *Other routine risk minimisation measures beyond the Product Information:* Prescription only medicine

Important Identified Risk Hypercalciuria (including nephrolithiasis and nephrocalcinosis)	
Evidence for linking the risk to the medicine	Scientific/Medical literature; AHFS, 2007; DIBASE/XARENEL SmPC; Case reports collected in RNF during post marketing phase. Module 2.5
Risk factors and risk groups	Acute or chronic administration of excessive doses of vitamin D analogs (including situations such as overdose and medication error) or enhanced responsiveness to physiologic amounts of cholecalciferol, may lead to hypervitaminosis D manifested by hypercalciuria (AHFS, 2007). Hypervitaminosis D is reversible upon discontinuation of treatment unless renal damage is severe (Drugdex, 2007). Vitamin D-associated hypercalciuria is a reported complication of acute or long-term administration of cholecalciferol.
Risk minimisation measures	*Routine risk communication:* – Proposed wording in section 4.2 of SmPCs Dibase capsules 2.000 I.U. and 6.000 I.U.: "In elderly patients already in treatment with cardiac glycosides or diuretics, it is important to monitor serum calcium. In case of hypercalcemia or renal

	failure, reduce the dosage or discontinue the treatment" – Contraindications in section 4.3 of SmPC – Warning in section 4.4 of SmPC – Listed in section 4.8 of SmPC – Warning in section 4.9 of SmPC – Warning in section 5.3 of SmPC *Routine risk minimisation activities recommending specific clinical measures to address the risk:* – Recommendation for monitor serum calcium levels and urinary calcium for elderly patients already being treated with cardiac glycosides or diuretics in section 4.4 of SmPC – Recommendation for monitoring the level of calcium in serum and urine in patients with sarcoidosis in section 4.4 of SmPC *Other routine risk minimisation measures beyond the Product Information:* Prescription only medicine

Important Identified Risk Overdose (including patients with sarcoidosis and overdose for concomitant administration of medicinal products or integrators which contain Vitamin D)	
Evidence for linking the risk to the medicine	Scientific/Medical literature; AHFS, 2007; DIBASE/XARENEL SmPC; Module 2.5; Case reports collected in RNF during post marketing phase.
Risk factors and risk groups	There is a potential for harm from accidental overdose for the medicinal products DIBASE/XARENEL that has been observed in the following circumstances: • Long term therapy at high dosages (first observed during the pre-clinical phase); • Concomitant administration of other medicinal products or integrators which contain vitamin D; • Patient affected by sarcoidosis or hyperparathyroidism.
Risk minimisation measures	*Routine risk communication:* – Warning in section 4.4 of SmPC

	– Warning in section 4.9 of SmPC *Routine risk minimisation activities recommending specific clinical measures to address the risk:* – Recommendation for monitor the level of serum 25-hydroxy-cholecalciferol in section 4.4 of SmPC *Other routine risk minimisation measures beyond the Product Information:* Prescription only medicine

Important Identified Risk Drug interaction with Thiazide diuretics	
Evidence for linking the risk to the medicine	Scientific/Medical literature; DIBASE/XARENEL SmPC; Module 2.5
Risk factors and risk groups	Patients (especially elderly) under treatment with thiazide diuretics.
Risk minimisation measures	*Routine risk communication:* – Proposed wording in section 4.2 of SmPCs Dibase/Xarenel capsules 2.000 I.U. and 6.000 I.U.: "In elderly patients already in treatment with cardiac glycosides or diuretics, it is important to monitor serum calcium. In case of hypercalcemia or renal failure, reduce the dosage or discontinue the treatment" – Warning in section 4.4 of SmPC – Warning in section 4.5 of SmPC *Routine risk minimisation activities recommending specific clinical measures to address the risk:* – Recommendation for monitor serum calcium levels and urinary calcium for elderly patients already being treated with cardiac glycosides or diuretics in section 4.4 of SmPC *Other routine risk minimisation measures beyond the Product Information:* Prescription only medicine

Important Identified Risk Drug interaction with Digitalis-containing medications	
Evidence for linking the risk to the medicine	Scientific/Medical literature; DIBASE/XARENEL proposed SmPC; Module 2.5
Risk factors and risk groups	Patients (especially elderly) under treatment with cardiac glycosides.
Risk minimisation measures	*Routine risk communication:* – Proposed wording in section 4.2 of SmPCs Dibase/Xarenel capsules 2.000 I.U. and 6.000 I.U.: "In elderly patients already in treatment with cardiac glycosides or diuretics, it is important to monitor serum calcium. In case of hypercalcemia or renal failure, reduce the dosage or discontinue the treatment" – Warning in section 4.4 of SmPC – Warning in section 4.5 of SmPC *Routine risk minimisation activities recommending specific clinical measures to address the risk:* – Recommendation for monitor serum calcium levels and urinary calcium for elderly patients already being treated with cardiac glycosides or diuretics in section 4.4 of SmPC – Recommendation for close medical supervision and, if necessary, electrocardiographic monitoring and calcium serum concentration checking in section 4.5 of SmPC *Other routine risk minimisation measures beyond the Product Information:* Prescription only medicine

Important Potential Risk Suspect drug interaction between Cholecalciferol and Warfarin: INR alteration	
Evidence for linking the risk to the medicine	Scientific/Medical literature; DIBASE/XARENEL SmPC; Case reports collected in RNF during post marketing phase.
Risk factors and risk groups	Patients receiving warfarin.
Risk minimisation measures	*Routine risk communication:*

	– Warning in section 4.5 of SmPC *Other routine risk minimisation measures beyond the Product Information:* Close monitoring of similar events will be undertaken during the routine pharmacovigilance activities Prescription only medicine

Important Potential Risk Potential for medication error	
Evidence for linking the risk to the medicine	Scientific/Medical literature; AHFS, 2007; DIBASE/XARENEL SmPC; Case reports collected in RNF during post marketing phase.
Risk factors and risk groups	Theoretically, all patients are potentially at risk for medication error.
Risk minimisation measures	Detailed Information such as Name of the medicinal product, Qualitative and quantitative composition, Pharmaceutical form, Posology and method of administration are clearly reported in both SmPC and PIL. *Other routine risk minimisation measures beyond the Product Information:* Prescription only medicine

Important Potential Risk Hypercalcaemia foetal and neonatal during use in pregnancy and lactation.	
Evidence for linking the risk to the medicine	Clinical Overview (Module 2.5) Hollis, 2007 Rey, 2016
Risk factors and risk groups	Patients with Vitamin D supplementation during pregnancy and lactation.
Risk minimisation measures	The following warning is reported in section 4.9 of SmPC: An overdose during the first 6 months of pregnancy may have toxic effects on the foetus: there is a correlation between excess intake or extreme maternal sensitivity to vitamin D during pregnancy and the delayed mental and physical development of the child, supravalvular aortic stenosis and retinopathy. Maternal hypercalcaemia can also lead to the suppression of parathyroid function in infants resulting in hypocalcaemia, tetany and convulsions.

Important Potential Risk Interaction between actinomiycina and imidazole antifungal agents	
Evidence for linking the risk to the medicine	Loose, 1983 Tanaka, 1971 Feldman, 1986 Allan R, 1986
Risk factors and risk groups	Patient in treatment with antifungal agents.
Risk minimisation measures	The following statement will be proposed in section 4.5 of SmPC: The cytotoxic agent actinomycin and imidazole antifungal agents interfere with vitamin D activity by inhibiting the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D by the kidney enzyme, 25-hydroxyvitamin D-1-hydroxylase.

II.*C Post-authorisation development plan*

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of DIBASE.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for DIBASE.