SUMMARY OF RISK MANAGEMENT PLAN

For

ALFACALCIDOL

Active substance(s) (INN or common name):	Alfacalcidol
Pharmaco-therapeutic group (ATC Code):	Vitamin D and analogues (A11CC03)
Name of Marketing Authorisation Holder or Applicant:	Strides Arcolab International Ltd.
Number of medicinal products to which this RMP refers:	3
Product(s) concerned (brand name(s)):	Alfacalcidol Strides 0.25microgram Capsules Alfacalcidol Strides 0.5microgram Capsules Alfacalcidol Strides 1.0microgram Capsules

Data lock point for this RMP	10-Apr-2014
Version number	3
Date of final sign off	24.04.2014

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Renal osteodystrophy (ROD)

Renal osteodystrophy (changes in bone caused by kidney failure), which is most evident in patients on kidney replacement therapy, usually begins when the kidney function starts to deteriorate. The spectrum of skeletal abnormalities seen in ROD is classified according to the state of bone turnover. In the past two decades, the frequency of high turnover ROD has decreased while low bone turnover has become increasingly recognized. Secondary hyperparathyroidism (excessive secretion of parathyroid hormone by the parathyroid glands in response to low blood calcium levels) represents a common disorder in patients with chronic kidney disease; it develops as a result of hyperphosphatemia (elevated level of phosphate in the blood), hypocalcaemia (low calcium levels in the blood) and impaired synthesis of renal vitamin D with reduction in serum calcitriol levels. Treatment measures include control of phosphorus retention and prevent hyperphosphatemia, maintaining serum calcium concentrations within the normal range and prevent excess parathormone secretion.

Hyperparathyroidism

Primary hyperparathyroidism (PHPT) (excessive secretion of parathyroid hormone by the parathyroid glands) is one of the most common endocrine diseases. Its clinical presentation has dramatically changed in the last 40 years, and now the disease typically affects elderly women and is characterized by mild hypocalcaemia (low calcium levels in the blood) and few traditional classic (bone and kidney) manifestations. Irradiation of the neck and upper chest for benign diseases is a well-known risk factor for the development of PHPT. Because this therapeutic procedure is no longer used, the number of radiation-associated cases of PHPT is expected to progressively decline in the future. Other environmental, nutritional, or medical treatment factors might influence the incidence of the disease, but the overall effect is unlikely to be relevant.

Hypoparathyroidism

Hypoparathyroidism (decreased function of the parathyroid glands with underproduction of parathyroid hormone) is a rare endocrine disorder whose incidence and prevalence have not been well defined. The diagnosis-based prevalence approach estimated 58,793 patients with chronic

hypoparathyroidism in the United States. The surgical-based incidence approach yielded 117,342 relevant surgeries resulting in 8901 cases over 12 months. Overall, 7.6% of surgeries resulted in hypoparathyroidism (75% transient, 25% chronic). The frequency of chronic hypoparathyroidism among patients included in the surgical database was estimated to be 58,625. The physician survey found that 75% of cases treated over the past 12 months were reported due to surgery and, 26% resulted in transient hypoparathyroidism and 5% progressed to a chronic state.

Neonatal hypocalcaemia

Hypocalcaemia occurs in as many as 30% of infants with very low birth weight (< 1500 g) and in as many as 89% of infants whose gestational age at birth was less than 32 weeks. A high incidence is also reported in infants of mothers with diabetes mellitus and in infants with extreme low concentration of oxygen in the body. Late-onset hypocalcaemia is more common in infants in developing countries where babies are fed cow's milk or formulas containing high amounts of phosphate than in countries where infants are fed human milk or formulas containing low amounts of phosphate. Most cases of early neonatal hypocalcaemia resolve within 48-72 hours without any clinically significant sequelae. Late neonatal hypocalcaemia secondary to exogenous phosphate load and magnesium deficiency responds well to phosphate restriction and magnesium repletion. When caused by hypoparathyroidism, hypocalcaemia requires continued therapy with vitamin D metabolites and calcium salts.

Nutritional and malabsorptive rickets and osteomalacia

Except in pediatric patients with chronic malabsorption syndromes or end-stage renal disease, nearly all cases of rickets occur in breastfed infants who have dark skin and receive no vitamin D supplementation. The incidence of rickets in Europe is similar to that in the United States. In sunny areas, rickets may occur when infants are bundled in clothing and are not exposed to sunlight. In some parts of Africa, deficiency of calcium, phosphorus, or both in the diet may also lead to rickets, especially in societies where corn is predominant in the diet. The frequency of rickets has been increasing internationally. Possible reasons include recommendations for children to wear sunscreen while outdoors and a tendency for children to spend more time indoors.

Pseudo-deficiency (D-dependent) rickets and osteomalacia

Pseudovitamin D deficiency rickets (PDDR), also called vitamin D-dependent rickets type I, is a form of hereditary rickets. It presents with low muscle tone, weakness, and growth failure, sometimes accompanied by seizures. Biochemical features include hypocalcaemia, elevated serum PTH levels, presence of amino acids in the urine together with typical radiological findings of rickets. Patients with PDDR have low circulating levels of 1α,25-dihydroxyvitamin D [1α,25-(OH)2D] with normal to elevated levels of 25-hydroxyvitamin D (25OHD). Massive doses of vitamin D or 25OHD3 and physiological doses of 1α-(OH)D3 or 1α,25-(OH)2D3 are necessary for cure of the rickets. Although PDDR is a rare disease, patients with mild clinical symptoms have been reported. Moreover, the serum1α,25-(OH)2D levels in the untreated state vary with some patients reported to have normal serum 1α,25-(OH)2D levels. Such mild clinical manifestations of the disease are suspected to be caused by reduced 1α-hydroxylase activity.

Hypophosphataemic vitamin D resistant rickets and osteomalacia

Hypophosphataemic rickets/osteomalacia (HRO) (form of rickets that is characterized by low serum phosphate levels) is a rare disorder of phosphate metabolism characterized by low serum phosphate levels leading to impaired mineralization of bone matrix. HRO is found to be common in females (70.5%) with positive family history observed in 35.3% patients. Young patients present with disproportionate short stature and classical features of rickets whereas adults present with bone pains, muscle disease and disorder of bone attachments. Biochemical abnormalities include hypophosphataemia, normal or low serum calcium, normal or high normal alkaline phosphatase, low or inappropriately normal serum 1, 25 dihydroxy vitamin D, normal serum intact parathormone concentration and low maximum tubular reabsorptive capacity for phosphorus/glomerular filtration rate. Mainstay of therapy includes oral phosphate with active vitamin D.

VI.2.2 Summary of treatment benefits

Alfacalcidol is a type of vitamin D. Vitamin D controls the levels of calcium and phosphate in body. . Body needs both of these substances for healthy bones and teeth. Alfacalcidol works by increasing the amount of vitamin D in body. This means the levels of calcium and phosphate in body will increase too.

Alfacalcidol Strides is used to treat diseases where the amount of calcium in body needs changing. It is used to treat:

• Changes in bone caused by kidney failure (osteodystrophy).

• Changes to parathyroid glands. These are small glands found in neck. They make a substance called the parathyroid hormone. This changes the amount of calcium in body.

- The glands may make the amount of calcium in blood too high. (hyperparathyroidism).
- The glands may make the amount of calcium in blood too low (hypoparathyroidism).

• Low levels of calcium in the blood of newborn babies (hypocalcaemia).

• Softening and deformity of the bones due to lack of calcium (rickets or osteomalacia).

Considering similarity to the currently marketed product, Strides Arcolab International Ltd has not conducted any studies for alfacalcidol on expected benefit.

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
High levels of calcium in blood (Hypercalcaemia)	Patients taking alfacalcidol with a cardiac glycoside, such as digoxin (medicines are used to treat problems with heart) may get too much calcium in blood which may cause an abnormal heart beat. Patients taking alfacalcidol with Thiazide diuretics, often called "water pills" (for	Yes Patients are advised not to take alfacalcidol capsules if they have hypercalcaemia (high levels of calcium in blood) or a condition called

Risk	What is known	Preventability
	increasing the amount of water (urine) that body makes) may also get too much calcium in blood. The patient may develop signs such as an increased need to pass urine than usual, increased thirst, dry mouth or a metallic taste in mouth, weakness or pain in muscles or bones and sick feeling or constipation which may be due to too much calcium levels in the blood. The patient may also have kidney stones which may cause a sharp spasm in one side of lower back. Too much calcium in blood is the side effects that most people get with alfacalcidol.	calcification (high levels of calcium in body tissues). Patients are advised to regularly check the level of calcium in blood while taking alfacalcidol capsules.
High levels of phosphate in blood (Hyperphosphataemia)	The patient may develop signs such as an increased need to pass urine than usual, increased thirst, dry mouth or a metallic taste in mouth, weakness or pain in muscles or bones and sick feeling or constipation which may be due to too much phosphate levels in the blood. The doctor may prescribe a medicine, a phosphate binding agent, to take along with alfacalcidol which helps to keep the right amount of phosphate in	Yes Patients are advised to regularly check the level of phosphate in blood while taking alfacalcidol capsules.

Risk	What is known	Preventability
	blood.	
Skin problems (Skin reactions)	The patient may develop a severe skin rash, itching and hives (urticaria) while receiving alfacalcidol.	Yes Patients are advised to tell their doctor if they develop itching or redness while taking alfacalcidol.
Acute kidney failure	The patients may develop following signs which are indicative of kidney problems: • Needing to pass water (urine) less often. • Swelling of any parts of body. • Fever with a pain in kidney side.	Yes Patients are advised to tell their doctor if they have any of the signs mentioned.

Important potential risks

Risk	What is known
Abnormal heart beat due to interaction with medicines used to treat heart problems (Arrhythmia due to interaction with cardiac glycosides or digatalis)	Patients taking alfacalcidol with a cardiac glycoside, such as digoxin (medicines are used to treat problems with heart) may get too much calcium in blood which may cause an abnormal heart beat.
Formation of calcium deposits (Calcinosis)	Patients are advised to not take Alfacalcidol Strides if they know that they have a condition called calcification. This means they have high levels of calcium in their body tissues. Patients are advised to tell doctor before taking Alfacalcidol Strides if they have any problems with kidneys. This includes kidney stones. Kidney stones may form. Kidney stones may cause a sharp spasm in one side of lower back.

Missing information

Risk	What is known
Use in pregnancy	Patients are advised to ask doctor or pharmacist for advice before taking alfacalcidol capsules, as there is no data available on the use of alfacalcidol in pregnant women.
Use in breast feeding females (during lactation)	As there is no data available on the use of alfacalcidolin breast feeding females, it should not be taken by breastfeeding females.

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 package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Alfacalcidol can be found in the Alfacalcidol's EPAR page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No studies planned.

VI.2.7 Summary of changes to the risk management plan over time

Version	Date	Safety Concerns	Comment
3.0		Following risks were added: *Important Identified Risk:* • Acute kidney failure *Important Potential Risk:* • Calcinosis	Part VI.2.1 Overview of disease epidemiology and Part VI.2.2 Summary of treatment benefits have been revised.
2.0	23-Dec-2013	Following risks were added: *Important Identified Risks:* • Hypercalcaemia • Hyperphosphataemia • Skin reactions *Important Potential Risk:* • Arrhythmia due to interaction with cardiac glycosides or digatalis *Missing Information:* • Use in pregnancy • Use during lactation	RMP template updated as per "Guidance on format of the risk management plan (RMP) in the EU for Generics". EMA/465933/2013 Rev.1 Dated: 25 July 2013.