Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

COLECALCIFEROL

UK/W/041/pdWS/001

Rapporteur:	UK
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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section X
INN (or common name) of the active substance:	Colecalciferol
MAH:	See section X
Pharmaco-therapeutic group (ATC Code):	Vitamin D, Colecalciferol ATC code: A11CC05
Pharmaceutical forms and strengths:	Colecalciferol oral solution 20000IU/ml Colecalciferol tablets 500IU Colecalciferol tablets 1000IU

I. EXECUTIVE SUMMARY

On 13th February 2012, one MAH submitted paediatric data for colecalciferol, in accordance with Article 45 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use:
Colecalciferol is a drug with well established therapeutic and safety profile, evident from the available scientific literature.
The designation of vitamin D goes back to McCollum, who proved in 1922 that the antirachitic effect of fish liver oil is due to the presence of an active substance that is essential to bone metabolism. Vitamin D_2 was structurally elucidated in 1932 and vitamin D_3 in 1936. After detection of the vitamin D receptor (VDR) in numerous tissues, more diseases were discovered to be at least partly related to vitamin D deficiency.

The MAH's currently approved colecalciferol (X: tablets, Y: oral solution/oil) formulations in Germany are licensed for the following indications:

- Prophylaxis of rickets (including rickets in infants and in preterm newborn infants)
- Prophylaxis in recognisable risk of a vitamin D deficiency disease in otherwise healthy persons without absorption disorder
- Supportive treatment of osteoporosis
- Prophylaxis in recognizable risk of a vitamin D deficiency in malabsorption
- Treatment of rickets and osteomalacia
- Treatment of hypoparathyroidism

The MAH concluded that no changes in any of the SmPC sections are needed.
The rapporteur assessed the submitted data and available literature and issued a request for clarifications to the MAH. The rapporteur in the day 89 report has identified some issues regarding the currently approved paediatric indications and posology of colecalciferol, which were submitted by the MAH. In particular, there were safety concerns regarding the prophylactic dose for rickets in premature infants and the treatment dose of vitamin D deficiency for all paediatric subsets. Additionally, clarifications were requested as to whether osteoporosis and hypoparathyroidism were licensed paediatric indications.
Comments from MSs were also taken into consideration.
In September 2012 the MAH submitted their response to the issues raised by the rapporteur and MSs. The MAH proposed amended posology for the different paediatric subgroups. The rapporteur welcomes these changes as moving to a direction of safer doses for the different paediatric subgroups. However, the studies submitted by the MAH did not provide sufficient evidence for the proposed doses.
The rapporteur circulated the final assessment report in May 2013.

II. RECOMMENDATION

The studies submitted by the MAH did not provide sufficient evidence for the proposed posology. The rapporteur acknowledges that this is largely due to the sparse literature data and the great variability of the doses recommended by international guidelines. At present and as a result of this procedure, the rapporteur concludes that an update of the current recommended posology for colecalciferol in children, which would be applicable for all colecalciferol containing products across Europe, cannot be proposed.
The rapporteur however, proposes the rewording of indications in sections 4.1 of the SmPC and an addition under the special warnings and precaution section 4.4 (as shown below). These changes are applicable for single active substance colecalciferol products (not combination products) that are already licensed for the paediatric population. The proposed wording for

section 4.1 can be used as a guide as there is great variability of the approved indications in the currently nationally authorised products.
The rapporteur also proposes the addition of a contraindication related to the risk of allergic reactions (due to the excipient soybean oil in the MAH's product-tablets) in section 4.3 of the SmPC and in the PIL. It is noted that the last change is specific to the MAH's product and cannot be widely implemented in all colecalciferol containing products.

Summary of outcome

- ☐ No change
- ☒ Change
- ☐ New study data
- ☐ New safety information
- ☒ Paediatric information clarified: sections 4.1, 4.3, 4.4
- ☐ New indication

SmPC CHANGES

- **SmPC changes proposed for all colecalciferol products (single active substance, not for combination products) licensed in children**

The rapporteur proposes the following wording in the SmPC:

Section 4.1 Therapeutic indications

Oral liquid formulation
- **Prophylaxis of rickets and osteomalacia in children and adults**
- **Prophylaxis of rickets in preterm newborns**
- **Prophylaxis of vitamin D deficiency in children and adults with an identified risk**
- **Prophylaxis of vitamin D deficiency in children and adults with malabsorption**
- **Treatment of rickets and osteomalacia in children and adults**

Tablets:
- **Prophylaxis of rickets and osteomalacia in children and adults**
- **Prophylaxis of vitamin D deficiency in children and adults with an identified risk**
- **Prophylaxis of vitamin D deficiency in children and adults with malabsorption**
- **Treatment of rickets and osteomalacia in children and adults**

Section 4.4 Special warnings and precautions for use

During long-term treatment with a daily dose exceeding 1,000 IU vitamin D the serum calcium values must be monitored.

- **Specific changes for MAH's product (X tablets)**

The rapporteur proposes the following wording in the SmPC:

Section 4.3 Contraindications

X tablets 500/1000 should not be used if the patient is allergic to peanut or soya.

- **PIL changes proposed for MAH's product (tablets)**

The rapporteur proposes the following wording in the PIL:

X tablets contain soybean oil. If you are allergic to peanut or soya, do not use this medicinal product.

III. INTRODUCTION

On 13th February 2012, the MAH submitted paediatric data for colecalciferol, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use, including:

- Published information, quality, non-clinically and clinically relevant data for the paediatric assessment as included in the line listing
- A short critical expert overview including justification that SmPC/PL changes are not necessary
- Previously submitted PSURs

The MAH's recommendations for updating the product information

Based on the data submitted, the MAH proposed no changes to the currently approved product SmPC/PIL, stated that the submitted paediatric studies do not influence the benefit: risk for colecalciferol and that no consequential regulatory action is needed.

IV. SCIENTIFIC INFORMATION ON COLECALCIFEROL

Vitamin D is a general term for biologically active secosteroids. Medically relevant are vitamin D2 (ergocalciferol), vitamin D3 (colecalciferol), the pro-vitamins 7-dehydrocholesterol and ergosterol, as well as the biologically active metabolites calcidiol (precursor of vitamin D hormone: 25-hydroxycolecalciferol or 25(OH)D) and calcitriol (vitamin D hormone: 1,25-dihydroxycolecalciferol).
Vitamin D_3 is contained in various, but usually very small, amounts in food, mainly in animal products, e.g. fish or cod liver oil. Generally the normal human diet represents on average only a scarce source of vitamin D. Individual basic foods have been enriched in many countries with various amounts of vitamin D for many years.
Vitamin D holds a special status among the vitamins since, due to the body's own ability to synthesize this vitamin, it does not always necessarily need to be taken in with the nutrition. Healthy adults are able to cover their requirements by the body's own synthesis of the vitamin if sufficiently exposed to sunlight. 7-Dehydrocholesterol, which is formed from cholesterol, functions as a provitamin. Under the influence of ultraviolet (UV) radiation and warmth it is converted in the skin to vitamin D_3. At body temperature, 50% of it is converted within 28 hours and 80% within 4 days.

The most important active metabolite is 1,25-dihydroxycolecalciferol (1,25- $(OH)_2D$) or calcitriol. The cellular effect of calcitriol is mediated via binding to a nuclear receptor protein, the vitamin D receptor (VDR) (Reichel, 1998). Calcitriol regulates the transcription of specific genes. The primary sites of activity for the vitamin D hormones are the bone, intestine, kidney and parathyroid. Cashman (2007) grouped the pharmacological effects of vitamin D into two categories: The "classical" mainly affecting calcium homeostasis with specific target tissue (bone, intestine and kidney) and the "non classical" effects unrelated to calcium homeostasis. The physiological effects of vitamin D are known to a wide extent and have been presented in numerous review articles and textbooks (Bässler et al., 2002; Basu and Dickerson, 1996; Christakos et al., 2003; Deluca and Catorna 2004; Holick, 2000; Holick, 2005; Holick, 2007; Jakob, 1999; Lips, 2006; Machlin, 1991; Reichel, 1998).

Vitamin D has effects in:

1. Bones

1,25(OH)2D stimulates the differentiation and function of osteoblasts and promotes a paracrine signal of the osteoblasts for recruitment of osteoclasts. At the same time 1,25(OH)2D promotes the differentiation of osteoclast precursors and thus their recruitment as well as the fusion of preosteoclasts into mature, multinucleated osteoclasts. Mechanisms of bone formation as well as resorption and mobilization are thus stimulated. Unilaterally increased bone resorption is prevented, however, by the 1,25(OH)2D -mediated inhibition of parathyroid hormone secretion.

2. Small Intestine

In the small intestine 1,25(OH)2D promotes both rapid and delayed calcium uptake. Rapid uptake is induced via the membrane receptor, whie a delayed phase reaches its peak following the synthesis of 1,25(OH)2D -dependent genes such as calbindin, after approximately 6 hours, and can continue for days. 1,25(OH)2D induces the differentiation of enterocytes and modulates the expression of brush border enzymes. The passive and active transport of phosphate is also stimulated.

3. Kidneys

In the kidney 1,25(OH)2D stimulates the expression of 24-hydroxylase and thus promotes its own degradation. In addition, it inhibits the excretion of calcium and phosphate by promoting tubular resorption.

3. Parathyroid Glands

The production of parathyroid hormone in the parathyroids is inhibited directly by 1,25(OH)2D. Parathyroid hormone secretion is inhibited additionally by the increased calcium uptake in the small intestine under the influence of 1,25(OH)2D. Calcium and phosphate absorption in the intestine, release of calcium and phosphate as well as mineralization in bone, and resorption of calcium and phosphate in the kidney are promoted. Through these effects, which must be regarded in relationship with the effects of parathyroid hormone and calcitonin, the calcium and phosphate levels that are necessary for normal ossification are maintained.

4. Other Organs

Calcitriol plays not only a pivotal role in systemic calcium homeostasis but also in the intracellular calcium homeostasis of various tissues. Vitamin D receptors are present in more than 30 different tissues and calcitriol can be locally produced in tissues that possess vitamin D receptors (Bikle, 2007). The number of genes known to be regulated by the vitamin D hormone is still growing. Effects on other cell systems include modulation of the immune system and inhibition of proliferation of cancer cells (Christakos et al., 2003). Epidemiological data indicate that a low vitamin D status is correlated with disturbed muscle function, tuberculosis, rheumatoid arthritis, type 1 diabetes, multiple sclerosis, inflammatory bowel diseases, hypertension and specific types of cancer (Barthel and Scharla, 2003; Bikle, 2007; Zittermann, 2003). Skeletal muscles have a vitamin D receptor and may require vitamin D for maximum function (Holick, 2007). The protective effect of vitamin D on fracture risk has been attributed primarily to bone mineral density changes. However, vitamin D may also directly improve muscle strength, thereby reducing fracture risk through fall prevention (Bischoff-Ferrari et al., 2004).

IV.1 Information on the pharmaceutical formulation used in the clinical studies

Most of the clinical studies submitted by the MAH do not provide information on the specific formulation of vitamin D used. The MAH submitted one study where X (colecalciferol tablets) was used (Pohlandt et al, 1976). No studies conducted by the MAH were submitted as part of this work-sharing procedure.

The MAH provided the following information on the currently approved colecalciferol formulations:
X is a tablet to be disintegrated on a teaspoon in water or milk and given directly into the mouth, ideally during a meal.
Regarding the excipients in these formulations, Y oral solution contains medium chain triglycerides and X tablets contain soybean oil.

Comments:
The rapporteur considers that both formulations presented by the MAH are suitable for use in the paediatric population. It is though noted that there is no information available on the acceptability and palatability of these formulations in children.
The MAH should also provide information as to whether X 1000IU tablets are dividable and in case they are, whether breaking them into half leads to delivery of the recommended half doses (500IU) where appropriate by the given posology in the current SmPC.

IV.2 Non-clinical aspects

Preclinical studies have not been provided or summarized by the MAH.

Comments:

The MAH has not provided information on non-clinical studies relevant to the paediatric use of colecalciferol.
Some preclinical information is available in the currently approved SmPC in section 5.3 regarding vitamin D overdosage during pregnancy in animals and in humans:

"*5.3 Preclinical safety data*
Reproduction toxicity
Vitamin D overdosage during pregnancy induced malformations in rats, mice and rabbits (skeletal defects, microencephaly, cardac malformation). In humans, high doses during pregnancy have been related to the occurrence of aortic stenosis syndrome and idiopathic hypercalcaemia in newborns. Anomalies of the face, physical and mental retardation, strabismus, enamel defects, craniosynostosis, supervalvular aortic stenosis, pulmonary stenosis, inguinal hernia, cryptorchidism in male progeny, as well as premature development of secondary characteristics in female progeny. However, several case reports are available reporting that normal children were born to mothers with hypoparathyroidism receiving very high doses."
The rapporteur could not identify in the literature any new non clinical data relevant to the paediatric use of colecalciferol.

IV.3 Clinical aspects

1. Introduction

Vitamin D deficiency is common. In cohort studies conducted in France, the prevalence of vitamin D deficiency was 15-30% in a sample of the urban adult general population, 59% in healthy individuals aged 60-79 years, and 98% in older individuals living in institutions and receiving no vitamin D supplements (Souberbielle et al., 2006). In Germany vitamin D deficiency was diagnosed in 40% of women and 30% of men aged between 50 and 80 years. Surprisingly, a much higher incidence (up to 90% of women during wintertime) was observed in southern European countries (Greece, Italy and Spain), as a result of the much rarer vitamin D supplementation (Scharla, 1998).
Factors known to influence vitamin D metabolism include UV exposure, maternal vitamin D status, length of gestation, breastfeeding, age and body mass index. The amount of UV exposure available for the synthesis of vitamin D depends on many factors other than time spent outdoors. These factors include the amount of skin pigmentation, body mass, degree of latitude, season, the amount of cloud cover, the extent of air pollution, the amount of skin exposed, and the extent of UV protection, including clothing and sunscreens. UV radiation is only very slight in regions north of the 40th latitude, especially during the winter months. Lifestyles or cultural practices that decrease time spent outdoors or increase the amount of body surface area covered by clothing when outdoors further limit sunlight exposure. Dietary factors include intake of vitamin D rich food, vitamin D supplementation, and the association of obesity with lower vitamin D levels.
It must also be taken into consideration that certain conditions (disorders of exocrine pancreatic function, reduced bile secretion, hepatic or renal disease) or therapy with various drugs (e.g. anticonvulsants) might cause a disturbance of vitamin D metabolism.

Comments:

The MAH provided an overview of the factors affecting vitamin D status and commented on the prevalence of vitamin D deficiency.
The rapporteur would like to add that there is evidence of a resurgence of vitamin D deficiency in children in the UK (Absoud 2011). The National Diet and Nutrition Survey (NDNS, 1997-1998) for young people (4–18 years old) in Great Britain has already reported that approximately 8% of children had 25-hydroxy Vitamin D (25[OH]D) levels <25 nmol/ L.
Cases of rickets in infants, attributable to inadequate vitamin D intake and decreased exposure to sunlight, continue to be reported in the United States and other Western countries, particularly with exclusively breastfed infants and infants with darker skin pigmentation (Wagner 2008). Calikoglu (2003) identified factors likely involved in what appears to be a resurgence in rickets; these include decreased sun exposure for the population as a whole, increased numbers of women breastfeeding and a decrease in the number of physicians routinely prescribing vitamin D supplementation for breastfed infants.

2. Clinical overview

a. Pharmacokinetics

Colecalciferol is absorbed up to 80% in the small intestine by passive diffusion after incorporation into mixed micelles. Absorption depends on the presence of bile and is improved by simultaneous uptake of milk and fat. Holmberg et al. (1990) compared absorption of a

pharmacological dose of vitamin D from two different lipid vehicles, peanut oil and medium chain triglycerides in man and found that in the fasting state the long-chain fatty acids from peanut oil facilitated vitamin D absorption. When vitamin D was ingested together with food no difference between the two formulations was observed.
Vitamin D_3 is bound in serum to vitamin D-binding protein (DBP). In two hydroxylation steps both endogenously synthesized vitamin D_3 as well as vitamin D_3 taken in with the nutrition or with medication is converted first in the liver (position 25) and then in the kidney (position 1) to its biologically active form 1,25-Dihydroxycolecalciferol (1,25(OH)2D) (calcitriol). Hydroxylation is only impaired in late stages of hepatic insufficiency or advanced renal insufficiency. 1α-hydroxylation can also take place in the placenta, the macrophages, skin or human bone. Extrarenal production alone does not suffice, however, for an adequate supply of the organism (Jakob, 1999). The α-hydroxylase activity depends on various regulative factors and is stimulated by parathyroid hormone and inhibited by plasma phosphate, plasma calcium and serum 1,25(OH)2D (Krapf, 1994). In vitamin D deficiency still normal or even increased calcitriol levels are often found as a result of the compensatory increase in parathyroid hormone stimulation. In contrast, there is scarcely any regulative control of the 25(OH)D concentration, which is a good indicator of the organism's supply of vitamin D (Scharla and Ziegler, 1994). Vitamin D is stored in the fatty tissue and has therefore a long biological half-life. After high vitamin D doses the concentrations in the serum may be elevated for several months. The excretion of colecalciferol and its metabolites takes place predominantly via the bile and only to a slight extent via the urine. Vitamin D and its metabolites undergo extensive enterohepatic recirculation.
The MAH noted that no specific data on the pharmacokinetic properties of colecalciferol in paediatric patients are available in the literature.

b. Clinical efficacy

The MAH stated that they have not performed or sponsored any new clinical trials in paediatric patients.
The MAH has reviewed the use of vitamin D in a number of conditions. These conditions reflect the available evidence in current literature and are not confined to the approved indications included in the currently SmPC.

LICENSED INDICATIONS

Prevention and Therapy of Rickets and Osteomalacia

Vitamin D deficiency leads to inadequate absorption and renal reabsorption of calcium and phosphate. This results in decreased calcium and phosphate levels and increased alkaline phosphatase in serum. The organism responds to the decreased calcium level with hyperparathyroidism. Clinical manifestations of deficiency are characteristic signs and symptoms in the skeletal and nervous system. Rickets in children and osteomalacia in adults are the most described (Erben, 1997).
The earliest sign of rickets is craniotabes and the late closure of the fontanelle. This is detected mainly before 12 months of age as round unossified areas in the skull. Beading of the ribs is almost a constant sign after the age of 6 months, and is caused by the swollen cartilaginous ends of the ribs. The arms and legs become deformed when the child begins to crawl or sit upright. Severe vitamin D deficiency reduces the growth rate and causes microcephaly with reduction in brain growth. Eruption of teeth is delayed. Biochemically, the plasma calcium concentration is often near to normal. Similarly, the plasma inorganic phosphate concentration, though often lowered, may be normal (Basu and Dickerson, 1996). The therapeutic efficacy of

colecalciferol in the prophylaxis and therapy of rickets and osteomalacia is based on many decades of medical experience as well as on numerous controlled and uncontrolled clinical trials, and is clearly proven. Vitamin D_3 therapy of rickets and osteomalacia leads to an improvement of clinical symptoms, a normalization of laboratory values (vitamin D, PTH, calcium and phosphate) and an improvement of bone deformities (Basu and Dickerson, 1996; Kruse, 1995).
Rickets can still be observed among children and adolescents living in Europe, and a significant proportion of healthy children and adolescents presents serum 25-(OH)D values below the threshold indicating an insufficient vitamin D status (Garabédian et al., 2005).

Optimal serum levels of 25(OH)D
There is no consensus on optimal levels of vitamin D as measured in serum. Severe vitamin D deficiency is defined by most experts as a 25(OH)D level of less than 20ng/ml (50nmol/l) (Holick, 2007) and light deficiency (insufficiency) as a 25-hydroxyvitamin D level of less than 30ng/ml (75nmol/l). A recent consensus panel suggested that 25ng/ml (62.5nmol/l) may be the minimal acceptable 25(OH)D level in children (Souberbielle et al., 2006). The MAH states that optimal 25(OH)D levels in children and adults are defined as >40ng/ml (>100nmol/l).

The following literature data were included in the MAH's efficacy analysis:

Literature Reviews:
- **Calikoglu and Davenport: Prophylactic Vitamin D Supplementation (2003)**
- **Basu and Dickerson: Vitamins in Human Health and Disease. Vitamin D (1996)**

Clinical studies:

Pohlandt et al: Kontrollierte Studie zur rachitisprophylaktischen Wirkung von (Colecalciferol+sodium fluoride 1000) (1976) (Article in German)
The authors investigated the rachitic prophylactic effect of colecalciferol 1000IU and colecalciferol and sodium fluoride 1000IU/0.25mg in 118 healthy newborns. The subjects were randomized and group 1 (N=57) received 1,000IU vitamin D daily and group 2 (N=61) 1,000IU vitamin D and 0.25mg sodium fluoride daily for 6 months. Rachitic symptoms, radiological changes and adverse effects were not observed in either groups.

Kruse: Pathophysiology of calcium metabolism in children with vitamin D-deficiency rickets (1995)
The authors investigated 51 untreated patients, 2 to 36 months of age, during three stages of vitamin D deficiency rickets. Nineteen of these patients were also studied during therapy with 5,000 to 10,000IU vitamin D3 and 0.5 to 1g calcium. The untreated patients had secondary hyperparathyroidism, low calcium and phosphate concentrations in serum, and increased bone turnover, whereas serum 1,25(OH)2D was low, normal, or even slightly elevated. Serum calcium level was positively correlated to serum 1,25(OH)2D and to OHP/creatinine ratio, indicating that normocalcemia in untreated rickets is at least partially maintained by 1,25(OH)2D-induced calcium mobilization from bone. During vitamin D treatment, serum 1,25(OH)2D values increased to supranormal concentrations in association with the restoration of the physiologic relationship of PTH to serum calcium and phosphate concentrations and urinary cAMP/creatinine ratio.

Zeghoud et al: Vitamin D prophylaxis during infancy: comparison of the long term effects of three intermittent doses (15, 5, or 2.5 mg) on 25-hydroxy-vitamin D concentrations (1994)

The long-term effect of a single oral dose of 5mg (=200,000IU) colecalciferol at birth and of 2.5mg (=100,000IU) at birth as well as after 3 and 6 months was investigated in 60 healthy infants in Algeria by Zeghoud et al. (1994) The results of a former study with a single dose of 15mg (600,000IU) colecalciferol were included. Two weeks after the first dose of 15, 5 and 2.5mg the vitamin D concentrations in serum were 307±160, 150±55 and 92±42nmol/l, respectively. Over a period of 6 months the 15mg dose led to an excessively high level of vitamin D and increased calcaemia. The authors consider the 2.5mg dose (100,000IU) every 3 months to be the best prevention against vitamin D deficiency for children, in whom a daily vitamin D supplementation is not possible.

Guillemant et al: Wintertime Vitamin D Deficiency in Male Adolescents: Effect on Parathyroid Function and Response to Vitamin D_3 Supplements (2001)

The authors investigated the vitamin D status and parathyroid function in a group of 54 French male adolescents, aged from 13 to 16 years old during a 3 years period. The summer 25(OH)D concentrations were higher than the winter ones. Conversely, the winter parathyroid hormone serum levels were higher than the summer ones. At the two winter time points the 25(OH)D concentrations were lower than 25nmol/l (10ng/ml) in 72% (2nd year) and 68% (3rd year) of the adolescents. In the late 18 months pairs of male adolescents were randomly assigned to either vitamin D_3 supplementation (2.5mg, i.e., 100,000IU) administered orally at three specific periods (end of September, November and January) or no vitamin D_3 treatment. In the vitamin D3-treated subjects, the concentrations of 25(OH)D and of parathyroid hormone (PTH) in March and September were not significantly different. In the control subjects, March 25(OH)D levels were low, with values below 25nmol/l in 78% of subjects, and PTH concentrations were significantly ($p<0.001$) higher than in September. In adolescents with low calcium intakes, this vitamin D_3 treatment was sufficient to maintain 25(OH)D concentrations at their summer levels throughout winter and to prevent an excessive wintertime rise in PTH levels.

Lehtonen-Veromaa et al: Vitamin D intake is low and hypovitaminosis D common in healthy 9- to 15- year-old Finnish girls (1999)

The prevalence of vitamin D deficiency, the effect of vitamin D supplementation on 25(OH)D concentration in serum, and the intake of vitamin D in 186 Finnish 9- to 15-year-old athletic and nonathletic girls was investigated in a 1-year follow-up study with three months of vitamin D supplementation (10µg (=400IU)/d) from October to January. At baseline the 25(OH)D concentration was 33.9nmol/l among all girls. In winter severe vitamin D deficiency (25(OH)D<20nmol/l) occurred in 13.4% of the participants and in 67.7% 25(OH)D was below 37.5nmol/l. By the next summer the mean 25(OH)D concentration was 62.9nmol/l and in only 1.6% of the subjects it was below 37.5nmol/l. The prevalence of severe vitamin D deficiency in the next winter was not significantly reduced by three months of vitamin D (10µg/d) supplementation. The daily dietary vitamin D intake (<5µg/d) and the daily supplementation dose (10 µg (=400IU)/d) were too low in the majority of participants.

Koo et al: Effect of three levels of vitamin D intake in preterm infants receiving high mineral-containing milk (1995)

Preterm infants were randomized to daily vitamin D intakes of 200IU, 400IU, or 800IU for up to one month. No radiological differences were observed between groups. The 25(OH)D levels in the group receiving 200IU vitamin D for 24–29 days did not change, whereas the groups receiving 400IU and 800IU for the same period of time showed an increase in 25(OH)D levels of approximately 30%. Similar studies also suggested that preterm infants' plasma 25(OH)D levels were maintained from early neonatal life to 3 months with administration of supplemental vitamin D of 400IU/d. No benefit in vitamin D status of forearm bone mineral density was observed at a higher dose of 900IU/d.

Molgaard et al: Vitamin D and bone health in early life (2003).

Children, who have received sufficient vitamin D during the first 4-8 months and thereafter an insufficient supply, may develop signs of vitamin D deficiency at the age of 1-3 years, with stunting of growth, gross bowing of the legs, muscle weakness, walking problems and deformation of the pelvis. Despite severe leg deformations, healing of these skeletal deformations may still occur with the correct treatment with vitamin D. It is easy to prevent rickets in all age-groups, and prevention should be given high priority.

The MAH also submitted clinical studies on the effect of maternal vitamin D status and maternal vitamin D supplementation to the offspring.

Reviews:

- **Hollis et al.: Assessment of dietary vitamin D requirements during pregnancy and lactation (2004)**
- **Salle et al: Perinatal metabolism of vitamin D (2000)**

Clinical studies:

- **Javaid et al.: Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: a longitudinal study (2006)**

The authors investigated the effect of maternal vitamin D status during pregnancy on childhood skeletal growth in 198 children born in 1991-1992 in a hospital in Southampton, UK. Body build, nutrition, and vitamin D status of their mothers had been characterized during pregnancy. The children were followed up at age 9 years to relate these maternal characteristics to their body size and bone mass. 49 (31%) mothers had deficient and 28 (18%) had severely deficient circulating concentrations of 25(OH)D during late pregnancy. Reduced concentration of 25(OH)D in mothers during late pregnancy was associated with reduced whole-body (r=0.21, p=0.0088) and lumbar-spine (r=0.17, p=0.03) bone-mineral content in children at age 9 years. Both the estimated exposure to ultraviolet B radiation during late pregnancy and the maternal use of vitamin D supplements predicted maternal 25(OH)D concentration ($p<0.001$ and p=0.0110, respectively) and childhood bone mass (p=0.0267). The authors conclude that maternal vitamin D deficiency is common during pregnancy. Vitamin D supplementation of pregnant women, especially during winter months, could lead to long-lasting reductions in the risk of osteoporotic fracture in later years of their offspring.

- **Bodnar et al: Maternal vitamin D deficiency increases the risk of preeclampsia (2007)**

A nested case-control study of pregnant women followed from less than 16 wk gestation to delivery (1997–2001) at prenatal clinics and private practices. Patients included nulliparous pregnant women with singleton pregnancies who developed preeclampsia (n _ 55) or did not develop preeclampsia (n _ 219). Women's banked sera were newly measured for 25(OH)D. Demonstrated that a 50nmol/l decline in 25(OH)D concentration doubled the risk of pre-eclampsia (adjusted odds ratio 2,4; 95% CI 1.1-5.4). Newborns of preeclampsia mothers were twice as likely as control newborns to have 25(OH)D less than 37.5nmol/liter (adjusted odds ratio 2.2; 95% CI 1.2-4.1).

Comments:

The MAH presented an overview of rickets. Severe vitamin D deficiency may also cause hypocalcaemic seizures or tetany, particularly in the neonatal period and again during the phase of rapid growth in adolescence. Children with vitamin D deficiency may be irritable and reluctant to weight bear, and manifest impaired growth. Increased susceptibility to infections and respiratory symptoms in children with vitamin D deficiency may be a manifestation of "rachitic

lung," where respiratory function is compromised by a pliable rib cage and muscle weakness. Severe vitamin D deficiency can result in cardiomyopathy and potentially fatal heart failure (Pearce 2010).
Serum circulating 25-hydroxyvitamin D [25(OH)D] level, measured by a reliable assay is the recommended biomarker to evaluate vitamin D status in patients who are at risk for vitamin D deficiency. Vitamin D deficiency is defined as a 25(OH)D below 20 ng/ml (50 nmol/liter) and vitamin D insufficiency as a 25(OH) D of 21–29 ng/ml (52.5–72.5) nmol/liter (The Endocrine Society Clinical Practice Guideline). However, as noted in literature, at the present time consensus has not been reached.

The MAH submitted paediatric studies on the efficacy of vitamin D in the prevention and treatment of rickets.
The rapporteur concludes that there is adequate scientific evidence that vitamin D supplementation results to an increase in 25(OH)D and subsequent prevention of rickets and osteomalacia. Vitamin D supplementation can abolish the effects of seasonal vitamin D fluctuation (Guillemant, 2001). There is also some evidence that intermittent doses of vitamin D could also provide protection against vitamin D deficiency in high risk infant populations which are unsuitable for daily vitamin D supplementation (Zeghoud, 1994). The rapporteur also concludes that vitamin D status and adequate intake of vitamin D in children should be continuously evaluated by physicians at all ages and especially in high risk populations, as short periods of supplementation do not guarantee long term adequacy of vitamin D (Lehtonen-Veromaa, 1999, Molgaard, 2003).

Dosing for prevention and treatment of rickets and osteomalacia

In the clinical overview the MAH stated that for the prevention of rickets in paediatric patients, 500-1000IU/day of colecalciferol are recommended and for the treatment of rickets 1000-5500IU/day of colecalciferol are recommended.

In section **4.2 Posology and method of administration** of the SmPC, the following information can be found:

"*The dosage must be determined individually by the treating doctor, depending on the nature and severity of the condition.*
Oral solution
During long-term treatment with Y Oil the serum and urinary calcium levels should be monitored regularly and the kidney function checked by measurement of serum creatinine.
If necessary, the dose must be adjusted according to the serum calcium levels.

- *Prophylaxis of rickets:*
  Infants and toddlers (0 to 2 years): 1 drop of Y Oil daily (equivalent to approx. 0.0167 mg or 667 IU vitamin D)
  Premature infants: 2 drops of Y Oil daily (equivalent to approx. 0.0334 mg or 1,333 IU vitamin D)
  Children (2 to 11 years) and adolescents: 2 drops of Y Oil daily (equivalent to approx. 0.0334 mg or 1,333 IU vitamin D)
- *Treatment of vitamin D deficiency disorders:*
  Infants, toddlers, children and adolescents: 2-8 drops of Y Oil daily (equivalent to approx. 0.0334 mg or 1,333 IU to 0.1333 mg or 5,333 IU vitamin D)
  Adults: 2-8 drops of Y Oil daily (equivalent to approx. 0.0334 mg or 1,333 IU to 0.1333 mg or 5,333 IU vitamin D)

Tablets 500 IU

During long-term treatment with X 500 with daily doses of over 500 IU calcium levels in the serum and urine should be monitored at regular intervals and renal function checked by measuring the serum creatinine level. The dose must be adjusted, if necessary, in accordance with the serum calcium values.

- *Prophylaxis of rickets:*
  Infants: 1 X tablet 500 daily (equivalent to 0.0125 mg or 500 IU vitamin D)
- *Prophylaxis of vitamin-D deficiency disease in patients with an identified risk without absorption disorder: 1 X tablet 500 daily (equivalent to 0.0125 mg or 500 IU vitamin D).*

Tablets 1000 IU

During long-term treatment with X 1000 with daily doses of over 500 IU calcium levels in the serum and urine should be monitored at regular intervals and renal function checked by measuring the serum creatinine level. The dose must be adjusted, if necessary, in accordance with the serum calcium values.

- *Prophylaxis of rickets:*
  Infants: ½ X tablet 1000 daily (equivalent to 0.0125 mg or 500 IU vitamin D)
- *Prophylaxis of vitamin-D deficiency disease in patients with an identified risk without absorption disorder: ½ X tablet 1000 daily (equivalent to 0.0125 mg or 500 IU).*

Comments:

In order to critically assess the current SmPC's proposed posology, the rapporteur performed a review of the current guidelines/recommendations on the supplementation of vitamin D for the prevention and treatment of vitamin D deficiency.

Clinical guidelines/recommendations

In February 2012 the *Chief Medical Officer for the UK* wrote to health professionals to recommend vitamin D supplementation to all at-risk groups. According to these recommendations, it is proposed that:
"All infants and young children aged 6 months to 5 years should take a daily supplement containing vitamin D in the form of vitamin drops, to help them meet the requirement set for this age group of 7-8.5 micrograms of vitamin D per day. However, those infants who are fed infant formula will not need vitamin drops until they are receiving less than 500ml of infant formula a day, as these products are fortified with vitamin D. Breastfed infants may need to receive drops containing vitamin D from one month of age if their mother has not taken vitamin D supplements throughout pregnancy. "

The *UK Department of Health* in its publication "Birth to five" (2009) recommends that vitamin drops containing Vitamin D (as well as vitamin A and C) are given as a supplement to formula fed infants older than 6 months or taking less than 500ml formula milk per day and to infants from the age of six month taking less than 500 ml formula milk daily, particularly if they are fussy eaters, live in the northern areas of the UK or are of Asian, African or Middle Eastern origin. Vitamin drops from one month until 5 years are recommended for breast-fed infants whose mothers have not taken Vitamin D during pregnancy or from one month where mothers wear concealing clothing when outdoors. Advice is also given for children on vegan or vegetarian diets (up to the age of 5 years).

BNF-C dosing for colecalciferol

Nutritional vitamin-D deficiency rickets
-By mouth

Child 1-6 months: 3000 IU/d, adjusted as necessary
Child 6 months-12 years: 6000 IU/d, adjusted as necessary
Child 12-18 years: 10000 IU/d, adjusted as necessary

Nutritional or physiological supplement; prevention of rickets
-By mouth
Neonate: 400 IU/d
Child 1 month-18 years: 400-600 IU/d

Vitamin D deficiency in intestinal malabsorption or in chronic liver disease
-By mouth or by intramuscular injection
Child 1-12 years: 10000-25000 units daily, adjusted as necessary
Child 12-18 years: 10000-40000 units daily, adjusted as necessary

Both *The American Academy of Paediatrics (AAP)* and the *Canadian Paediatric Association* recommend 400IU/d of vitamin D for children at risk for vitamin D deficiency (AAP 2008, Wagner 2008). AAP also states that breastfed and partially breastfed infants should be supplemented with 400 IU/day of vitamin D beginning in the first few days of life. Supplementation should be continued unless the infant is weaned to at least 1 L/day or 1 qt/day of vitamin D–fortified formula or whole milk. All non-breastfed infants, as well as older children who are ingesting <1000 mL/day of vitamin D fortified formula or milk, should receive a vitamin D supplement of 400 IU/day. Adolescents who do not obtain 400 IU of vitamin D per day through vitamin D fortified milk (100 IU per 8-oz serving) and vitamin D fortified foods (such as fortified cereals and eggs yolks) should receive a vitamin D supplement of 400 IU/day.

The Endocrine Society Clinical Practice Guideline provides the following recommendations:
-Infants and children aged 0–1 yr require at least 400 IU/d of vitamin D and children 1 yr and older require at least 600 IU/d to maximize bone health. Whether 400 and 600 IU/d for children aged 0–1 yr and 1–18 yr, respectively, are enough to provide all the potential non skeletal health benefits associated with vitamin D to maximize bone health and muscle function is not known at this time. However, to raise the blood level of 25(OH)D consistently above 30 ng/ml may require at least 1000 IU/d of vitamin D.
-Obese children and children on anticonvulsant medications, glucocorticoids, antifungals such as ketoconazole, and medications for AIDS are given at least two to three times more vitamin D for their age group to satisfy their body's vitamin D requirement.
-The maintenance tolerable upper limits (UL) of vitamin D, which is not to be exceeded without medical supervision, should be 1000 IU/d for infants up to 6 months, 1500 IU/d for infants from 6 months to 1 yr, at least 2500 IU/d for children aged 1–3 yr, 3000 IU/d for children aged 4–8 yr, and 4000 IU/d for everyone over 8 yr. However, higher levels of 2000 IU/d for children 0–1 yr, 4000 IU/d for children 1–18 yr, and 10,000 IU/d for children and adults 19 yr and older may be needed to correct vitamin D deficiency
-Infants and toddlers aged 0–1 yr who are vitamin D deficient, should be treated with 2000 IU/d of vitamin D_2 or vitamin D_3, or with 50,000 IU of vitamin D_2 or vitamin D_3 once weekly for 6 wk to achieve a blood level of 25(OH)D above 30 ng/ml, followed by maintenance therapy of 400–1000 IU/d
-Children aged 1–18 yr who are vitamin D deficient, should be treated with 2000 IU/d of vitamin D2 or vitamin D3 for at least 6 wk or with 50,000 IU of vitamin D2 once a week for at least 6 wk to achieve a blood level of 25(OH)D above 30 ng/ml, followed by maintenance therapy of 600–1000 IU/d.

From the review it is clear that there is currently no consensus on the dosing regimes of vitamin D.

The rapporteur is of the view that the paediatric dosing for the 500/1000IU tablets is within the international guidelines for the prevention of vitamin D deficiency. As far as the oral solution's paediatric dosing is concerned, the rapporteur would like to make the following comments:

- For the prophylaxis of rickets, the infant and toddlers' dose of 667 IU vitamin D appears acceptable. However the rapporteur has identified in the literature the following warning regarding vitamin D posology in preterm infants: The administration of 800–1000 IU vitamin D per day according to the recommendations of ESPGHAN (European Society for Paediatric Gastroenterology, Hepatology and Nutrition) induces 25(OH)D values compatible with vitamin repletion without reaching levels that could be considered as toxic. Nevertheless, such an intake should not be prolonged over the theoretical term due to the potential risk of vitamin D intoxication (Rigo et al, 2007). Therefore, the proposed dose for premature infants 1333IU for the prophylaxis of rickets appears high.
- The treatment of vitamin D deficiency is 2-8 drops of the colecalciferol solution daily (1333-5333IU) irrespective of the patient's age, i.e. the same dose range is recommended for infants and adults. The rapporteur deduces from this posology that an infant could be treated with 5333IU daily, which in that case would be a high dose with potential toxicity risk and clearly above the recommended upper doses. The rapporteur is aware that in established rickets high doses might be used but in order to avoid overdosage, it would be better if the appropriate posology for different paediatric subsets is given in the SmPC and a warning is included that in severe cases higher doses might be used under medical supervision.

In conclusion, the rapporteur would like to request the MAH to consider these issues identified, review the evidence available and either justify the current licensed SmPC doses or propose an appropriate change of the paediatric recommendation in section 4.2.

Prevention and Supportive Therapy of Osteoporosis

The MAH submitted the following data regarding the use of vitamin D for the treatment of osteoporosis. Long-standing, mild insufficiency of vitamin D is now recognized as one cause of osteoporosis (Vieth, 2001) and evidence indicates that muscle function in elderly people is affected by vitamin D insufficiency (Sahota, 2007). Nurmi et al. (2005) analyzed the serum 25(OH)D status in 223 patients with an acute hip fracture in southeastern Finland (61°N). Severe vitamin D deficiency, defined as 25(OH)D <37.5nmol/l, was found in 53% of the patients. Half (50%) of the patients living in their own homes, 55% of those in residential homes, and 61% of institutionalized elderly had vitamin D deficiency. Simonelli et al. (2005) found a 25(OH)D level <39ng/ml in more than 97% of all patients hospitalized for fracture. To assess the therapeutic efficacy of colecalciferol in osteoporosis, randomized placebo-controlled studies were conducted. There is international consensus that a patient suffering from osteoporosis should receive calcium therapy. Most studies have investigated, therefore, a combination of vitamin D + calcium versus placebo. Therapy-induced reduction of fracture incidence was regarded as the most important primary target parameter. Bone mineral density (BMD) is often determined as a surrogate parameter, e.g. in the controlled studies by Adachi et al. (1996), Buckley et al. (1996), Dawson-Hughes et al. (1991). In some studies the number of falls was considered Bischoff et al. (2003).

The SmPC of the colecalciferol formulations presented in this report state in section **4.2 Posology and method of administration:**

Oral solution

- *Supportive treatment in osteoporosis:*
  2 drops of Y Oil daily (equivalent to approx. 0.0334 mg or 1,333 IU vitamin D)

Tablets 500

- Supportive treatment in osteoporosis:
  2 X tablets 500 daily (equivalent to approx. 0.025mg or 1.000 IU vitamin D).

Tablets 1000IU

- Supportive treatment in osteoporosis:
  1 X tablet 1000 daily (equivalent to 0.025 mg or 1000 IU vitamin D)

Comments:

Osteoporosis is a reduction of bone mineral mass per volume unit of bone tissue in the absence of mineralization defects (i.e. osteomalacia). Dual energy X-ray absorptiometry (DEXA) is the most widely used technique to assess bone mass in adults and children. Although great importance is often given to DEXA, it should be remembered that there is no evidence that densitometric data can predict the likelihood of fracture or improve the overall management of children with chronic illness (Munns, 2005). The ISCD (International Society for Clinical Densitometry) in their Paediatric Position Statement identified the diagnosis of osteoporosis in children as having not only low bone mass (below 2 SD scores for body size) but also having had a clinically significant fracture history. Bisphosphonates although unlicensed, are the most widely used medications for the treatment of paediatric osteoporosis.

The MAH submitted no paediatric studies for the use of vitamin D in children with osteoporosis.

The rapporteur conducted a literature search and identified the following paediatric information: In a study by Bowden (2008) a high prevalence of vitamin D insufficiency was found in children with primary and secondary osteopenia or osteoporosis referred to a paediatric metabolic bone clinic. In this study vitamin D insufficiency was common in children with recognized osteopenia and osteoporosis caused by primary metabolic bone disease or secondary to chronic illnesses and could be one of the risk factors for low bone density. This study emphasized the importance of assessing vitamin D status in children with low bone density and/or multiple fractures.

If there is evidence of vitamin D deficiency and/or poor dietary calcium intake it would be appropriate to replace such deficits, but routine calcium and vitamin D supplementation is not recommended (Shaw, 2003). A Cochrane review (Winzenberg, 2010) did not support vitamin D supplementation to improve bone density in healthy children with normal vitamin D levels but suggested that supplementation of deficient children might be clinically useful.

There are no long-term, prospective, randomized, controlled studies on large numbers of paediatric patients aimed to establish the safety and efficacy of calcium and vitamin D in the therapy of osteoporosis.

The rapporteur is of the view that vitamin D has been used as supportive treatment of osteoporosis in children and its use in selected cases could be justified by the existing literature despite the absence of controlled studies. Vitamin D and calcium status should be evaluated in patient with osteoporosis and if found deficient should be treated.

It is not clear from the currently approved SmPC if the indication “supportive treatment of osteoporosis” is confined to adults or applies for children as well, as no posology for children is given in section 4.2. Therefore, the MAH should clarify if osteoporosis is a paediatric indication as well as adult and if that is the case, propose appropriate paediatric posology to be included in the SmPC.

Therapy of Hypoparathyroidism

Hypoparathyroidism may be transient, genetically inherited, or acquired. Genetically inherited forms arise from defects of parathyroid gland development, defects in the parathyroid hormone

(PTH) gene, defects in the calcium-sensing receptor gene, defects in PTH action, defects in the autoimmune regulator gene, and genetic syndromes. Acquired hypoparathyroidism may be due to an autoimmune process or may occur after neck irradiation or surgery.
The MAH stated that therapy with vitamin D compounds is necessary besides oral calcium substitution. The most extensive experience has been gained with colecalciferol (Bässler et al., 2002). Although the various vitamin D metabolites can be used, genuine vitamin D is still described as the substance of choice but comparative studies of the different vitamin D metabolites are lacking.

In a retrospective study in Germany by Schilling and Ziegler (1997) data from 59 children and 270 adults with hypoparathyroidism were collected. 1,25(OH)2D was the only vitamin D agent that was administered in the treatment of children, whereas in adults 52% were treated with dihydrotachysterol, 28 % with genuine vitamin D3, and 20 % with 1,25(OH)2D. There was a positive correlation between serum 25(OH)D levels and administered vitamin D3 doses. In patients treated with vitamin D3, serum calcium levels correlated significantly with serum 25(OH)D levels whereas they did not correlate with administered calcium doses. Vitamin D3 daily doses ranging between 10,000 and 70,000IU (median daily dose=35,000IU) were needed to achieve normocalcemia. The doses required showed great inter-individual differences.

The SmPC of the colecalciferol oral solution states in section **4.2 Posology and method of administration:**

"Oral solution

- *Treatment of hypoparathyroidism*

The recommended dose range is 10,000 to 200,000 IU vitamin D per day depending on the serum calcium levels. Most of the patients are treated with 15-30 drops daily (equivalent to 10,000–20,000 IU vitamin D). The serum calcium levels have to be checked initially every 4-6 weeks, and later every 3-6 months. The dose has to be adjusted according to these values.

Comments:

Hypoparathyroidism is a rare paediatric disorder, associated with low or undetectable parathyroid hormone (PTH) levels, which produces abnormalities in mineral metabolism that include hypocalcemia, hyperphosphatemia, and hypomagnesemia. The clinical presentation may include neuromuscular irritability causing tetany, muscle cramping, spasms, and seizures. In adults, the disorder is usually a complication of neck surgery or radiation. In children, the condition is most often idiopathic or due to inherited disorders such as autoimmune polyglandular failure syndrome type 1 or an activating mutation in the calcium-sensing receptor (Winer, 2010).

In USA and in the UK, vitamin D (ergocalciferol) and to a lesser extent vitamin D (colecalciferol) have been used rather commonly. Dihydrotachysterol has been used extensively in the United States and in Europe and to some extent in the United Kingdom. 25-Hydroxy colecalciferol is available in the United States, while 1 alpha hydroxy colecalciferol is available in Europe but not in the United States. 1 ,25-dihydroxycolecalciferol is available both in Europe and in the United States. The advantage of using 1-hydroxylated forms of vitamin D is that they act more quickly and are also much more potent (O'Riordan, 1994).

The BNF-C contains the following regarding treatment of hypothyropidism:
"Persistent hypocalcaemia requires oral calcium supplements and either a vitamin D analogue for hypoparathyroidism and pseudohypoparathyroidism or natural vitamin D if due to vitamin D deficiency".

Therefore, the rapporteur concludes, based on the limited data identified, that 1 ,25-dihydroxycolecalciferol or 1 alpha hydroxy colecalciferol are the preferred vitamin D forms used in the treatment of hypoparathyroidism. However, colecalciferol still has a place, especially after the initial stabilisation of newly diagnosed patients.
The rapporteur agrees with the MAH that the required dose is highly specific for each individual and it is a challenge for the clinician to balance treatment posology.
As in the case of osteoporosis, it is not clear in the SmPC whether colecalciferol is indicated in the treatment of hypoparathyroidism in children as paediatric posology is not provided in section 4.2. Therefore, the MAH should clarify if hypoparathyroidism is a paediatric indication and if that is the case, propose appropriate paediatric posology for the SmPC/PIL.

LITERATURE REVIEW OF OTHER (UNLICENSED) USES

Prevention and supportive therapy of cardiovascular disease

There is recent literature evidence that vitamin D is a potent endocrine suppressor of renin biosynthesis to regulate the renin-angiotensin system (Li et al., 2004). In cell cultures, 1,25(OH)2D directly suppresses renin gene transcription by a VDR-dependent mechanism. The authors conclude (Li, 2003) that the concept of vitamin D regulation of blood pressure provides a basis for the potential use of vitamin D in prevention and treatment of hypertension.

Prevention and supportive therapy of infections

Recent studies of the gene encoding LL-37, an antimicrobial peptide (Zasloff, 2006) revealed that it contains sites for the vitamin D receptor (VDR). The active form of vitamin D, 1,25(OH)2D, boosts levels of LL-37 in human neutrophils. 1,25(OH)2D also induces expression of LL-37 in keratinocytes in tissue culture and after topical administration onto the skin of human subjects. Polymorphism in the gene encoding the vitamin D receptor may influence the host response to infections (Roth et al., 2004). This is the experimental basis for the clinical observation that vitamin D deficiency is linked with increased prevalence and severity of infectious diseases (Cannel et al., 2006).

Prevention and supportive therapy of autoimmune diseases

In animal models of autoimmunity, vitamin D prevents the development of experimental autoimmune encephalomyelitis, reduces the incidence of diabetes, and prolongs graft survival in animal models of transplantation. In humans, vitamin D has led to an anti-proliferative effect in psoriasis and immunomodulatory effect in scleroderma (Lemire, 2000). Lemire evaluated the immunomodulatory properties of vitamin D. He demonstrated at a cellular and molecular level that vitamin D preferentially targets helper T cell activity (Th1) by inhibiting the secretion of both Interleukin-2 (IL-2) and IFN-γ by Th1 and by suppressing the secretion pro-Th1 cytokine IL-12 by antigen-presenting cells. Vitamin D further inhibits class II antigen expression and enhances suppressor cell activity.
Szodoray et al. (2008) pointed out that both experimental and clinical data provide evidence that vitamin D can decrease the prevalence of certain autoimmune diseases, such as type 1 diabetes mellitus (IDDM), multiple sclerosis (MS), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and inflammatory bowel diseases (IBD). The authors conclude that serum vitamin D levels may be important in the pathogenesis of these autoimmune diseases. Vitamin D receptor polymorphism can be associated with several immune-related diseases, including childhood and adult asthma (Poon et al., 2004; Raby et al., 2004).

Prevention and supportive therapy of diabetes

Zella et al. (2003), and Zella and Deluca (2003) could show in a mice model that vitamin D deficiency increased the incidence of type 1 diabetes in female mice from 46% (n=13) to 88%

(n=8) and from 0% (n=10) to 44% (n=9) in male mice as of 200 days of age when compared to vitamin D-sufficient animals.

In a meta-analysis of four case-control studies, Zipitis and Akobeng (2008) demonstrated that the risk of type 1 diabetes was significantly reduced in infants who were supplemented with vitamin D compared to those who were not supplemented (pooled odds ratio 0.71, 95% CI 0.60 to 0.84). These results were confirmed by a cohort study.
Regular doses of vitamin D at a dose of 2,000IU/d early in life have been shown to reduce the risk of developing type 1 diabetes (up to an 80% reduction projected over the next 30 years (Harris, 2005; Schwalfenberg, 2008).

In a birth-cohort study by Hyppönen et al. (2001), 12,055 pregnant women in Finland, who gave birth in 1966, were enrolled. Data of the children was collected in the first year of life about frequency and dose of vitamin D supplementation and presence of suspected rickets. The primary outcome measure was the diagnosis of type 1 diabetes in 1997. Of the 10,366 children included in analyses, 81 were diagnosed with diabetes during the study. Vitamin D supplementation was associated with a decreased frequency of type 1 diabetes when adjusted for neonatal, anthropometric, and social characteristics. 88 % of children were given vitamin D supplements regularly. The development of diabetes was associated with low intake of vitamin D and signs of rickets during the first year of life. Ensuring adequate vitamin D supplementation for infants could help to reverse the increasing trend in the incidence of type 1 diabetes.

Prevention and supportive therapy of multiple sclerosis

Due to the influence of vitamin D on the modulation of the immune system, the interest in the role of vitamin D in the pathogenesis and severity of multiple sclerosis (MS) has been increasing over the last years. Vitamin D3 decreases the proliferation of pro-inflammatory T lymphocytes and influences the production of cytokines, both of which contribute to the pathogenesis of MS (Alroy et al., 1995; Cantorna et al., 1998; Kimball et al., 2007; May et al., 2004; Takeuchi et al., 1998). Therefore, low serum 25(OH)D levels are associated with increased multiple sclerosis prevalence and risk (Burton et al., 2008). 25(OH)D levels considerably above 100 nmol/l are considered as target serum levels in MS patients. Evidence from large prospective epidemiologic studies suggests that compared with individuals with 25(OH)D levels between 99.2 and 152.9nmol/l, individuals with lower levels of vitamin D have a significantly higher risk of developing MS (Hiremath et al., 2009).

Prevention and supportive therapy of cancer

The vitamin D status in relation to cancer risk was evaluated in a PubMed database search by Garland et al. (2006) including 63 observational studies, thereof 30 in colon cancer, 13 in breast cancer, 26 in prostate cancer, and 7 in ovarian cancer, and several that assessed the association of vitamin D receptor genotype with cancer risk. The majority of these studies found a protective relationship between sufficient vitamin D status and lower risk of cancer. At least 18 different cancers have been found to be related to the vitamin D status (Grant et al., 2005), among them prostate, bladder, oesophageal, gastric, pancreatic, rectal, renal, and corpus uteri cancer, and non Hodgkin`s lymphoma. Not only the cancer risk is increased in vitamin D deficiency, vitamin D has also been found to improve the prognosis of these cancers (Grant et al., 2005).Therefore, it is not surprising that D3 potentiates the anticancer effect of many cytotoxic and antiproliferative anticancer agents (Deeb et al., 2007).
The MAH concluded that based on this evidence “screening for vitamin D deficiency and aggressive vitamin D repletion should be considered for all people with cancer. Prevention and supportive therapy of cancer are meaningful in adults as well as in paediatric patients. Recommended doses in paediatric patients are 500-1000IU/day of colecalciferol.”

Comments:

There is growing evidence that vitamin D acts in systems other than the skeleton. This is unsurprising given that vitamin D influences the action of more than 200 human genes in a wide range of tissues (Cannell 2008). In adults, new evidence supports a potential role for vitamin D in maintaining innate immunity and preventing diseases such as diabetes and cancer. The new data may eventually refine what constitutes vitamin D sufficiency or deficiency (Wagner 2008).
The MAH quoted some animal and adult studies demonstrating these effects in animals as well as clinical studies in adults. Evidence of similar effects in children is still scarce.

Vitamin D has sparked considerable interest as a modifiable environmental factor in autoimmune diseases. There is preliminary evidence that vitamin D deficiency could be causally related to a variety of autoimmune diseases. Future studies should evaluate whether supplemental vitamin D administration prevents the onset or ameliorates the clinical manifestations of autoimmune diseases (Kinder and Hagaman, 2011).

The MAH submitted some data regarding the effect of vitamin D supplementation in the incidence of type I diabetes and it appears that this is the field mostly studied in children, although data come mainly from prospective observational studies. The rapporteur identified studies in the literature showing a high frequency of vitamin D deficiency in children with type I diabetes (Bener, 2009, Janner 2010), whereas other studies showed similar frequency with healthy subjects (Svoren 2009, Mutlu 2011).

A recent randomized controlled trial of vitamin D supplementation among children with pneumonia was associated with a reduction in repeat episodes of pneumonia (Manaseki-Holland 2010). It has also been postulated that vitamin D might play a role in childhood asthma. Vitamin D may protect against wheezing illnesses through its role in upregulating antimicrobial proteins or through its multiple immune effects and effects on lung development. In addition, vitamin D may play a therapeutic role in steroid resistant asthmatics, and lower vitamin D levels have recently been associated with higher risks for asthma exacerbations (Litonjua, 2009).

The rapporteur concludes that well designed clinical trials are needed to investigate whether vitamin D has additional therapeutic benefits in paediatric patients, other than the known skeletal effects and to determine the appropriate dose to achieve these potentially beneficial effects of vitamin D. Therefore, the rapporteur concludes that based on the evidence submitted during this paediatric work-sharing procedure, no addition in the currently licensed paediatric indications is justified.

c. Clinical safety

The MAH stated that regarding the safety of vitamin D formulations, overall, X tablets and Y oral solution are safe and well tolerated.

a. Information currently available the SmPC

Contraindications:
X tablets and Y oral solution are contraindicated in patients with hypersensitivity to the active ingredient or any of the excipients, in hypercalcemia, hypercalciuria, or restricted mobility.
Warnings and precautions:

Although vitamin D_3 is well tolerated in clinical studies, it is not recommended in patients with a history of renal calculi, with sarcoidosis and when taking additional doses of vitamin D. Particular caution is also recommended when additional doses of vitamin D via other medicinal products is taken. In pseudo-hypoparathyroidism, the therapy has to be adjusted or stopped as soon as the parathyroid glands recover.

Interactions:

Interactions with vitamin D_3 have been described for digitalis, thiazide diureticics, barbiturates, corticosteroids, rifampicin and isoniazid.

Pregnancy and lactation:

During pregnancy and lactation, a sufficient intake of vitamin D is required. Overdose (Hypercalcemia, transplacental passage of vitamin D metabolites to the fetus) may involve teratogenic risks of physical and mental retardation and special forms of aortic stenosis. Vitamin D and its metabolites pass into breast milk. Overdose in infants induced by nursing mothers has not yet been observed.

Adverse reactions:

Nature, severity and outcome of adverse reactions in the paediatric population do not differ from those observed in adults. The following adverse reactions have been described under vitamin D_3: Gastrointestinal disorders: Gastrointestinal complaints such as constipation, flatulence, nausea, abdominal pain, or diarrhea. Skin and subcutaneous tissue disorders: Hypersensitivity reactions such as pruritus, rash, or urticaria. Metabolism and nutrition disorders. Hypercalcemia and hypercalciuria in case of prolonged administration of high doses

Overdose:

After acute or chronic overdose of vitamin D_3, hypercalcaemia can be caused, which can range from an asymptomatic increase in serum calcium through to life-threatening hypercalcaemia syndrome (Reichel, 1998). Signs and symptoms of vitamin D intoxication are not characteristic and may include arrhythmia, vomiting, constipation, thirst, polydipsia, polyuria, dehydration, hypercaliuria with formation of renal calculi, nephrocalcinosis, muscle weakness, adynamia and disorientation. In addition, chronic overdose may lead to calcification of vessels and tissues.

Hypervitaminosis is reversible at an early stage. Treatment consists in withdrawal of vitamin D therapy, rehydration, and reduction of dietary calcium intake. In severe cases forced diuresis, glucocorticoids, biphosphonates and calcitonin can be used to reduce the calcium level (Machlin, 1991).

b. Post marketing experience:

Y oil is marketed in 20 countries and X tablets are approved in 7 countries. Both formulations are considered to be well tolerated to date, as described in a total of seven periodic safety update reports (PSURs).

The post-marketing experience with both products confirms the safety of colecalciferol in the recommended doses and the positive benefit-risk evaluation of the products in adults as well as in paediatric patients. No change of the benefit-risk ratio can be derived from the safety data evaluated in PSURs.

Comments:

No new safety information that would warrant regulatory action has been submitted by the MAH.

Excessive intake of vitamin D produces a syndrome known as vitamin D intoxication, which is characterised by hypercalcemia, renal stones, and renal calcification, with kidney failure and death. The safe upper intake level of vitamin D in children has not been entirely defined. It appears that in adults, toxicity is almost never observed at serum levels below 500 nmol/L, corresponding to oral intakes in excess of 20,000–50,000 IU/day (Heaney, 2008).

In a review analysing the safety of oral vitamin D (Glade, 2011) identified the following:

In one study, preadolescent and adolescent girls exhibited maximum serum 25-OHD concentrations of up to about 250 nmol/L with no adverse reactions or side effects after 1 y of consuming 14 000 IU of vitamin D once every week. In a similar study, preadolescent and adolescent boys and girls exhibited maximum serum 25-OHD concentrations of up to about 500 nmol/L with no adverse reactions or side effects after 1 y of consuming 14 000 IU of vitamin D once every week. Children 6 to 16 y old infected with the human immunodeficiency virus were administered 100 000 IU of oral vitamin D once every 2 mo for 1 y. Serum 25-OHD concentrations fluctuated on a 2-month cycle, reaching maximum of around 70 nmol/L about 1 month after vitamin administration and reaching minimum just before readministration. None of the children developed hypercalcemia or hypercalciuria during the year-long study. Despite evidence from this review that high doses of vitamin D could be well tolerated by children, the administration of vitamin D in preterm infants, as mentioned in a previous section, should not be prolonged due to the potential risk of vitamin D intoxication (Rigo et al, 2007).

In 2010 FDA issued a warning of the potential risk of overdosing infants with liquid vitamin D after identifying that some products with droppers could allow medication errors. The rapporteur is of the view that the risk of overdosing is higher with the oily solution as there is evidence in the literature of higher variability in dosing children with oral droplets (Brown D, 2004).

The rapporteur noted that the current SmPC has adequately addressed the risk and the consequences of overdosage in all patients under the sections: 4.6 Pregnancy and lactation, 4.8 Undesirable effects, 4.9 Overdose and 5.3 Preclinical safety data. Nevertheless, the rapporteur identified some issues in the oral solution's SmPC regarding the dosing of premature infants for the prophylaxis of rickets and the dosing for treatment of vitamin D deficiency in children, which could potentially lead to overdosing. These are explained in detail in sections IV.2b and V.

X tablets contain soybean oil as an excipient. Soy protein allergy is estimated at 0.5% in the general population and 3-6% in children. Depending on the degree of residual protein in refined oils, an individual has the potential of allergic reactions. In accordance with the EU guidance on the excipients in the label and package leaflet of medicinal products for human use (2003), the following statement should be included in the information of the package leaflet: "X contains soybean oil. If you are allergic to peanut or soya, do not use this medicinal product." In the SmPC under section 4.3 the following wording should be added: "X tablets 500/1000 should not be used if the patient is allergic to peanut or soya."

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION AT DAY 89

Colecalciferol, a form of vitamin D, is a well established drug for the prevention and treatment of rickets and vitamin D deficiency. An increasing number of publications on the effect of vitamin D in almost every system might expand the list of indications in the forthcoming years.
The safety profile of colecalciferol is well known including the major safety consideration which is the risk of overdosage.
The MAH provided a review of the literature on the efficacy and safety of colecalciferol and concluded that from the available data the benefit/risk balance is not changed and therefore no changes in any of the SmPC sections are needed.

There is evidence of a resurgence of vitamin D deficiency in children. Age appropriate formulations are not available in all countries, as is the case in the UK.

The rapporteur, after reviewing the evidence submitted by the MAH and performing a comprehensive literature search concluded:

- It is not clear from the SmPC if supportive treatment of osteoporosis is confined to adults or is recommended for children as well, as no posology for the paediatric population is given in section 4.2.
- It is also not clear from the SmPC if the indication "treatment of hypoparathyroidism" is confined to adults or is also recommended in the paediatric population as well, as no posology for children is given in section 4.2.
- Oral solution (Y): The dose for premature infants (1333IU daily) for the prophylaxis of rickets appears high compared to current agreed international guidelines.
- Oral solution (Y): The treatment of vitamin D deficiency is 2-8 drops of the colecalciferol solution daily (1333-5333IU) irrespective of the patient's age meaning that the same dose range is recommended for infants and adults. The rapporteur deduces from this posology that an infant could be treated with 5333IU, which in that case would be a high dose with potential toxicity risk.

The MAH was requested to address the issues raised by the rapporteur providing all available evidence regarding the currently approved paediatric indications and posology.
The rapporteur requested the MAH to:

- provide information as to whether X 1000IU tablets are dividable and in case they are, whether breaking them into half leads to delivery of the recommended half doses of 500 IU where appropriate by the given posology in the current SmPC.
- clarify if osteoporosis and hypoparathyroidism are paediatric indications as well as adult and if that is the case, propose appropriate paediatric posology for the SmPC. The SmPC of colecalciferol should be updated with specific wording regarding the use in the paediatric population for the relevant licensed indications listed in section 4.1 with paediatric posology under headings of the paediatric and adult indications in section 4.2.
- consider the issues identified regarding the paediatric posology of Y oil/oral solution. The MAH should review the evidence available and either justify the current licensed SmPC doses or propose changes of the paediatric recommendations in section 4.2.The rapporteur is aware that in established rickets high doses might be used but in order to avoid overdose, it would be better if the posology for different paediatric subsets is given in the SmPC with an additional statement that in severe cases higher doses might be used under medical supervision included.
- include the following statement in the information of the package leaflet: "X tablets contain soybean oil. If you are allergic to peanut or soya, do not use this medicinal product." In the SmPC under section 4.3 the following wording should be added: "X tablets 500/1000 should not be used if the patient is allergic to peanut or soya", according to the EU guidance on the excipients in the label and package leaflet of medicinal products for human use (2003)

VI. ADDITIONAL COMMENTS FROM MEMBER STATES

Following the circulation of the Day 70 PdAR, the rapporteur received comments from 3 MSs that fully support the rapporteur's overall conclusion and request for additional information. Comments were also received from a MS that overall endorsed the rapporteur's opinion and had the following additional comments:

"*In a German guideline concerning rickets due to vitamin D deficiency (Vitamin-D-Mangel-Rachitis) the dosing recommendation for prophylaxis is 500 IU of vitamin D during the first year of life. Thus the recommendation in the SPCs – which recommend a prophylaxis for children up to 2 years – are not in accordance with the German guideline. The German guideline gives no recommendation for premature infants. There is no explanation given for the high dose listed in the SPC of X 1000 IU for pre-term new-born infants."*

The rapporteur considered that the comment from the MS regarding the dosing recommendations for rickets prophylaxis reflect the variation in national guideline as captured in pages 15 to 18 assessment report. The MAH was requested to address the comments from the MS as part of their response to the additional clarifications requested in order to optimize the proposed posology for the paediatric population.

VII. MAH RESPONSES TO THE PRELIMINARY PDAR DAY 89

Question 1:
The MAH is requested to provide information as to whether X 1000IU tablets are dividable and in case they are, whether breaking them into half leads to delivery of the recommended half doses of 500 IU where appropriate by the given posology in the current SmPC.

Response:
The MAH provided adequate information regarding the X tablets divisibility and the uniformity of the halves.

Comments:
The rapporteur reviewed the provided quality information. Issue resolved.

Question 2:
The MAH is requested to clarify if osteoporosis and hypoparathyroidism are paediatric indications as well as adult and if that is the case, propose appropriate paediatric posology for the SmPC. The SmPC of colecalciferol should be updated with specific wording regarding the use in the paediatric population for the relevant licensed indications listed in section 4.1 with paediatric posology under headings of the paediatric and adult indications in section 4.2.

MAH Response:
Whereas hypoparathyroidism may occur in paediatric patients (Schilling and Ziegler, 1997), osteoporosis is a typical indication in adults.

In order to clearly identify which indications only apply to certain age groups, the MAH proposes to differentiate between indications in paediatric patients and in adults by adding the respective age groups in the indication wording of affected indications. Furthermore, as the term "infant"

has up to now not been used as defined by pertinent guidelines, but has included patients from birth to 2 years of age, the MAH proposes to correctly describe the relevant age groups as "newborns, infants and toddlers". Moreover, indications will be re-ordered to display prophylaxis indications first, followed by treatment indications. Indications for X tablets are restricted to those that are already approved in at least some of the EU countries and for which dosing with the available tablet strengths is feasible.

Indications for Y oil:

- Prophylaxis of rickets in newborns, infants and toddlers
- Prophylaxis of vitamin D deficiency disease in patients with an identified risk
- Prophylaxis of vitamin D deficiency symptoms in patients with malabsorption
- Treatment of rickets or osteomalacia
- Supportive treatment of osteoporosis in adults□□
- Treatment of hypoparathyroidism

Indications for X tablets:

- Prophylaxis of rickets in newborns, infants and toddlers
- Prophylaxis of vitamin D deficiency disease in patients with an identified risk
- Treatment of rickets or osteomalacia
- Supportive treatment of osteoporosis in adults□□

In order to facilitate identification of the appropriate dosing in paediatric patients for the physician, the MAH agrees to separate dosing recommendations for the paediatric population and those for adults into different subsections of SmPC section 4.2

Rapporteur's comments:

The MAH is proposing the reordering of the indications and some additional improvements in the indication wording to facilitate the distinction between the adult and paediatric indications. The rapporteur agrees with the MAH that the paediatric indications should reflect current clinical use as documented in the data submitted in this European paediatric work sharing procedure; however the adult indications are not within the scope of this procedure and therefore cannot be altered.
The MAH has proposed to specify the indication of prophylaxis of rickets only in newborns, infants and toddlers while in the currently approved SmPC, section 4.1 of the oral solution contains a generic wording without age-specific limitation.
Interestingly the tablets' SmPCs wording mentions only "*Prophylaxis of rickets in infants*". It is noted that there is a great variation in the prophylaxis guidelines across Europe, with no consensus regarding the cut off age in very young children (see page 16-17 of this report). For example in Germany supplementation is recommended during the 1st year of life. In the UK the guidance issued by the Chief Medical Officer in February 2012 recommends vitamin D supplementation to all at risk infants and young children aged 6 months to 5 years. In the majority of published guidelines, vitamin D supplementation as prophylaxis is recommended for all children that do not obtain the recommended daily amount through nutrition. The MAH is suggesting that "*as the indication has been restricted to newborns, infants and toddlers…if any rickets prophylaxis in older children and adolescents is required in rare cases, this would be addressed under prophylaxis of vitamin D deficiency in patients with an identified risk*". However this could be misleading for prescribers. The MAH did not provide robust justification for the proposed limitation of the prophylaxis of rickets indication to children below the age of 2 years. The rapporteur concludes that there can not be an agreement regarding the age limitation of the prophylaxis of rickets as national clinical practises vary across Member States. The rapporteur considers that the separate indication regarding the preterm newborns should be maintained for

the liquid formulation as it reflects a very specific use of vitamin D in this paediatric population.

The MAH also proposes to reword the indication of "*Prophylaxis in recognisable risk of a vitamin D deficiency disease in otherwise healthy persons without absorption disorder*" to "*Prophylaxis of Vitamin D deficiency disease in patients with an identified risk*". The rapporteur is of the view that the wording should include children and adults. The rapporteur consider this change acceptable as apart from the otherwise healthy paediatric patients which are at risk by not obtaining the full daily amount of vitamin D through nutrition, there are children which are at risk due to coexisting morbidities such as obesity, HIV, on anticonvulsants, glucococorticoids or antifungals. Finally the MAH proposes to refine the prophylaxis of vitamin deficiency in patients with malabsorption as follows: "*Prophylaxis of vitamin D deficiency symptoms in patients with malabsorption*". This indication is applicable to both paediatric and adult patients and this should be clearly stated in the SmPC. However it is not clear why the MAH does not include this indication in section 4.1 of the tablets.
The MAH has responded to the rapporteur's question regarding other indications stating that hypoparathyroidism may occur in paediatric patients (Schilling and Ziegler, 1997), however osteoporosis is a typical indication in adults.
The rapporteur agrees that hypoparathyroidism is also a paediatric disease which requires treatment with calcium and vitamin D. Although 1 ,25-dihydroxycolecalciferol is the preferred vitamin D form used in the treatment of hypoparathyroidism, colecalciferol still has a place. However, the MAH failed to provide evidence on the appropriate posology to recommend its use in paediatric patients. Please see also comments in question 3.

The rapporteur does not agree that osteoporosis is a typical indication in adults. There is growing evidence on the prevalence and potential severe health implications of paediatric osteoporosis, particularly in children with chronic illnesses and concomitant use of drugs which affect bone metabolism such as corticosteroids. However treatment of paediatric osteoporosis remains largely controversial. There is scarce evidence [Bowden 2008 and Shaw 2003, and a Cochrane review (Winzenberg, 2010)] suggesting that the use of Vitamin D should be considered as supportive treatment of osteoporosis in children who have additional risks to develop vitamin D deficiency. However in the majority of the publications routine supplementation is not recommended (Roth 2007). It is therefore concluded that no new data suggesting the routine use of colecalciferol in paediatric osteoporosis have been identified during this paediatric work-sharing procedure.

Rapporteur's proposed SmPC wording for Section 4.1

Oral liquid formulation

- Prophylaxis of rickets and osteomalacia in children and adults
- Prophylaxis of rickets in preterm newborns
- Prophylaxis of vitamin D deficiency in children and adults with an identified risk
- Prophylaxis of vitamin D deficiency in children and adults with malabsorption
- Treatment of rickets and osteomalacia in children and adults

Tablets:

- Prophylaxis of rickets and osteomalacia in children and adults
- Prophylaxis of vitamin D deficiency in children and adults with an identified risk
- Prophylaxis of vitamin D deficiency in children and adults with malabsorption
- Treatment of rickets and osteomalacia in children and adults

Question 3:

The MAH was requested to consider the issues identified regarding the paediatric posology of Y oral solution. The MAH should review the evidence available and either justify the current licensed SmPC doses or propose changes of the paediatric recommendations in section 4.2.The rapporteur is aware that in established rickets high doses might be used but in order to avoid overdose, it would be better if the posology for different paediatric subsets is given in the SmPC with an additional statement that in severe cases higher doses might be used under medical supervision included.

MAH Response:

In the comprehensive risk assessment of Hathcock et al (2007), based on relevant, well-designed human clinical trials of colecalciferol, including paediatric patients, 10,000 IU/day of vitamin D3 is considered as the NOAEL (No Observed Adverse Effect Level). The authors point out that up to this NOAEL, an increase in the serum calcium level and thus any toxic effects are not expected. Also, DiVasta (2010) pointed out that colecalciferol doses of up to 10,000 IU/day in paediatric patients did not lead to any toxic effect (DiVasta et al., 2010). The maximum recommended dose in all paediatric indications (except hypoparathyroidism) of X tablets and Y oil is 5,000 IU per day. Therefore, any toxic effect of this dose that is only 50% of the NOAEL is not expected. Nevertheless, in order to increase the safety of colecalciferol in paediatric patients to a maximum possible, the MAH proposes to include in the product information a recommendation for regular monitoring of the serum calcium level in long-term treatment with colecalciferol doses exceeding 1,000 IU/day.

Regarding treatment of rickets, as different colecalciferol doses for the treatment of vitamin D deficient musculoskeletal diseases are recommended in the literature (Fuleihan et al., 2006; Gordon et al., 2008; Hillmann et al., 2008; DiVasta et al., 2010) for different age groups, the MAH agrees to specify the dose recommendations for this indication for different age groups.

In conclusion, the following dose recommendations will apply to the paediatric population based on International Units:

Prophylaxis of rickets
Newborns, infants and toddlers (0 to < 2 years): 500 IU vitamin D daily.
Preterm newborns: 1,000 IU vitamin D daily.

Prophylaxis of vitamin D deficiency disease in patients with an identified risk
All age groups: 500 IU vitamin D daily.

Prophylaxis of vitamin D deficiency symptoms in patients with malabsorption
All age groups: 3,000 IU to 5,000 IU vitamin D daily.

Treatment of rickets
Newborns, infants, toddlers, and young children (0 to 5 years): 1,000 IU to 2,000 IU vitamin D daily.
Older Children (> 5 years) and adolescents: 2,000 IU to 5,000 IU vitamin D daily.

Treatment of hypoparathyroidism
All age groups: The recommended dose range is 10,000 to 200,000 IU vitamin D per day depending on the serum calcium levels. Most of the patients are treated with up to 10,000 (to 20,000 IU) vitamin D daily. The serum calcium levels have to be checked initially every 4-6 weeks, and later every 3-6 months. The dose has to be adjusted according to these values.

These dose recommendations based on International Units will be implemented for each pharmaceutical form in number of tablets or drops as appropriate in line with the indications listed for each form in the response to Question 2.

Rapporteur's comments:

As mentioned in the discussion of the previous MAH response, only the changes in section 4.2 in relation to the use of colecalciferol in the paediatric population are reviewed by the rapporteur and no changes in the adult posology are acceptable as they are outside the scope of this paediatric work-sharing procedure.
The MAH is proposing a dose of 500 IU daily for prophylaxis of rickets for children 0 to 2 years and a similar prophylactic dose of 500 IU vitamin D daily for all age groups in patients with an identified risk. The rapporteur notices that the majority of the international guidelines for prevention of rickets recommend a daily dose of 400 IU. This dose appears to be widely used across Europe as identified by the 2010 NUI that in 9 countries the recommended posology is 400 IU/day (see page 17 of this report). However it is noted that there is no universal consensus as for example in Germany the daily recommendation is 500 IU. The MAH has not provided any evidence supporting the dose of 500IU. Additionally no data have been submitted to support the dose of 500 IU in all age group at risk of vitamin D deficiency. Based on current literature this dose is increased to at least 600 IU for children older than 1 year. It is also noted that obese children, children on anticonvulsants, glucocorticoids, antifungals and AIDS medications require at least two to three times more Vitamin D for their age group (the Endocrine Society Clinical Practice Guidelines 2011).

For the prophylactic dose in premature infants please see comments in question 5.

The MAH is proposing for patients with malabsorption a daily dose of 3000 to 5000 IU for all age groups as prophylaxis for vitamin D deficiency. No evidence for this posology has been provided by the MAH.

Similarly the MAH is proposing the following doses for the treatment of rickets without providing any evidence to support this posology :
Newborns, infants, toddlers, and young children (0 to 5 years): 1,000 IU to 2,000 IU vitamin D daily.
Older Children (> 5 years) and adolescents: 2,000 IU to 5,000 IU vitamin D daily.

For the treatment of hypoparathyroism the MAH is proposing that all age groups (children and adults) should be receiving a dose range of 10,000 to 200,000 IU vitamin D per day depending on the serum calcium levels. There is limited data on the treatment of hypoparathyroidism with colecalciferol in the paediatric population. The MAH in their initial application has quoted a reference of Bassler et al, 2002 regarding the use of Vitamin D in treatment of hypoparathyroidism. This reference unfortunately was not included in the literature submitted. The rapporteur considers that the posology cannot be modified as the MAH has not submitted further evidence to support the use of vitamin D in such high doses in children with hypoparathyroidism.

From this review it is evident that there is no consensus for the posology in treating rickets and vitamin D deficiency in children. There is a relative agreement in guidelines regarding the prophylactic dose for rickets, set at 400IU daily but the cut off age for this supplementation varies significantly. The Endocrine Society suggests 600IU for children older than 1 year. For the treatment of hypothyroidism in children dosing recommendations and literature evidence is almost absent.
The MAH, following the rapporteur's recommendations and requests for clarification, proposed to change the paediatric posology in the SmPC to meet more generally accepted doses. The rapporteur recognises and welcomes the direction of the changes to avoid unsafe dosing. In particular, the MAH has lowered the high dose for the prophylaxis of rickets in preterm infants,

as this has been identified in the day 89 report. However, evidence supporting the specific changes in dosing has not been submitted.
In conclusion, the MAH did not provide robust evidence to support the proposed changes in the SmPC and therefore no changes in the posology for prophylaxis and treatment of rickets and vitamin D deficiency can be accepted as part of the paediatric work-sharing procedure under Article 45.

Question 4:

The MAH is requested to include the following statement in the information of the package leaflet: "X tablets contain soybean oil. If you are allergic to peanut or soya, do not use this medicinal product." In the SmPC under section 4.3 the following wording should be added: "X tablets 500/1000 should not be used if the patient is allergic to peanut or soya", according to the EU guidance on the excipients in the label and package leaflet of medicinal products for human use (2003).

MAH Response:

The MAH agrees to include the respective information in SmPC section 4.3.
The MAH suggested the following wording:

"X must not be used in patients hypersensitive to cholecalciferol, **soya oil, arachis (peanut) oil** or to any of the **other** excipients of X."

Rapporteur's comments:

The rapporteur agrees with the changes suggested by the MAH. Issue resolved.

Question 5:

Following the circulation of the Day 70 PdAR, the rapporteur received comments from MS who fully supported the rapporteur's overall conclusion and request for additional information. Comments were also received from one MS that overall endorsed the rapporteur's opinion and had the following additional comments:

"In a German guideline concerning rickets due to vitamin D deficiency (Vitamin-D-Mangel-Rachitis) the dosing recommendation for prophylaxis is 500 IU of vitamin D during the first year of life. Thus the recommendation in the SmPCs – which recommend a prophylaxis for children up to 2 years – are not in accordance with the German guideline. The German guideline gives no recommendation for premature infants. There is no explanation given for the high dose listed in the SPC of X 1000 IU for pre-term new-born infants."

The MAH is requesting to address these comments as part of their response to the additional clarifications requested in order to optimize the proposed posology for the paediatric population.

MAH Response:

Efficacy and safety of 1,000 IU cholecalciferol/day were investigated in the study by Pohlandt et al. (1976) in 118 newborns. The subjects were randomized and group 1 (N=57) received 1,000 IU vitamin D daily and group 2 (N=61) 1,000 IU vitamin D and 0.25mg sodium fluoride daily for 6 months. Adverse effects were not observed in any group. Furthermore, up to now the indication "Treatment of rickets in premature infants" has been recommended by the German authorities in their "Mustertext" with a dose recommendation of 1,000 IU/day.

In the product information of X tablets and Y oil, while treatment during the first year of life is a definite indication, rickets prophylaxis in the second year of life is only recommended, especially during the winter months. This is in accordance with current literature (e.g. Zipitis et al., 2006) and leaves the decision on whether or not to continue treatment in the second year to the physician.

Rapporteur's comments:

For premature newborns the MAH is proposing a dose of 1000 IU vitamin D daily. The MAH has not provided any data to support this dose. The study quoted above does not provide any evidence on the efficacy or the safety of this dose in this vulnerable population. The existing guidelines are not in agreement as the AAP guidelines (2008) propose 400UI in premature neonates (Taylor et al 2009) and the ESPGHAN (Agostoni C., 2010) propose 800-1000IU per day. The amount of supplementation should be appropriately calculated after subtracting the amount of vitamin D included in fortified preterm formulas.
The rapporteur concludes that no specific posology can be recommended for preterm infants as a result of this procedure based on the available literature and guidelines. However, the direction of the change proposed by the MAH is welcomed as is closer to what is considered a safer dose for preterm infants.

ADDITIONAL CHANGES PROPOSED IN THE SmPC

The MAH has proposed a lot of changes for the SmPC of X tablets and Y oil. The majority of these changes are specific to these colecalciferol products and therefore not within the scope of this work sharing procedure. The MAH is advised that if update of the SmPC is needed, appropriate regulatory procedures should be undertaken to vary the current product licenses.

Section 4.2 Posology and method of administration

The MAH has proposed to delete the following statement and replace it with a monitoring recommendation in section 4.4:

"During long-term treatment with {Tradename} the serum and urinary calcium levels should be monitored regularly and the kidney function checked by measurement of serum creatinine. If necessary, the dose must be adjusted according to the serum calcium levels."

Comment:
The rapporteur considers that, according to SmPC guidelines, there should be a statement in Section 4.2 warning physicians to monitor children receiving high doses of Vitamin D (>1000 IU/day) and children on long term treatment with cross reference to statement in Section 4.4

Duration of treatment

~~The duration of use depends on the course of the disease.~~

Prophylaxis of rickets
Newborns and infants receive {Tradename} from the second week of life until the end of the first year of life. In the second year of life further doses of {Tradename} are recommended, especially during the winter months

Treatment of rickets and osteomalacia ~~induced by vitamin D deficiency~~
Therapy should be continued for one year.

All other indications
The ~~treatment~~ duration **of treatment** ~~in prophylaxis of a vitamin D deficiency disease and in supportive treatment in osteoporosis~~ depends on the course of the underlying disease

Comments:
Current guidelines recommend that the duration of treatment of rickets should be for 6 weeks followed by prophylactic doses, as it is not advisable to continue treatment doses for a year due to the risk of vitamin D intoxication. Therefore, the rapporteur does not support the inclusion of the sentence "therapy should be continued for a year".

For the rest of the proposed changes, please see comment in the beginning of this section.

Method of administration

Tablets 500 IU/1000 IU
Newborns, i*nfants and toddlers (0 to* **<** *2 years)*
The tablets are disintegrated on a teaspoon in water or milk and given directly into the mouth, ideally during a meal.
~~It is not advisable to add the dissolved tablet to the infant's bottle or spoon food since complete ingestion cannot be guaranteed.~~ If the **disintegrated** tablets are ~~nevertheless to be administered in food, they are not to be added until it has boiled~~ **added to the infant's bottle or spoon feed, take care that the meal is consumed completely, as otherwise the entire dose is not ingested.**
The disintegrated tablets should be added to the cooked and adequately cooled feed only.
~~The vitamin D content must be taken into consideration if food with added vitamins is used.~~

Children from 2 years of age, adolescents and adults
Swallow the tablet(s) with sufficient liquid

Oral solution
Newborns, i*~~l~~nfants and toddlers (0 to < 2 years)*
{Tradename} is preferably given ~~by~~ **with** a teaspoon**ful** of milk or water. ~~Care should be taken that the entire dose is ingested~~. **If the drops are added to bottle or spoon feed care should be taken that the meal is consumed completely, as otherwise not the entire dose is ingested. The drops should be added to the cooked and adequately cooled feed only.**

Children ~~(~~***from 2*** ~~to 11~~ *years* ***of age***~~)~~*, adolescents* ~~(12 to 18 years)~~ *and adults*
{Tradename} is taken ~~by~~ **with** a teaspoon**ful** of liquid.

Comments:

The tablet size is related to the ability of a child to swallow a tablet. Young children may be able to accept small tablets, but not large size ones. This is mainly the case in medicines where age appropriate formulations (i.e. oral liquid) are not available. The size of the tablets influences the age range for which they are considered acceptable. The rapporteur does not support the inclusion of the sentence

"***Children from 2 years of age, adolescents and adults***
Swallow the tablet(s) with sufficient liquid"

For the rest of the proposed changes, please see comment in the beginning of this section.

Section 4.4 Special warnings and precautions for use

During long-term treatment with a daily dose exceeding 1,000 IU vitamin D the serum calcium values must be monitored.

Comments:
The rapporteur agrees with the changes suggested by MAH.

The MAH had an additional comment that additional text had been proposed in accordance with pertinent EU guidelines for SmPC sections 4.5, 4.8 and 5.1, for which no comments were received.
The MAH proposed the following:

Section 4.5 Interaction with other medicinal products and other forms of interaction

Paediatric population
Interaction studies were only performed in adults

Section 4.8 Undesirable effects

Paediatric population
Frequency, type and severity of adverse reactions in children are similar to those seen in adults.

Section 5.1 Pharmacodynamic properties

Paediatric population
The efficacy and safety of colecalciferol in the paediatric population was described in ~~3~~**6** published clinical studies. Main indications for the use of colecalciferol in paediatric patients were prophylaxis of rickets in **newborns**, infants **and toddlers** (**0 to <2 years**, up to 1000IU/day) or ~~prevention~~ treatment of vitamin D ~~deficiency~~ **deficient musculoskeletal** disease in **infants, toddlers and young** children (**0 to 5 years, ≥~~2~~**,000IU/day) **or older children and adolescents (2000IU to 5000IU/day).** In these indications, colecalciferol was effective and well tolerated in paediatric patients.

Rapporteur's Comments:

The rapporteur notes that in the original submission it was not clear that the text in these sections was additional and not within the currently approved SmPC.
The MAH has not provided any evidence for the statements proposed in sections 4.5 and 4.8 and therefore the rapporteur does not support the addition of this text. In section 5.1, the MAH quotes studies using the exact posology for different paediatric subgroups as proposed in section 4.2; however it is unknown to which studies the MAH is referring. The rapporteur

considers the changes in sections 4.2 not acceptable due to the lack of evidence submitted in this procedure and similarly does not support the inclusion of this text in section 5.1.

VIII. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

One MAH submitted paediatric data for colecalciferol containing medicinal products, in accordance with Article 45 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. Colecalciferol is a well established drug for the prevention and treatment of rickets.
The rapporteur proposes the rewording of indications in sections 4.1 of the SmPC and an addition under the special warnings and precaution section 4.4 (as shown below). These changes are applicable for single active substance colecalciferol products (not combination products) that are already licensed for the paediatric population. The proposed wording for section 4.1 can be used as a guide as there is great variability of the approved indications in the currently nationally authorised products.

The rapporteur also proposes the addition of a contraindication related to the risk of allergic reactions (due to the excipient soybean oil in the MAH's product-tablets) in section 4.3 of the SmPC and in the PIL. It is noted that the last change is specific to the MAH's product and cannot be widely implemented in all colecalciferol containing products.

The rapporteur in the day 89 report requested the MAH to review the paediatric posology of vitamin D in the SmPC, as there were safety concerns regarding the prophylactic dose for rickets in premature infants and the treatment dose of vitamin D deficiency for all paediatric subsets. The MAH addressed these issues and proposed amended posology for the different paediatric subgroups.
The rapporteur welcomes any changes moving to a direction of safer dosing for the different paediatric subgroups. However, the studies submitted by the MAH did not provide sufficient evidence for the proposed posology. The rapporteur acknowledges that this is largely due to the sparse literature data and the great variability of the doses recommended by international guidelines. There is difficulty defining the vitamin D requirements for each age group. This might be partly due to various factors influencing vitamin D status. Additionally, the levels at which 25(OH)D should be raised to achieve skeletal benefits have not been fully established. The levels of 25(OH)D to achieve nonskeletal benefits are even less elucidated. Future studies and expert scientific discussion internationally are needed before reaching a consensus on the appropriate dosing in children.
At present and as a result of this procedure, the rapporteur concludes that an update of the current recommended posology for colecalciferol in children, which would be applicable for all colecalciferol containing products across Europe, cannot be proposed.
The MAHs are encouraged to review the gaps in existing knowledge for the use of colecalciferol in children and conduct studies which could lead to recommendations for appropriate dosing for the prevention and treatment of vitamin D deficiency in children.

SmPC CHANGES

- **SmPC changes proposed for all colecalciferol products (single active substance, not for combination products) licensed in children**

The rapporteur proposes the following wording in the SmPC:

Section 4.1 Therapeutic indications (to be used as guide)

Oral liquid formulation

- **Prophylaxis of rickets and osteomalacia in children and adults**
- **Prophylaxis of rickets in preterm newborns**
- **Prophylaxis of vitamin D deficiency in children and adults with an identified risk**
- **Prophylaxis of vitamin D deficiency in children and adults with malabsorption**
- **Treatment of rickets and osteomalacia in children and adults**

Tablets:

- **Prophylaxis of rickets and osteomalacia in children and adults**
- **Prophylaxis of vitamin D deficiency in children and adults with an identified risk**
- **Prophylaxis of vitamin D deficiency in children and adults with malabsorption**
- **Treatment of rickets and osteomalacia in children and adults**

Section 4.4 Special warnings and precautions for use

During long-term treatment with a daily dose exceeding 1,000 IU vitamin D the serum calcium values must be monitored.

- **Specific changes for X tablets**

The rapporteur proposes the following wording in the SmPC:

Section 4.3 Contraindications

X tablets 500/1000 should not be used if the patient is allergic to peanut or soya.

- **PIL changes proposed for X tablets**

The rapporteur proposes the following wording in the PIL:

X tablets contain soybean oil. If you are allergic to peanut or soya, do not use this medicinal product.

IX. LITERATURE REFERENCES

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X. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

MAH	MS	Name of the medicinal product	Strength	Pharmaceutical form	AS
Merck KGaA	CZ	Vigantol	20000 IU/ML	por gtt sol	Colecalciferol
Merck Pharma GmbH	DE	Vigantol Oel	0.5mg/ml	emulsion, oral drops	Colecalciferol
Merck Pharma GmbH	DE	Vigantoletten 1000	25 µg	tablet	Colecalciferol
Merck Pharma GmbH	DE	Vigantoletten 500	12.5 µg	tablet	Colecalciferol
Merck KGaA	LU	Vigantoletten 1000	25 µg	tablet	Colecalciferol
Merck KGaA	LU	Vigantoletten 500	12.5 µg	tablet	Colecalciferol
Merck KGaA	LU	Vigantoletten 1000	25 µg	tablet	Colecalciferol
Merck KGaA	LU	Vigantoletten 500	12.5 µg	tablet	Colecalciferol