COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Colevit 800 IE, 1000 IE, 7000 IE, and 30000 IE film-coated tablets

(cholecalciferol)

NL/H/4075/001-004/DC

Date: 6 August 2019

This module reflects the scientific discussion for the approval of Colevit 800 IE, 1000 IE, 7000 IE, and 30000 IE film-coated tablets. The procedure was finalised at 28 June 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
DBP	Vitamin D-Binding Protein
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Colevit 800 IE, 1000 IE, 7000 IE, and 30000 IE film-coated tablets from Pharma Patent Kft.

The product is indicated for:

- Treatment of vitamin D deficiency (serum 25(OH)D <25 nmol/l)
- Prevention of vitamin D deficiency in high-risk patients
- As an adjunct to specific therapy for osteoporosis in patients with vitamin D deficiency or at risk of vitamin D insufficiency

Colevit is indicated in adults, the elderly and adolescents.

A comprehensive description of the indications and posology is given in the SmPC.

Marketing authorisations for different types of cholecalciferol oral dosage forms (tablets, drops, film-coated tablets) have been issued in most European countries since decades. VTG Hungária Kft has decided to develop film-coated tablets containing 800 IE, 1000 IE, 7000 IE, and 30000 IE cholecalciferol.

The concerned member state (CMS) involved in this procedure was Greece.

The application is based on article 10a of Directive 2001/83/EC, a so called bibliographic application based on the well-established medicinal use of cholecalciferol.

II. QUALITY ASPECTS

II.1 Introduction

Colevit 800 IE is a yellow coloured, round film-coated tablet with smooth convex surface on both sides.

Colevit 1000 IE is a yellow coloured, round film-coated tablet with smooth convex surface on both sides, and 'D' embossed on one side.

Colevit 7000 IE is a yellow coloured, round film-coated tablet with smooth convex surface on both sides, and 'W' embossed on one side.

Colevit 30000 IE is a yellow coloured, round film-coated tablet with smooth convex surface on both sides.

The different tablet strengths are distinguishable by the used embossing and size

Each tablet contains cholecalciferol 800 IE, 1000 IE, 7000 IE or 30000 IE, equivalent to 0.02 mg, 0.025 mg, 0.175 mg or 0.75 mg vitamin D3.

The film-coated tablets are packed in opaque PVC/PVdC-Alu blisters.

The excipients are:
Tablet core - cellactose 80 (lactose monohydrate and powdered cellulose (E460 (ii)), modified food starch, maize starch, croscarmellose sodium (E468), sucrose, colloidal anhydrous silica (E551), colloidal hydrous silica (E551), magnesium stearate (E572), sodium ascorbate (E301) and medium chain triglycerides, DL-alpha-tocopherol (E307).
Tablet coating - Opadry II Yellow 85F 32659, consisting of: polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol, talc (E553b), quinoline yellow aluminium lake (E104) and yellow iron oxide (E172).

The 800 IE and 1000 IE strengths are fully dose proportional as well as the 7000 IE and 30000 IE product strengths.

II.2 Drug Substance

The active substance is cholecalciferol, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Cholecalciferol is sensitive to heat, oxidation and light, so it is stabilised in different premix forms. Cholecalciferol concentrate (powder form) is used in this product.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 24 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. This is a well-established use application. No bioequivalence or clinical studies have been performed. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The main steps of the manufacturing process are blending of the ingredients, compression and film-coating. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for two pilot scale batches per tablet strength and three industrial scale batches of the 800 IE, 1000 IE and 30000 IE strength in accordance with the relevant European guidelines.

Control of excipients
The excipients used are well known. The specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, dimensions, average weight, uniformity of mass, disintegration time, resistance to crushing, identity, assay, antioxidant content microbial contamination, and uniformity of dosage units. The release and shelf life specification are not identical for the assay and antioxidant content. The specification is acceptable. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided for four laboratory (one per strength) and eight pilot scale batches (two per strength) at 25°C/60% RH (18 months), 30°C/65% RH (12 months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were packaged in the proposed packaging.
According to the available long term stability results a decrease in assay levels is seen (going out of specification (OOS) at 40°C/75% RH). There is a slight tendency towards weight increase (going out of specification for the highest strength at 40°C/75% RH). At 30°C/65% RH after 12 months of storage, all parameters tested remained within specification.

Based on the data submitted a shelf life was granted of 18 months for the 1000 IE, 7000 IE and 30000 IE strength. For the 800 IE strength, the MAH submitted 24 month stability data for three batches packed in the proposed packaging. As all results of these stability data are within the specifications, the claimed shelf life of 24 months for the 800 IE strength is justified. Furthermore, the claimed storage condition 'Store below 25°C. Store in the original package in order to protect from light' for all strengths is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Colevit has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

The two forms of the vitamin that are best known and which are of nutritional significance are ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). Vitamin D can be obtained from the diet and by the action of sunlight on the skin. Vitamin D3 is produced in the skin by an ultraviolet light-induced photolytic conversion of 7-dehydrocholesterol to previtamin D3 followed by thermal isomerisation to vitamin D3. The active form of vitamin D3 is 1,25–dihydroxyvitamin D3 (1,25-(OH)2D3) and is formed following sequential hydroxylations in the liver and kidney.

Most of the biological activities of 1,25-(OH)2D3 are mediated by a high-affinity receptor (vitamin D receptor, VDR) that acts as a ligand-activated transcription factor. The genomic and nongenomic actions of vitamin D combine to produce a multitude of responses in target cells.

Vitamin D deficiency underlies the pathogenesis of rickets in children and osteomalacia in adults. 1,25-(OH)2D3 regulates calcium and phosphate metabolism via three target tissues: kidney, small intestine and bone. In the kidney, 1,25-(OH)2D3 regulates calcium transport in

the proximal tubule; in the small intestine, it regulates calcium and phosphate uptake from the gut. 1,25-(OH)2D3 is also involved in the maintenance of plasma calcium levels via bone resorption and formation. 1,25-(OH)2D3 regulates the synthesis of parathyroid hormone (PTH) by a negative feedback mechanism. Subsequent investigations revealed that its deficiency and insufficiency, measured as serum 25-(OH)D of <30 ng/ml, are associated with also nonskeletal diseases such as autoimmune diseases, inflammatory bowel disease, bacterial and viral infections, cardiovascular disease, cancer and neurocognitive disorders. Low vitamin D levels are also associated with increased risk of all-cause mortality.

It is recognised that 1,25-(OH)2D3 also exerts non-genomic actions that are manifested, in the main, as the activation of signalling molecules, such as phospholipase C and phospholipase A2 (PLA2), phosphatidylinositol-3 kinase (PI3K) and p21ras, and the rapid generation of second messengers (Ca^{2+}, cyclic AMP, fatty acids and 3-phosphoinositides such as phosphatidylinositol 3,4,5 trisphosphate), accompanied by the activation of protein kinases, such as protein kinase A, src, mitogen-activated protein (MAP) kinases, protein kinase C (PKC) and Ca^{2+}-calmodulin kinase II. On the other hand, the metabolic, anti-inflammatory and antifibrotic properties of vitamin D provide plausible mechanisms by which vitamin D may impact on the various steps of disease progression and severity. It has been known for some time that vitamin D has anti-proliferative and anti-fibrotic properties and plays an important role in the regulation of extracellular matrix, little has been known until recently about the effects of vitamin D on protection of liver cells.

III.2 Pharmacokinetics

Vitamin D is metabolised to the steroid hormone 1,25-(OH)2D3, a process which is promoted by PTH. The hydroxylated metabolites 25(OH)D, 24,25(OH)2D, and 1,25(OH)2D are also lipophilic molecules. Because of their low solubility in the aqueous media of plasma, vitamin D compounds are transported in the circulation bound to plasma proteins. The most important of these carrier proteins is the vitamin D-binding protein (DBP). Only 5% of the total DBP of normal human plasma is occupied with vitamin D compounds. Therefore, under normal physiological conditions, nearly all circulating vitamin D compounds are protein bound, which has a great influence on vitamin D pharmacokinetics. DBP-bound vitamin D metabolites have limited access to target cells and are, therefore, less susceptible to hepatic metabolism and subsequent biliary excretion, which prolongs their half-life in circulation.

Albumin and lipoproteins are also important plasma carrier proteins with lower affinities for vitamin D metabolites than DBP. The first step in the metabolic activation of vitamin D3 is hydroxylation of carbon 25. This reaction occurs primarily in the liver, although other tissues including skin, intestine, and kidney have been reported to catalyse 25-hydroxylation of vitamin D.

The final cleavage product of 1,25(OH)2D3, calcitroic acid, is biologically inert. Other polar metabolites of cholecalciferol have also been isolated, including 25,26 dihydroxycholecalciferol. A further metabolite may be produced in the kidney by 24-hydroxylation of 1,25(OH)2D3 to form 1,24,25(OH)3D3. There is also an enterohepatic

recirculation of vitamin D and its metabolites, largely conjugated as glucuronides before secretion into the bile, and bile fistulae may thus lead to vitamin D depletion. Because of their high lipid solubility, cholecalciferol and its metabolites are eliminated slowly from the body. Cholecalciferol has a plasma half-life of 19 to 25 hours and a terminal half-life (the time needed for the amount of a compound present in all body stores to decrease by half) of weeks to months. Metabolites are eliminated primarily (96%) through the bile and faeces.

III.3 Toxicology

In animals chronic excess of vitamin D may cause hypercalcaemia, resulting in deposition of calcium in soft issues and bone demineralisation, anorexia, weight loss, anaemia, and weakness. In monkeys the cholecalciferol (vitamin D3) was shown to be significantly more toxic than vitamin D2. At doses that far higher than the human therapeutic range, some level of teratogenicity has been observed in animal studies. Excess vitamin D during gestation in rabbits led to decrease foetal viability, increased number of abortions and induced supravalvular aortic lesions in the offspring. High doses of vitamin D appear to affect maternal calcium, phosphate and cholesterol homeostasis and neonatal calcium homeostasis. In rodents, administration of high levels of vitamin D during gestation results in retarded foetal and placental growth, loss of ossification of foetal bones and foetal skeletal degeneration. The doses in use, were significantly (two to four orders) higher that that is in use of human, should be normalised when compared to human data. The results and doses with toxic signs or LD50 are clearly different in species, therefore the nonclinical experimental data were inconsistent with the type of administration or duration of treatment, and therefore interpolation to human may not be plausible to perform.

Our current understanding of the components of the vitamin D signal transduction machinery allows us to theorise in broad terms about how vitamin D toxicity might arise from hypervitaminosis D. Of the three hypotheses put forward to explain the triggering event for toxicity, increases in total 25(OH)D and free 1,25(OH)2D3 concentrations are the most plausible, although they remain unproven. However, even in the absence of definitive evidence to establish the responsible metabolite, the wealth of animal studies and human anecdotal reports of vitamin D intoxication indicate that plasma 25(OH)D is a good biomarker for toxicity, and the threshold for toxic symptoms is ~750 nmol/l. This threshold value implies that 25(OH)D concentrations up to the currently considered upper limit of the normal range, namely 250 nmol/l, are safe and still leave a broad margin for potential medication error because values significantly higher than this value have never been associated with toxicity.

No genotoxicity was observed in studies *in vivo* or *in vitro*. No adverse effects were seen in results of the reported carcinogenicity studies involving cholecalciferol.

III.4 Ecotoxicity/environmental risk assessment (ERA)

An ERA is not required for vitamins, because they are unlikely to result in significant risk to the environment.

III.5 Discussion on the non-clinical aspects

The application for Colevit is based on well-established use. This is endorsed, since cholecalciferol has been registered for this indication for a long time and the dose is not increased. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Cholecalciferol is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics and pharmacodynamics

Because of their low solubility in the aqueous media of plasma, vitamin D compounds are transported in the circulation bound to plasma proteins. The most important of these carrier proteins is the vitamin D-binding protein (DBP). Under normal physiological conditions, nearly all circulating vitamin D compounds are protein bound, which has a great influence on vitamin D pharmacokinetics. DBP-bound vitamin D metabolites have limited access to target cells and are, therefore, less susceptible to hepatic metabolism and subsequent biliary excretion, which prolongs their half-life in circulation. Albumin and lipoproteins are also important plasma carrier proteins with lower affinities for vitamin D metabolites than DBP.

The final cleavage product of 1,25(OH)2D3, calcitroic acid, is biologically inert. Other polar metabolites of cholecalciferol have also been isolated, including 25,26 dihydroxycholecalciferol. A further metabolite may be produced in the kidney by 24-hydroxylation of 1,25(OH)2D3 to form 1,24,25(OH)3D3. There is also an enterohepatic recirculation of vitamin D and its metabolites, largely conjugated as glucuronides before secretion into the bile, and bile fistulae may thus lead to vitamin D depletion. Because of their high lipid solubility, cholecalciferol and its metabolites are eliminated slowly from the body. Cholecalciferol has a plasma half-life of 19 to 25 hours and a terminal half-life (the time needed for the amount of a compound present in all body stores to decrease by half) of weeks to months. Metabolites are eliminated primarily (96%) through the bile and faeces. Skeletal muscle and adipose tissue may provide a large storage reservoir from which vitamin D may be slowly released as plasma levels fall. In cross-sectional studies, especially those performed in populations living at relatively elevated latitudes in North America, Europe,

and Asia, serum levels of the 25OHD metabolite are maximal some 30 to 60 days after peak sunlight exposure in the summer months.

Overall, the pharmacokinetic properties of cholecalciferol are adequately summarised.

Bridging data of the test product with the products referred to in the literature
The MAH provided literature data that indicate that only minor differences in absorption are present between formulations. It is argued that due to the long whole body half life of 25(OH)D, these minor changes in absorption are not clinically relevant. This is supported with the provided literature, which indicates that the improvement in 25(OH)D concentrations depends more on the total dose administered within a period and not as much on the formulation or the dose of a tablet.
Despite the fact that the MAH did not provide any *in vivo* data or dissolution data with their applied formulation, the literature provided by the MAH showed that the total dose within a period is more important. The MAH also provided data supporting a linear dose-response relationship. This relationship provides rationale for the administration of 30000 IE/week from a pharmacokinetic point of view.
Even though the MAH did not compare the applied formulations and the currently marketed formulations, the rationale of the MAH is accepted as the quality of the vitamin D capsules is acceptable and in line with Ph.Eur.

IV.3 Clinical efficacy

The indications of vitamin D3 film-coated tablets (prevention and treatment of vitamin D deficiency conditions; adjuvant therapy of osteoporosis) belong to the traditional therapeutic use of this active agent. These indications (i.e. the efficacy and safety of oral vitamin D substitution) have been proven in many smaller and larger studies, including randomised, double blind, controlled clinical trials. Vitamin D3 is routinely co-administered with different types of antiabsorptive drugs, mainly bisphosphonates and with calcium constitutes the basis of adjunctive therapy of osteoporosis.

For usage as an adjunct to specific therapy for osteoporosis, daily doses of approximately 800 IE of vitamin D3 have been systematically investigated in clinical studies. Similar doses are well established in prevention of vitamin D deficiency in adults, but less common in adolescents. A number of publications show that daily, weekly and monthly dosing of the same cumulative doses results in comparable 25(OH)D3 serum level in adult patients.
Higher doses (up to 4000 IE daily in adults) may be necessary in the treatment of vitamin D deficiency, (25(OH)D <25 nmol/l). In these cases, the dose should be adjusted dependent upon desirable serum levels of 25(OH)D, the severity of the disease and the patient´s response to treatment. Data on higher doses in adolescents have not been provided.

Result of a recent open labelled, randomised, controlled study showed the treatment regimes of a daily dose of 1000 IE; versus weekly dose of 7000 IE and a monthly dose of 30000 IE possess similar efficacy in normalisation of 25(OH)D levels in deficient patients. There is no difference in bioavailability of applied doses revealed when compared the

outcome parameter as 25(OH)D levels. The treatment of vitamin D deficient patients with 1000 IE/day dose regimes are considered effective to restore the 25(OH)D values to close normal range (above 20 ng/ml).

IV.4 Clinical safety

Urolithiasis may occur after chronic (several years) exposure to modest (1000 to 2000 IE/day) dietary supplements of vitamin D, or vitamin D may facilitate renal stone formation in patients with a predisposing cause, such as renal infection or metabolic disease. Maintenance of patients, who absorb calcium poorly (for a variety of reasons) with supplementary vitamin D, often leads to hypercalciuria and the need to reduce the vitamin D dose. Long-term supplementation with vitamin D of patients without malabsorption eventually increases the absorption of calcium to a point that promotes hypercalcuria, which in turn would promote deposition of calcium in the kidneys. Patients who have above normal calcium intakes would be especially at risk, as would patients who already have idiopathic hypercalciuria or some other cause of renal stone formation.

Dyslipidemic effects of cholecalciferol, characterised by decreases in high-density lipoprotein (HDL) cholesterol and increases in low-density lipoprotein (LDL) cholesterol, have been observed when the vitamin was given alone in postmenopausal women; beneficial lipid changes of hormone replacement therapy (HRT) may be blunted by addition of cholecalciferol.

Excessive inputs of vitamin D produce a syndrome known as vitamin D intoxication, which is characterised by hypercalcemia, renal stones, and renal calcification, with kidney failure and death. Except for infrequent cases of accidental or intentional poisoning, this syndrome is rarely seen today. The mechanism for hypercalcemia, which is generally considered the initial expression of toxicity, is unclear. Our current understanding of the components of the vitamin D signal transduction machinery allows us to theorise in broad terms about how vitamin D toxicity might arise from hypervitaminosis D. However, even in the absence of definitive evidence to establish the responsible metabolite, the wealth of animal studies and human anecdotal reports of vitamin D intoxication indicate that plasma 25(OH)D3 is a good biomarker for toxicity, and the threshold for toxic symptoms is ~750 nmol/l versus the normal serum levels of 75 nmol/l. This threshold value implies that 25(OH)D concentrations up to the currently considered upper limit of the normal range, namely 250 nmol/l, are safe and still leave a broad margin for error because values significantly higher than this value have never been associated with toxicity.

The MAH states that a thorough evaluation of the literature, mostly published since the Food and Nutrition Board promulgated the tolerable upper intake level (TUIL or UL) for vitamin D in 1997, supports the need to consider the increased UL for vitamin D. There are no documented cases of vitamin D intoxication at serum 25(OH)D levels <500 nmol/l. It would take continuous oral intakes in excess of 25000 IE/day to produce such a level. Evaluating a large body of literature, till there are no physiological reasons for oral intakes as high as 10000 IE/day, nevertheless, it is worth noting that a daily dose that high can be

produced by sun exposure and that typical 25(OH)D levels produced at that intake are on the order of 220 nmol/l, far below the level at which toxicity manifestations might occur. Daily oral intakes as high as 10000 IE are still safe, that results in a weekly total dosage of 70000 IE. This further supported by recent data from clinical studies of daily dose equivalent from 4000 IE up to 7200 IE where similar safety profile was reported as by lower daily doses. However, hypercalcemia/hypercalciuria were reported in a few cases.
Although vitamin D intoxication may be rare, several studies have shown that high doses of vitamin D had the undesirable effect of increasing falls and fractures in older adults.
Hypercalcaemia has occurred when calcium salts are given with thiazide diuretics or vitamin D. Vitamin D increases the gastrointestinal absorption of calcium and thiazide diuretics decrease its urinary excretion. Plasma calcium concentrations should be monitored in patients receiving the drugs together.

Hypercalcaemia during pregnancy may produce congenital disorders in the offspring, and neonatal hypoparathyroidism. However, the risks to the foetus of untreated maternal hypoparathyroidism are considered greater than the risks of hypercalcaemia due to vitamin D therapy.
Vitamin D is distributed into breast milk, and its concentration appears to correlate with the amount of vitamin D in the serum of exclusively breast-fed infants. The American Academy of Pediatrics considers the use of vitamin D to be usually compatible with breast feeding, although they and others recommend that the infant be closely monitored for hypercalcaemia or clinical manifestations of vitamin D toxicity if the mother is taking pharmacological doses of vitamin D. Reports found doses up to 6400 IE/day safe for lactating women.

IV.5 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Colevit.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• Aggravation of hypervitaminosis D • Hypersensitivity reaction to the active substance or any excipients
Important potential risks	• Use in renal impairment • In patients suffering from sarcoidosis there is a risk of increased metabolism of vitamin D to its active form • Concomitant treatment with other sources of vitamin D • Hypercalcaemia, hypercalciuria, nephrolithiasis
Missing information	• Hypersensitivity to cholecalciferol in children during breast-feeding

	• High dose therapy during pregnancy-potential harm for new-born

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.6 Discussion on the clinical aspects

Cholecalciferol, the active substance of Colevit, is considered widely established. For this authorisation, reference is made to clinical studies and experience with cholecalciferol. Cholecalciferol has been shown to be effective in the treatment of vitamin D deficiency and bone loss. The provided clinical overview is sufficient. No new clinical studies were conducted. This is accepted.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Colevit 800 IE, 1000 IE, 7000 IE, and 30000 IE film-coated tablets has a proven chemical-pharmaceutical quality. Colevit is an effective drug, which is considered widely established. The benefit/risk balance is considered positive.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that well established use has been demonstrated for Colevit, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 28 June 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/4075 1-4/IA/002	Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location	--	12-8-2019	Approval	--