COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Fedivelle 1,000 IU and 20,000 IU soft capsules

# (cholecalciferol)

# NL/H/4841/001-002/DC

# Date: 8 September 2020

**This module reflects the scientific discussion for the approval of Fedivelle 1,000 IU and 20,000 IU soft capsules. The procedure was finalised at 15 July 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.**

# List of abbreviations

| | |
|---|---|
| ASMF | Active Substance Master File |
| 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 Fedivelle 1,000 IU and 20,000 IU soft capsules, from Theramex Ireland Limited.

The 1,000 IU product strength is indicated as:

- Treatment of vitamin D deficiency (serum 25(OH)D < 25nmol/l) in adults and adolescents.
- Prevention of vitamin D deficiency in adults with an identified risk.
- An adjunct to specific therapy for osteoporosis in patients with vitamin D deficiency or at a risk of vitamin D insufficiency in adults.

The 20,000 IU product strength is indicated as initial treatment of clinically relevant vitamin D deficiency in adults.

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

This decentralised procedure concerns a bibliographical application based on well-established medicinal use of cholecalciferol. For this type of application, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years in the specific therapeutic use. The results of non-clinical and clinical trials are replaced by detailed references to published scientific literature. The MAH also submitted data showing that the composition of Cholecalciferol Will Pharma is similar to the composition of other products that have been widely used world-wide for the same indications.

Cholecalciferol has been widely marketed and used in the proposed indications for more than 10 years. Cholecalciferol is a well-established active substance in a variety of different pharmaceutical presentations.

The concerned member states (CMS) involved in this procedure were Spain and Italy.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

# II. QUALITY ASPECTS

## II.1 Introduction

Fedivelle 1,000 IU is a yellow coloured transparent, round shaped soft gelatin capsule containing a clear and colourless liquid. Each capsule contains 1,000 IU cholecalciferol (equivalent to 25 micrograms vitamin $D_3$).
Fedivelle 20,000 IU is a light yellow colour transparent, round shaped soft gelatin capsule containing a clear and colourless liquid. Each capsule contains 20,000 IU cholecalciferol (equivalent to 500 micrograms vitamin $D_3$).

The soft capsules are packed in white opaque PVC/PVdC/Al blisters.

The excipients are:
*Capsule content* – medium-chain triglycerides and all-*rac*-α tocopheryl acetate
*Capsule shell* – gelatin (E441), glycerol (E422), liquid sorbitol partially hydrated (E420), tartrazine yellow supra (E102) and purified water

The tablet strengths are dose proportional.

## II.2 Drug Substance

The active substance is cholecalciferol, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white crystalline powder and it is practically insoluble in water, freely soluble in ethanol (96 per cent), and soluble in trimethylpentane and in fatty oils. Issues in regards to polymorphism are not relevant, as the finished product is present in solution in the final finished 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.

<u>Manufacturing process</u>
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 in line with Ph. Eur. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for four batches.

Stability of drug substance
The active substance is stable for 36 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. Development trials of both Cholecalciferol 1,000 IU and 20,000 IU capsules have been carried out with different combinations of excipients to finalise the manufacturing process and specifications. The observations during the manufacturing process are summarised, such as the capsule weight, shell weight, content weight, description, die roll pressure, ribbon thickness, and temperature. The trial batches were also tested for description, identification, disintegration, uniformity of dosage units, assay, impurities, and microbial contamination.
As the active substance is already dissolved, there is no reason to perform dissolution testing on the finished product. Thus it is acceptable that no dissolution test was developed.
In addition, as cholecalciferol is “practically insoluble in water”, there is no point in comparing dissolution profiles in physiological pHs, as required in the Bioequivalence Guideline, of the proposed formulation against other cholecalciferol products on the EU market or the products used in literature.

Manufacturing process
First, the fill medicament preparation is performed. Secondly, multiple excipients are heated, the molten mass is added and the blend is mixed. Thirdly, the encapsulation procedure is followed. The capsules are then dried, inspected, polished and packed. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full-scaled batches.

Control of excipients
Reference is made to the Ph. Eur. or other European regulations. These 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 description, identification, average net content, individual net content, disintegration, uniformity of dosage units, assay, purity (any

individual impurity and total impurities) and microbiological contamination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life specifications are identical. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three full-scaled 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 have been provided for three production scaled batches stored at 25°C/60%RH, 30°C/75%RH, and 40°C/75%RH for six months. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PVdC/Al blister pack. There are no clear changes or trends observed at any of the storage conditions. It was demonstrated that the drug product (both strengths) are not sensitive to light.

*1,000 IU strength*: For 1,000 IU a development batch 24 months long-term stability data is available. For the three stability batches 18 months data are available.

The claimed shelf-life of 36 months can be accepted based on 24 months data for 1 batch.

*20,000 IU strength*: Based on the 36 months long-term data and 6 months accelerated data, the claimed shelf-life of 36 months can be herewith accepted. The storage condition 'No special storage condition required' can be accepted.

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 Fedivelle 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

Vitamin $D_3$ (cholecalciferol) is the product of a cholesterol-like precursor (7-dehydrocholesterol) after it has been irradiated by ultraviolet light. The most well-known effect of vitamin D is maintenance of normal blood levels of calcium and phosphate, which are in turn needed for the normal mineralisation of bone, muscle contraction, nerve conduction, and general cellular function in all cells of the body. In addition, vitamin D has

widespread effects on cellular differentiation and proliferation, can modulate immune responsiveness and central nervous system function and may act as a chemo preventive agent against several malignancies including cancers of the prostate and colon. Cholecalciferol is biologically inactive and requires metabolism, mainly within in the liver and kidney, to be converted to the hormonal form 1,25 dihydroxycholecalciferol (1,25(OH)2D). Activation of the vitamin D receptor by 1,25 (OH)2D within cells of the intestine, bone, kidney and parathyroid gland has an effect on the homeostasis of serum calcium and phosphorous levels, and as such on bone mineralisation and remodelling.

## III.2 Pharmacokinetics

Vitamin $D_3$ exhibits a short circulating half-life and is efficiently captured by storage sites such as adipose tissues and muscles and by the liver, where the vitamin undergoes its first anabolic biotransformation through a C-25 hydroxylation reaction. In rats, most of the radioactivity of orally administered [3H]-cholecalciferol remained as the parent substance and was detected in increased amounts in the liver, kidney and fat tissue. Adipose tissue is the major storage site for vitamin $D_3$ in its several forms. The total vitamin D in the rat liver decreased in an exponential fashion from 19% of the dose at 5 hours to 0.6% at 72 hours, but the ester content remained at a relatively constant low value from 5 hours, so that by 72 hours it represented 67% of the total vitamin D.
Vitamin D and its metabolites undergo an enterohepatic recirculation, of which the metabolites largely are conjugated as glucuronides before secretion into the bile. 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 of weeks to months. Metabolites are eliminated primarily through the bile and faeces.

## III.3 Toxicology

The toxic action of vitamin $D_3$ is usually attributed to a disturbance of whole-body calcium homeostasis. Significant lethality occurred in mice treated with a single high oral dose of calcitriol (4 mg/kg), the hormonal metabolite of cholecalciferol. Vitamin D was tested negative for genotoxic potential in the Ames test and a micronucleus assay. It is an endogenous substance produced naturally by contact of the skin by ultraviolet light; therefore any cancer potential risk from this replacement therapy is not expected to exceed that of a population with normal vitamin D level. Overdoses of vitamin D should be avoided during pregnancy as permanent hypercalcemia has been related to adverse effects on the developing foetus. There are no indications that vitamin D at therapeutic doses is teratogenic in humans. The excipient profile and impurities observed are within the acceptable limit.

## III.4 Ecotoxicity/environmental risk assessment (ERA)

Since Vitamin $D_3$ is a naturally occurring substance, it is exempt from an environmental risk assessment according to guideline EMEA/CHMP/SWP/4447/00.

### III.5 Discussion on the non-clinical aspects

The MAH relied on the comprehensive scientific literature and collected a sufficient amount of information on pharmacological and toxicological properties of the active substance. Based on the information reviewed and on the long experience in humans it appears that Vitamin $D_3$ is able to prevent and/or cure vitamin D deficiencies and associated risks. Vitamin $D_3$ does not present any toxicological concern, since toxicity is only observed in exceeding doses far beyond those recommended for administration and therefore not relevant when the product is taken according to the directions laid out in the SmPC. Cholecalciferol is a well-known active substance and has well-documented non-clinical pharmacological, pharmacokinetic and toxicological characteristics.

## IV. CLINICAL ASPECTS

### IV.1 Pharmacokinetics/pharmacodynamics

Vitamin D can be obtained from the diet and by the action of sunlight on the skin. The two forms of the vitamin that are best known and which are of nutritional significance are ergocalciferol (vitamin $D_2$) and cholecalciferol (vitamin $D_3$). Only some selected food contains significant amounts of vitamin $D_2$ and $D_3$. Vitamin D is absorbed in the small intestine, a process that requires the presence of fat, bile (mainly deoxycholic acid) and pancreatic enzymes, and is transported via lymph incorporated in chylomicrons, to the liver.

However, in normal circumstances most of the Vitamin $D_3$ is produced in the skin by an ultraviolet light-induced photolytic conversion of 7-dehydrocholesterol to previtamin $D_3$ followed by thermal isomerisation to vitamin $D_3$. The active form of vitamin $D_3$ is 1,25–dihydroxyvitamin $D_3$ (1,25-(OH)2D3) and is formed following sequential hydroxylations in the liver and kidney, a process which is promoted by parathyroid hormone (PTH). Vitamin D and its hydroxylated metabolites 25(OH)D, 24,25(OH)2D, and 1,25(OH)2D are lipophilic molecules.

Because of their low solubility in the aqueous medium 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 dihydroxy-

cholecalciferol. 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 30–60 days after peak sunlight exposure in the summer months.

Considering the pharmacological properties of cholecalciferol, particularly the extremely long body half-life of ~2 months, minor differences in absorption that may due to slightly different formulations (excipients of tablets, dissolution profile, formulation), are unlikely to have impact on the therapeutic goal, e.g. to achieve the vitamin D status as reflected by serum 25(OH)D concentrations.

## IV.2 Bridging data of the products in the application with the products referred to in the literature

The MAH provided an extended overview. From the presented data it can be expected that the pharmacokinetics of cholecalciferol are comparable to the studies presented in the clinical overview, taking into account the comparison of the pharmaceutical form (soft capsule with oil based solution) and ingredients of the product to be marketed and those mentioned in literature. In literature it was shown that small differences in constituents does not lead to changed pharmacokinetic behaviour for cholecalciferol. Moreover, the proposed formulation, does not contain critical excipients.

## IV.3 Clinical efficacy

The MAH has presented literature data of studies using different vitamin D doses. The proposed indications are acceptable in adults and in line with registered SmPC of comparable products.

Treatment of vitamin D deficiency in adults

Although there is no consensus on optimal levels of 25-hydroxyvitamin D as measured in serum, vitamin D deficiency is defined by most experts as a 25-hydroxyvitamin D level of less than 20 ng per millilitre (50 nmol per liter).

The MAH submitted 19 studies to support the proposed indication and posology for treatment of vitamin D deficiency. These studies used a variety of dosing schedules to achieve normal 25(OH)D levels after a certain period of treatment including loading doses

and/or several weeks or months of treatment. For the initial treatment of clinically relevant vitamin D deficiency appropriate doses to be considered are in the range of 800-4,000 IU/day as also indicated for instance in NL SmPCs of the Benferol (NL/H/3500/001-004) and Will Pharma (NL/H/2963/001-006) products. A lower maintenance dose should be considered one month after loading dose.

Prevention of vitamin D deficiency in adults

To support the indication and posology of prevention of vitamin D deficiency, the MAH submitted several studies. Current NL SmPCs of the Benferol (NL/H/3500/001-004) and Will Pharma (NL/H/2963/001-006) products recommend doses of max. 25,000 IU/month and 800-1600 IU/day, respectively. This is consistent with the MAH's proposals.

Treatment and prevention of vitamin D deficiency in adolescents

The MAH submitted 15 articles in support of the use of vitamin D in prevention and treatment of vitamin D deficiency in adolescents.

In children over 12 years of age a daily dose of 400-1,000 IU depending on the severity of the disease and the patient's response to treatment has been recommended (see also the SmPC of Cholecalciferol mibe 1,000 IU, DE/H/3562/002). Vitamin D3 1,000 daily is therefore acceptable in adolescents.

Osteoporosis

In the first round the MAH provided four studies and six reviews/meta-analyses evaluating the effect of supplementation with cholecalciferol (and calcium) on the frequency of hip fractures and other nonvertebral fractures. Three studies evaluated the effect of supplementation with cholecalciferol on BMD. Benefits were not observed for the lower cholecalciferol dose (400 IU). The MAH submitted several new references studying vitamin D supplementation as an adjunct to specific therapy for osteoporosis in patients with vitamin D deficiency or at a risk of vitamin D insufficiency in adults. 17 of these references concerned studies published in 2010 or before.

The effect of cholecalciferol in osteoporosis has been investigated in many studies available in literature, often in combination with calcium. A generally accepted dose of cholecalciferol for osteoporosis patients is 800-1,000 IU daily or its weekly or monthly equivalent. This is consistent with the MAH's proposals.

## IV.4 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 Fedivelle.

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

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| Important identified risks | None |
| Important potential risks | None |
| Missing information | None |

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

### IV.5 Discussion on the clinical aspects

The MAH has submitted an application for the following indications:

- Treatment of vitamin D deficiency (serum 25(OH)D < 25nmol/l) in adults and adolescents.
- Prevention of vitamin D deficiency in adults with an identified risk.
- An adjunct to specific therapy for osteoporosis in patients with vitamin D deficiency or at a risk of vitamin D insufficiency in adults.

The MAH submitted bibliographical data which is sufficient for approval based on "well-established medicinal use" in accordance with Directive 2001/83/EC article 10(a).

*Benefits*
The clinical benefit of treating and preventing vitamin D deficiency is well known, as well as the clinical benefit of adjunct to specific therapy for osteoporosis. The bibliographic data submitted showed vitamin D deficiency was resolved or improved as indicated by increases in serum 25OH-D levels. The MAH submitted and discussed several studies to support the treatment and prevention of vitamin D deficiency and osteoporosis.

*Risks*
The safety profile of cholecalciferol is well-known. In general, vitamin D is well tolerated. However, there is a risk for toxicity, especially with higher dosages. Hypercalcaemia and hypercalciuria are the main adverse events. Monthly vitamin D doses in adults are approved in some registered EU procedures.
The safety of the use of high monthly doses of vitamin D in adolescents is very limited and cannot be well-established, while such doses are currently not registered in the Netherlands and thus should be avoided.
A study published by Bischoff-Ferrari et al. in 200 patients (in 3 different dose groups) treated up to 1 year identified an increased risk of falls with the 60,000 IU per month dose (Bischoff-Ferrari et al. 2016[1]). These data were obtained only in elderly with a prior fall and the risk for new falls was assessed as secondary endpoint, limiting conclusion about this risk. More data are needed to identify whether such risk is well-established.

## 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 a

[1] Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, et al. Monthly high-dose vitamin D treatment for the prevention of functional decline: a randomized clinical trial. JAMA Intern Med. 2016;176(2):175-183.

pilot test, followed by two rounds with 10 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 package leaflet of medicinal products for human use.

# VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Fedivelle 1,000 IU and 20,000 IU soft capsules have a proven chemical-pharmaceutical quality. Fedivelle 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 Fedivelle, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 July 2020.

## 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 |
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