EDA Assessment Report for human medicinal product

(Scientific Discussion)

Hidroferol 0.266 mg Soft Capsule

Calcifediol monohydrate

Date: February, 2026.

I. Introduction

-Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for Hidroferol Soft Capsules from RX HEALTHCARE

-The product is indicated for the treatment of vitamin D deficiency in adults and to prevent vitamin D deficiency in adults with identified risks such as in patients with malabsorption syndrome, chronic kidney disease – mineral bone disease (CKD-EMO) or any other identified risk.

II. Quality Aspect

Drug Substance

- A CEP has been submitted for evaluation.
- The drug substance is white or almost white crystals, practically insoluble in water, freely soluble in ethanol (96 per cent), soluble in fatty oils.
- The drug substance specifications correspond to those of the current Ph. Eur. monograph for said drug substance, including the additional routine determination of residual solvents.
- Analytical methods are in line with the current version of the European pharmacopeia monograph and the certificate of suitability (CEP).
- The API manufacturer provided batch analysis results of 3 batches. The results of all tests were well within specification limits and batch data was found acceptable.
- The drug substance is packed under nitrogen in a glass vial closed by a rubber stopper and an aluminium cap, in a seal bag, placed in a carboard box.
- The stability study of the API supports the proposed retest period of 5 years when packaged under nitrogen in airtight containers and stored protected from light at temperatures not exceeding 25ºC.

Medicinal Product

- **Product Description**

-Orange soft gelatin capsules containing a clear, low viscous and free from particles liquid.
-The product is packed in PVC/PVDC/Al blisters and further placed in cardboard box.

-The excipients are:

*Capsule Content: Anhydrous Ethanol and Medium-chain triglycerides.

*Capsule Shell: Gelatin, Glycerol, Sorbitol solution, Titanium dioxide, Orange yellow colorant and purified water.

- **Pharmaceutical development:**

-The development of the product has been described, the choice of excipients is justified and their functions explained. The development focused on the formulation of a solid dosage form of the API taking into consideration the challenging solubility of the API. Therefore, the soft capsules have been selected to administer calcifediol in a solubilized form. Additionally, the challenging photostability issue of the API during the manufacturing process has been adequately addressed.

-Overall, the choices of the packaging, manufacturing process, compatibility, overage physicochemical properties and microbiological attributes are justified.

- **Manufacturing process:**

-The manufacturing process consists of Dissolving the API, Encapsulation and Packaging.

-The manufacturing process has been adequately validated on three full production scale batches per strength. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

- **Control of excipients**

-All excipients comply with Ph. Eur and European standard for coloring agents.

- **Control of Drug Product**

-Product specification include Appearance, Identification, Assay, Related substances, Disintegration, Dissolution, Colorant Identification, Ethanol content, Uniformity of dosage units and Microbial content.

-The Analytical methods used in testing the finished pharmaceutical product were presented in the dossier. They were reviewed and found to be suitable for the required testing.

-Batch Analysis from the proposed production site were provided for 3 batches. The results of all tests are well within specification limits and batch data is acceptable.

- **Container closure system**

-The drug product is packaged in PVC/PVdC/Aluminium blisters, the blisters are further packaged in a carton box.

- **Stability of FPP**

- Stability of finished pharmaceutical product is submitted in accelerated (40°C/75% RH) and long-term (25°C/60% RH, 30°C/65% RH & 30°C/75% RH) storage conditions. Detailed review was carried out for all stability indicating parameters and all found in line with their acceptance criteria throughout all time intervals. The provided stability study supports the proposed shelf life of 48 months when stored below 30°C.

- **Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies**

-The CEP certified that Calcifediol Monohydrate meets the criteria described in the current version of the monograph "Pproducts with risk of transmitting agents of animal spongiform encephalopathies" no. 1483 of the European Pharmacopoeia. Moreover, a declaration/certificate of TSE/BSE free is submitted for Gelatin in the soft capsules.

Summary basis of opinion:
From Chemistry, Manufacture and Control perspective, the main concerns found during the evaluation process were as follow:

For the Drug product:
-Risk assessment of elemental impurities according to ICH Q3D guideline should be provided.

The Quality of the drug product has been found satisfactory after:
-The FPP manufacturer has provided the risk assessment of elemental impurities as requested and none of the elemental impurities could be found above levels considering a 30% permitted daily intake (PDE) limit for orally administered drug products.

III. Non-Clinical & Clinical Aspects

- **Introduction**

-Calcifediol monohydrate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature.

-Calcifediol monohydrate is used to treat vitamin D deficiency or insufficiency, refractory rickets (vitamin D resistant rickets), familial hypophosphatemia and hypoparathyroidism, and in the management of hypocalcemia and renal osteodystrophy in patients with chronic renal failure undergoing dialysis. Also used in conjunction with calcium in the management and prevention of primary or corticosteroid-induced osteoporosis.

- **Mechanism of action**

-Calcifediol is transformed in the kidney by 25-hydroxyvitamin D3-1-(alpha)-hydroxylase to calcitriol, the active form of vitamin D3. Calcitriol binds to intracellular receptors that then function as transcription factors to modulate gene expression. Like the receptors for other steroid hormones and thyroid hormones, the vitamin D receptor has hormone-binding and DNA-binding domains. The vitamin D receptor forms a complex with another intracellular receptor, the retinoid-X receptor, and that heterodimer is what binds to DNA. In most cases studied, the effect is to activate transcription, but situations are also known in which vitamin D suppresses transcription. Calcitriol increases the serum calcium concentrations by: increasing GI absorption of phosphorus and calcium, increasing osteoclastic resorption, and increasing distal renal tubular reabsorption of calcium. Calcitriol appears to promote intestinal absorption of calcium through binding to the vitamin D receptor in the mucosal cytoplasm of the intestine. Subsequently, calcium is absorbed through formation of a calcium-binding protein.

- **Pharmacokinetics**

-Calcifediol monohydrate (25-hydroxyvitamin \(D_{3}\) monohydrate) is a highly bioavailable, direct precursor to active vitamin D, featuring rapid intestinal absorption (peak in ~5.5 hours), a 12–21 day half-life, and linear, predictable dose-response kinetics. It is less lipophilic than vitamin \(D_{3}\), allowing better efficacy in obesity and fat malabsorption.

Absorption: Near 100% absorption, independent of bile acids, and faster than Vitamin \(D_{3}\).
Distribution: Primarily bound to Vitamin D-binding protein (DBP) in blood, with lower adipose tissue storage than cholecalciferol. Metabolism: Converted in the kidney (via 1-alpha-hydroxylase, CYP27B1) to active calcitriol [\(1,25-(OH)_{2}D_{3}\)]. It is also converted to 24,25-dihydroxycholecalciferol (inactive).

Elimination: Primarily excreted in the bile. Potency: 3–8 times more potent than vitamin \(D_{3}\) in raising serum 25(OH)D levels.
Clinical Pharmacokinetics: Time to Peak (T_{max}): Approx. 5.5 hours, or up to 7 days with large doses. Half-life ((t{1/2}): Approximately 12 to 21 days.

- **List of Clinical Studies:**

-Efficacy and Safety: Randomised, controlled, double-active blind, double-dummy, multicentre, phase III-IV study of superiority or non-inferiority Active comparator (cholecalciferol).

***Based on the clinical study Hidroferol 0.266 mg Soft Capsule submitted to EDA, found to recommend the approval of the marketing authorization of product.**