Plenachol 20 000 IU Capsules
Plenachol 40 000 IU Capsules

PL 17507/0226-0227

UKPAR

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LAY SUMMARY

Plenachol 20 000 and 40 000 IU Capsules
(cholecalciferol, capsules, 20 000 and 40 000 IU)

This is a summary of the Public Assessment Report (PAR) for Plenachol 20 000 IU Capsules (PL 17507/0226) and Plenachol 40 000 IU Capsules (PL 17507/0227). It explains how Plenachol 20 000 and 40 000 IU Capsules were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Plenachol 20 000 and 40 000 IU Capsules.

For practical information about using Plenachol 20 000 and 40 000 IU Capsules, patients should read the package leaflet or contact their doctor or pharmacist.

What are Plenachol 20 000 and 40 000 IU Capsules and what are they used for?
Plenachol 20 000 and 40 000 IU Capsules contain the active substance cholecalciferol (also known as vitamin D₃). Plenachol 20 000 and 40 000 IU Capsules are medicines with ‘well-established use’. This means that the medicinal use of the active substance cholecalciferol is well established in the European Union for at least 10 years, with recognised efficacy and an acceptable level of safety.

Plenachol 20 000 and 40 000 IU Capsules are used for:
- The prevention of vitamin D deficiency when there is a significant risk of deficiency or an increased demand for vitamin D.
- The treatment of vitamin D deficiency that has been confirmed by laboratory tests.

How do Plenachol 20 000 and 40 000 IU Capsules work?
Plenachol 20 000 and 40 000 IU Capsules contain the active substance cholecalciferol (also known as vitamin D₃). Vitamin D is required in the body to help in the absorption of calcium. Vitamin D can be found in some foods and is also produced by the body when skin is exposed to sunlight. Vitamin D helps the kidneys and intestine absorb calcium which helps build bones.

How are Plenachol 20 000 and 40 000 IU Capsules used?
The pharmaceutical form of Plenachol 20 000 and 40 000 IU Capsules is a capsule and the route of administration is oral.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

This medicine should be taken exactly as advised by the doctor or pharmacist. The capsules should be swallowed whole (not chewed) with a drink of water. This medicine is best absorbed when taken with a large meal.

Initial treatment of vitamin D deficiency:
Plenachol 20 000 IU Capsules:
- Two capsules to be taken weekly for 7 weeks.
Plenachol 40 000 IU Capsules:
- One capsule to be taken weekly for 7 weeks.

The doctor must decide on an individual basis whether any further treatment (follow-on or long-term) with this medicine is necessary.
During long-term treatment, the calcium levels in the blood and urine should be monitored regularly and kidney function tested by measurement of serum creatinine. If necessary, the dosage must be adjusted according to the blood calcium values (see section 2 ‘Special Precautions’ of the package leaflet).

Plenachol 20 000 and 40 000 IU Capsules can only be obtained with a prescription.

**What benefits of Plenachol 20 000 and 40 000 IU Capsules have been shown in studies?**
As cholecalciferol is a well-known substance, and its use in the prevention and treatment of vitamin D deficiency and certain bone conditions (osteoporosis or osteomalacia) together with other medicines is well established, the applicant (Auden Mckenzie Limited) presented data from the scientific literature. The literature provided confirmed the efficacy and safety of cholecalciferol in the treatment of vitamin D deficiency (including prevention).

**What are the possible side effects of Plenachol 20 000 and 40 000 IU Capsules?**
For the full list of all side effects reported with Plenachol 20 000 and 40 000 IU Capsules, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

**Why are Plenachol 20 000 and 40 000 IU Capsules approved?**
The MHRA decided that Plenachol 20 000 and 40 000 IU Capsules’ benefits are greater than their risks and recommended that they be approved for use.

**What measures are being taken to ensure the safe and effective use of Plenachol 20 000 and 40 000 IU Capsules?**
A Risk Management Plan has been developed to ensure that Plenachol 20 000 and 40 000 IU Capsules are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflet for Plenachol 20 000 and 40 000 IU Capsules, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

**Other information about Plenachol 20 000 and 40 000 IU Capsules.**
Marketing Authorisations for Plenachol 20 000 and 40 000 IU Capsules were granted in the UK on 06 October 2014.

The full PAR for Plenachol 20 000 and 40 000 IU Capsules follows this summary.

For more information about treatment with Plenachol 20 000 and 40 000 IU Capsules, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in November 2014.
Plenachol 20 000 IU Capsules
Plenachol 40 000 IU Capsules

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Auden Mckenzie Limited Marketing Authorisations for the medicinal products Plenachol 20 000 and 40 000 IU Capsules (PL 17507/0226-0227) on 06 October 2014. The products are prescription-only medicines (POM) indicated for prevention and treatment of vitamin D deficiency.

These applications were submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be applications for a product containing an active substance of well-established use.

In its biologically active form Vitamin D stimulates intestinal calcium absorption, incorporation of calcium into the osteoid, and release of calcium from bone tissue. In the small intestine it promotes rapid and delayed calcium uptake. The passive and active transport of phosphate is also stimulated. In the kidney, it inhibits the excretion of calcium and phosphate by promoting tubular resorption. The production of parathyroid hormone (PTH) in the parathyroids is inhibited directly by the biologically active form of vitamin D₃. PTH secretion is inhibited additionally by the increased calcium uptake in the small intestine under the influence of biologically active vitamin D.

Bibliographic data on cholecalciferol have been submitted to support these applications. No new non-clinical or clinical studies were conducted for these applications, which is acceptable given that these are bibliographic applications for a product containing an active ingredient of well-established use.

During assessment of these applications major objections regarding clinical efficacy were raised. The applications were referred to the Commission on Human Medicines (CHM) who met on 12 December 2013 to consider the applications. In response to the CHM consultation, the applicant provided efficacy data to support the requested indications and posology of the products. The data provided was adequate and the issues were resolved.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE
INN: Cholecalciferol
Chemical name: (5Z,7E)-9,10-Secholesta-5,7,10(19)-trien-3β-ol
Structure:

![Structure of Cholecalciferol]

Molecular formula: C_{27}H_{44}O
Molecular weight: 384.6 g/mol
Appearance: White or almost white crystalline powder
Solubility: Practically insoluble in water, freely soluble in ethanol (96 per cent) and soluble in trimethylpentane and in fatty oils.

Cholecalciferol is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance cholecalciferol are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

DRUG PRODUCT
Other Ingredients
Other ingredients consist of the pharmaceutical excipients medium-chain triglycerides, butylhydroxyanisole, colloidal anhydrous silica, hypromellose, gellan gum (E418), sodium citrate and the capsule shell [comprised of hypromellose and titanium dioxide (E171)]. Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of gellan gum which complies with United States Pharmacopoeia (USP) standards and the capsule shell (comprised of hypromellose and titanium dioxide) which complies with suitable in-house specifications.

Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

A Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE) statement has been issued by the supplier to confirm that Vitamin D₃ is prepared synthetically in a
process that includes wool grease (lanolin) from healthy live sheep from category A and B countries that do not present a risk to BSE/TSE contamination.

**Pharmaceutical Development**
The objective of the development programme was to formulate a safe, efficacious, capsule containing 20 000 IU or 40 000 IU of cholecalciferol.

Suitable pharmaceutical development data have been provided for these applications.

**Manufacturing Process**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot scale and has shown satisfactory results. The applicant has committed to perform process validation on future commercial scale batches.

**Control of Finished Product**
The finished product specifications are satisfactory. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

**Container Closure System**
All strengths of the finished product are packed in polyvinyl chloride/polyvinylidene chloride (PVC/PVdC) foiled aluminium blisters in pack sizes of 4, 10 and 20 capsules. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations (Regulation (EU) No. 10/2011) concerning materials in contact with foodstuff.

**Stability**
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years with the storage conditions ‘store this medicinal product in the original package in order to protect from light’ have been set. These are satisfactory

Suitable post approval stability commitments have been provided to continue stability studies on batches of the finished product.

**Bioequivalence**
A bioequivalence study was not necessary to support applications of this type.

**Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling**
The SmPCs, PIL and labelling are satisfactory from a pharmaceutical perspective.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.
MAA (Marketing Authorisation Application) Forms
The MAA forms are satisfactory from a pharmaceutical perspective.

Expert Report (Quality Overall Summary)
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of Marketing Authorisations is recommended.
NON-CLINICAL ASSESSMENT

As the pharmacodynamic, pharmacokinetic and toxicological properties of cholecalciferol are well-known, no further non-clinical studies are required and none have been provided.

The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

The Marketing Authorisation holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). This is acceptable as vitamins are unlikely to result in significant risk to the environment.

There are no objections to the approval of these applications from a non-clinical point of view.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
No new clinical pharmacology data have been submitted and none are required for applications of this type. The clinical pharmacology of cholecalciferol is well-known.

EFFICACY
No new efficacy data have been submitted and none are required for applications of this type. The clinical efficacy of cholecalciferol is well-established. Efficacy is adequately reviewed in the clinical overview.

SAFETY
No new safety data were supplied or required for these bibliographic applications. Safety is adequately reviewed in the clinical overview. The safety profile of cholecalciferol is well-known.

CLINICAL EXPERT REPORT (CLINICAL OVERVIEW)
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A satisfactory Risk Management Plan has been provided.

SUMMARIES OF PRODUCT CHARACTERISTICS (SmPCs), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The SmPCs, PIL and labelling are acceptable from a clinical perspective. The PIL is consistent with the details in the SmPCs and in line with the current guidance. The labelling is in line with the current guidance.

MAA FORMS
These are satisfactory.

CONCLUSION
The grant of Marketing Authorisations is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Plenachol 20 000 and 40 000 IU Capsules are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of cholecalciferol are well-known, no additional data were required.

CLINICAL
No new clinical data were submitted and none were required for applications of this type.

The published literature supports the efficacy of these products in the proposed indications. The efficacy of cholecalciferol is well-known. The presented evidence for well-established use of the active substance is sufficient.

The safety profile of cholecalciferol is well-known. The literature review identified no new or unexpected safety issues or concerns.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with cholecalciferol is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.
Plenachol 20 000 IU Capsules
Plenachol 40 000 IU Capsules

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STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the Marketing Authorisation applications on 20 March 2013.
2. Following standard checks and communication with the applicant the MHRA considered the applications valid on 28 March 2013.
3. Following assessment of the applications the MHRA requested further information relating to the dossier on 05 July 2013.
4. The applicant responded to the MHRA’s request providing further information on the dossier on 25 September 2013.
5. The applications were referred to the Commission on Human Medicines (CHM) who met on 12 December 2013 to consider the applications and requested further information relating to the dossier on 07 January 2014.
6. The applicant responded to the CHM’s request, providing further information on the dossier on 27 March 2014.
7. Following the CHM referral, the MHRA requested further information relating to the dossier on 15 July 2014.
8. The applicant responded to the MHRA’s requests, providing further information on the dossier on 23 July 2014.
9. The applications were granted on 06 October 2014.
SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
UKPAR Plenachol 20 000 & 40 000 IU Capsules

Plenachol®
40 000 IU Capsules
(Cholecalciferol)

40 000 IU

Plenachol®
40 000 IU Capsules
(Cholecalciferol)

4 Capsules

Aster Mcleod
Aster McLeod is registered UK trademark. PL No. 17507/0227
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