InVita D3 25,000 IU oral solution

PL 24837/0039

UKPAR

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LAY SUMMARY
InVita D3 25,000 IU oral solution
(cholecalciferol)

This is a summary of the Public Assessment Report (PAR) for InVita D3 25,000 IU oral solution (PL 24837/0039). It explains how InVita D3 25,000 IU oral solution was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use InVita D3 25,000 IU oral solution.

For practical information about using InVita D3 25,000 IU oral solution, patients should read the package leaflet or contact their doctor or pharmacist.

What is InVita D3 25,000 IU oral solution and what is it used for?
InVita D3 25,000 IU oral solution contains the active substance cholecalciferol (equivalent to vitamin D3).
InVita D3 25,000 IU is used:
- for the prevention of vitamin D deficiency when there is a significant risk of deficiency or an increased demand for vitamin D
- with other medicines to treat certain bone conditions, such as thinning of the bone (osteoporosis)
- to treat vitamin D deficiency that has been confirmed by laboratory tests

How is InVita D3 25,000 IU oral solution used?
InVita D3 25,000 IU oral solution is taken by mouth. This medicine is best absorbed when taken with a large meal. The contents of the ampoule can either be emptied directly in the mouth or onto a spoon and taken orally.

Use in adults
The recommended dose for:
- Prevention of vitamin D deficiency:
  1 ampoule of InVita D3 25,000 IU once monthly. Higher doses may be required based on the advice of the doctor.

- Addition to specific therapy for osteoporosis:
  1 ampoule of InVita D3 25,000 IU once monthly.

- Treatment of vitamin D deficiency:
  2 ampoules of InVita D3 25,000 IU once weekly for 6-8 weeks, followed by maintenance therapy (1400-2000 IU once daily may be required), based on the advice of the doctor.

Use in children and adolescents
The recommended dose for:
- Prevention of vitamin D deficiency in 0-1 years:
  1 ampoule of InVita D3 25,000 IU every 8 weeks

- Prevention of vitamin D deficiency in 1-18 years:
  1 ampoule of InVita D3 25,000 IU every 6 weeks

- Treatment of vitamin D deficiency in 0-18 years:
1 ampoule of InVita D3 25,000 IU once every 2 weeks for 6 weeks (followed by maintenance therapy of 400-1000 IU/day).

In children, InVita D3 can be mixed with a small amount of children’s foods, yogurt, milk, cheese or other dairy products. This medicine should not be added into a bottle of milk or container of soft food, in case the child does not consume the whole portion, and does not receive the full dose.

This high strength formulation is not recommended for use in pregnant and breast feeding women.

For further information on how InVita D3 25,000 IU oral solution is used, please refer to the Summary of Product Characteristics and the Patient Information Leaflet available on the MHRA website.

InVita D3 25,000 IU oral solution can only be obtained on prescription from a doctor.

**How does InVita D3 25,000 IU oral solution work?**
InVita D3 25,000 IU oral solution is a vitamin product containing cholecalciferol (equivalent to vitamin D3). Vitamin D3 acts to maintain normal concentrations of calcium and phosphate in plasma by facilitating their absorption from the small intestine, enhancing their mobilisation from bone and decreasing their excretion by the kidney.

**How has InVita D3 25,000 IU oral solution been studied?**
As cholecalciferol is a well-known substance and has a well-established use, the applicant (Consilient Health Limited) presented data from the scientific literature. The literature provided confirmed the efficacy and safety of cholecalciferol for the prevention and treatment of vitamin D deficiency and as an adjunct to specific therapy for osteoporosis in patients with vitamin D deficiency or at risk of vitamin D insufficiency.

**What are the Benefits and risks of InVita D3 25,000 IU oral solution?**
Cholecalciferol is a well-known active ingredient. Cholecalciferol-containing products have been available in the European Union for many years and have an established favourable benefit-risk profile.

For information about side effects that may occur with taking InVita D3 25,000 IU oral solution, please refer to the package leaflet or the Summary of Product Characteristics available on the MHRA website.

**Why is InVita D3 25,000 IU oral solution approved?**
The use of InVita D3 25,000 IU oral solution for the approved indications is well-established. Literature data have been submitted to support this application. No new or unexpected safety concerns arose from this application. It was, therefore, considered that the benefits of InVita D3 25,000 IU oral solution outweigh the risks and the grant of a Marketing Authorisation was recommended.

**What measures are being taken to ensure the safe and effective use of InVita D3 25,000 IU oral solution?**
A Risk Management Plan has been developed to ensure that InVita D3 25,000 IU oral solution is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for InVita D3 25,000 IU oral solution, including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about InVita D3 25,000 IU oral solution**
A Marketing Authorisation was granted in the UK on 24th April 2014.

The full PAR for InVita D3 25,000 IU oral solution follows this summary.
For more information about treatment with InVita D3 25,000 IU oral solution, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in June 2014.
InVita D3 25,000 IU oral solution

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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 Consilient Health Limited a Marketing Authorisation for the medicinal product InVita D3 25,000 IU oral solution (PL 24837/0039) on 24th April 2014. The product is a prescription-only medicine (POM) indicated for prevention and treatment of vitamin D deficiency and as an adjunct to specific therapy for osteoporosis in patients with vitamin D deficiency or at risk of vitamin D insufficiency.

The application was submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be an application 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 this application. No new non-clinical or clinical studies were conducted for this application, which is acceptable given that this is bibliographic application for a product containing an active ingredient of well-established use.

During assessment of this product major objections regarding clinical efficacy were raised. The application was referred to the Commission on Human Medicines (CHM) and a pre-hearing was held on 13th September 2013. As the Commission were not reassured by the Company’s responses, a second pre-hearing was held on 14th November 2013. The applicant provided efficacy data for a number of high dose vitamin D regimens but none were identical to the one requested for the application. Subsequently the applicant provided the clinical justification that bridged between the posology requested and the bibliographic data presented within the application. The data provided was adequate and the issues were resolved.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE
INN: Cholecalciferol
Chemical name: \((5Z,7E)-9,10\text{-Secocholesta-5,7,10(19)\text{-t}}\text{rien-3\beta-ol}\)
Structure:

![Chemical structure of cholecalciferol](image)

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.

DRUG PRODUCT
Other Ingredients
Other ingredients consist of the pharmaceutical excipients tocopherol acetate, polyglyceryl oleate (E475), olive oil, refined and sweet orange peel oil. Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of polyglyceryl oleate (E475) and sweet orange peel oil which comply with an in-house specification.

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

A 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, stable oral solution containing 25000 IU of cholecalciferol.
Suitable pharmaceutical development data have been provided for this application.

**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 using the pilot batches and has shown satisfactory results. The applicant has committed to perform further process validation on three full scale commercial-scale batches.

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

**Container Closure System**
The product is packed in a transparent polyvinylchloride (PVC), polyvinylidenechloride (PVDC) and polyethylene (PE) ampoules, with pack sizes of 1, 2, 3 and 4 ampoules. 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 concerning materials in contact with food.

**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 36 months with storage conditions “Do not store above 30°C” and “Store 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 SmPC, PIL and labelling are satisfactory from a pharmaceutical perspective.

A satisfactory user testing of the package leaflet was provided by the applicant.

**MAA (Marketing Authorisation Application) Forms**
The MAA form is 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 a Marketing Authorisation 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 this product 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 this bibliographic application. 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.

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

**MAA FORM**
This is satisfactory.

**CONCLUSION**
The grant of a Marketing Authorisation is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of InVita D3 25,000 IU oral solution 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 this product 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 SmPC, PIL and labelling are satisfactory and in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the product 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 is, therefore, considered to be positive.
InVita D3 25,000 IU oral solution

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STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the Marketing Authorisation application on 10th August 2012.
2. Following standard checks and communication with the applicant the MHRA considered the application valid on 21st August 2012.
3. Following assessment of the application the MHRA requested further information relating to the dossier on 19th November 2012 and 3rd May 2013.
4. The applicant responded to the MHRA’s requests, providing further information on the dossier on 26th February 2013 and 29th May 2013.
5. The application was granted on 24th April 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.