Adcal-D3 Caplets, 750 mg/200 I.U, film-coated tablets
(calcium carbonate, vitamin D₃)

PL 16508/0039

UKPAR

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Adcal-D3 Caplets, 750 mg/200 I.U, film-coated tablets (calcium carbonate, vitamin D₃)

PL 16508/0039

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted ProStrakan Limited a Marketing Authorisation (licence) for the medicinal product Adcal-D3 Caplets, 750 mg/200 I.U, film-coated tablets (PL 16508/0039) on 13th July 2011. This is a P licensed medicine, available only from pharmacies, under the supervision of a pharmacist.

Adcal-D3 Caplets, 750 mg/200 I.U, film-coated tablets contain calcium and vitamin D₃, which are both essential for healthy bones and teeth. These tablets provide extra calcium and vitamin D₃ to the diet. It is therefore used in conditions where the body’s calcium and vitamin D levels need to be increased.

Adcal-D3 Caplets can be prescribed by doctors for certain bone conditions, e.g. osteoporosis. Studies show that taking calcium and vitamin D₃ over a long time can prevent hip and other non-vertebral bone fractures in later life.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of Adcal-D3 Caplets, 750 mg/200 I.U, film-coated tablets outweigh the risks; hence a Marketing Authorisation has been granted.
Adcal-D3 Caplets, 750 mg/200 I.U, film-coated tablets
(calcium carbonate, vitamin D₃)

PL 16508/0039

SCIENTIFIC DISCUSSION

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**INTRODUCTION**

Based on the review of the data on quality, safety and efficacy, the MHRA granted ProStrakan Limited a Marketing Authorisation for the medicinal product Adcal-D3 Caplets, 750 mg/200 I.U, film-coated tablets (PL 16508/0039) on 13th July 2011. The product is a P licensed medicine.

This is an abridged, bibliographic application for Adcal-D3 Caplets, 750 mg/200 I.U, film-coated tablets, submitted under Article 10a (well-established use) of Directive 2001/83/EC, as amended.

Adcal-D3 Caplets, 750 mg/200 I.U, film-coated tablets are used as an adjunct to specific therapy for osteoporosis and in situations requiring therapeutic supplementation of malnutrition, e.g. in pregnancy and established vitamin D dependent osteomalacia.

The tablets are also used in the prevention and treatment of calcium deficiency/vitamin D deficiency especially in the housebound and institutionalised elderly subjects. Deficiency of the active moieties is indicated by raised levels of PTH, lowered 25-hydroxy vitamin D and raised alkaline phosphatase levels which are associated with increased bone loss.

No new non-clinical or clinical efficacy studies were necessary for this application, which is acceptable given that this was a bibliographic application for a product containing an active of well-established use. Bioequivalence studies are not necessary to support this bibliographic application.

The MHRA considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) 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.

The MAH has provided adequate justification for not submitting a Risk Management Plan (RMP). Calcium carbonate and vitamin D₃ are well-known active drug substances and have been widely-used to treat osteoporosis and deficiency symptoms for many years. This application refers to the Marketing Authorisation for Adcal-D₃ Chewable tablets (PL 16508/0001; ProStrakan Limited), licensed for use in osteoporosis and other indications in the UK since December 1998. The safety profile of the product is therefore well-characterised and considered to be acceptable in the patient population in which it is indicated.

The Marketing Authorisation Holder has provided adequate justification for not submitting a detailed Environmental Risk Assessment (ERA). Vitamins are exempted from the requirement for an ERA and calcium, in the form of calcium carbonate, occurs naturally in the environment. There are no environmental concerns associated with the method of manufacture or formulation of the product.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

Calcium Carbonate

Nomenclature:

INN: Calcium Carbonate
Molecular formula: CaCO₃
Molecular weight: 100.09 g/mol (anhydrous)
CAS No: 471-34-1
Physical form: White powder
Solubility: Practically insoluble in water

The active substance, calcium carbonate, is the subject of a European Pharmacopeia (Ph. Eur.) monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

Appropriate specifications have been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specifications.

The active substance is stored in appropriate packaging. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary packaging in direct contact with the active substance complies with relevant Ph. Eur. requirements and satisfies Directive 2002/72/EC (as amended); it is suitable for contact with foodstuffs.

Appropriate stability data have been generated for active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and an appropriate retest period has been applied.
ACTIVE SUBSTANCE

Colecalciferol

Nomenclature:
INN: Colecalciferol

Chemical names: (5Z,7E)-9,10-secocholesta-5,7,10(19)-trien-3β-ol or (5Z,7E)-(3S)-9,10-secocholesta-5,7,10(19)-trien-3-ol

Structure:

Molecular formula: C_{27}H_{44}O
Molecular weight: 384.65 g/mol
CAS No: 67-97-0
Physical form: White powder
Solubility: Practically insoluble in water, freely soluble in ethanol (96%), soluble in trimethylpentane and in fatty oils

The active substance, colecalciferol, is the subject of a European Pharmacopeia (Ph. Eur.) monograph.

All aspects of the manufacture and control of colecalciferol are supported by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability (CEP). The certificate is accepted as confirmation of the suitability of colecalciferol for inclusion in this medicinal product.
MEDICINAL PRODUCT

Description & Composition

Adcal-D3 Caplets, 750 mg/200 I.U, film-coated tablets are presented as pale orange, capsule-shaped, film-coated tablets. Each tablet contains 750 mg calcium carbonate Ph. Eur., equivalent to 300 mg calcium, and 200 International Units (IU) colecalciferol, equivalent to 5 μg vitamin D₃.

Other ingredients consist of pharmaceutical excipients, namely colloidal silicon dioxide, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, modified food starch, sucrose, sodium ascorbate cryst., medium chain triglycerides, silicon dioxide, DL-alpha-tocopherol and pregelatinized starch making up the tablet core; and hypromellose, polydextrose, acacia, talc, titanium dioxide (e171), iron oxide yellow (e172) and iron oxide red (e172) constituting the film-coating. Appropriate justification for the inclusion of each excipient has been provided.

All excipients of the tablet core comply with their respective European Pharmacopoeia monographs. The film-coating complies with satisfactory in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product. None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used.

Pharmaceutical development

Details of the pharmaceutical development of the medicinal product have been supplied and are satisfactory. The objective was to develop a highly stable, film-coated tablet formulation that provides a good availability of the active ingredients, calcium carbonate and colecalciferol.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies were conducted on pilot-scale batches and the results were satisfactory. A commitment has been made by the MAH that full process validation will be conducted on commercial scale batches in accordance with the process validation protocol.

Finished product specification

Finished product specifications are provided for both release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are
compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

**Container Closure System**

Adcal-D3 Caplets, 750 mg/200 I.U, film-coated tablets are licensed for marketing in HDPE bottles, with polyethylene caps and silica gel desiccants, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 112 or 224 film-coated tablets.

Satisfactory specifications and Certificates of Analysis for all packaging components have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. The stability data support a shelf-life of 18 months, with the storage instructions ‘Do not store above 25°C’.

**Quality Overall Summary**

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

**PRODUCT INFORMATION:**

The approved Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory. Mock-ups of the PIL and labelling have been provided. The labelling fulfils the statutory requirements for Braille.

PIL user-testing has been accepted based on a bridging statement provided by the applicant making reference to the successful user-testing of the PIL for Adcal-D3 Chewable tablets (PL 16508/0001). The text, content and layout of the proposed PIL are essentially identical to the approved PIL for the reference product. The bridging is accepted.

The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the MHRA for approval before those packs are marketed commercially.

**Conclusion**

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. There are no objections to approval of Adcal-D3 Caplets, 750 mg/200 I.U, film-coated tablets from a pharmaceutical point of view.
NON-CLINICAL ASSESSMENT

This is an abridged, bibliographic application for Adcal-D3 Caplets, 750 mg/200 I.U, film-coated tablets, submitted under Article 10a of Directive 2001/83/EC, as amended.

Specific non-clinical studies have not been performed, which is acceptable considering that this was a bibliographic application for a product containing active ingredients of well-established use.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA).

There are no objections to approval of Adcal-D3 Caplets, 750 mg/200 I.U, film-coated tablets from a non-clinical point of view.
CLINICAL ASSESSMENT

1. INTRODUCTION AND BACKGROUND

This is an abridged, bibliographic application for Adcal-D3 Caplets, 750 mg/200 I.U, film-coated tablets, submitted under Article 10a (well-established use) of Directive 2001/83/EC, as amended.

Calcium and vitamin D3 administration has been well-proven as a specific therapy for osteoporosis and vitamin D dependant osteomalacia, in situations where therapeutic supplementation is required, for example pregnancy and old age. A metabolite of vitamin D3 regulates the uptake of intestinal calcium and the combination medication has been shown to enhance the uptake of the calcium supplied. The adverse event rate is low with such treatment and it is well-tolerated, especially amongst the older population to which it is specifically targeted.

1.1 Indications

Adcal-D3 Caplets, 750 mg/200 I.U, film-coated tablets are used as an adjunct to specific therapy for osteoporosis and in situations requiring therapeutic supplementation of malnutrition, e.g. in pregnancy and established vitamin D dependent osteomalacia.

The tablets are also used in the prevention and treatment of calcium deficiency/vitamin D deficiency especially in the housebound and institutionalised elderly subjects. Deficiency of the active moieties is indicated by raised levels of PTH, lowered 25-hydroxy vitamin D and raised alkaline phosphatase levels which are associated with increased bone loss.

The indications are in line with those for the previously approved Adcal-D3 Chewable tablets (PL 16508/0001) and are, therefore, acceptable.

1.2 Dose and Dose Regimen

The recommended dose of Adcal-D3 Caplets, 750 mg/200 I.U, film-coated tablets is two tablets to be taken twice a day, preferably two tablets each morning and two tablets each evening. Full details concerning the posology are provided in the SmPC.

The proposed dosing and regimen is consistent with that for the previously approved Adcal-D3 Chewable tablets. Dosing 2 tablets, twice a day means that the level of supplementation provided in the medication is equivalent to that provided by the chewable tablet.

2. CLINICAL PHARMACOLOGY

2.1 Pharmacokinetics

2.1.1 Introduction

Both calcium and vitamin D3 are endogenously occurring substances within the body. Calcium is actively absorbed into the body and its levels are controlled by various calcium homeostasis mechanisms, one of which vitamin D3 is involved in.
2.1.2 Absorption
Calcium, after oral administration, is absorbed from the small intestine by active transport and passive diffusion. Between 18-40% of administered calcium is absorbed. Active transport is mediated by the active metabolite of vitamin D₃, calcitriol and it is of particular importance in a calcium poor diet. Different calcium salts show different levels of absorption, with carbonate being the best absorbed (23-26% in one study). Absorption is also dependent on body size, oestrogen status (post-menopausal women absorb much less), vitamin D status, age and genetic polymorphisms.

Vitamin D₃ (as 25-hydroxyvitamin D₃) is readily absorbed, once bound to chylomicrons, via the portal system and the lymphatic system. The mean level of absorption for supplementation has been shown to be about 78%.

2.1.3 Distribution
Skeletal calcium accounts for 99% of the calcium in the body. Of the remaining 1%, 45% is bound to plasma proteins (mainly albumin), 5% is in anion complexes (phosphate, citrate, etc.) and 50% is in the ionic form, which is the physiologically active form.

The distribution of vitamin D₃ is closely linked to its metabolism and the metabolites are released into the circulation to have their effect on calcium homeostasis. Non-hydroxylated vitamin D₃ is stored in the adipose tissue and voluntary muscles. There is some storage of 25-hydroxyvitamin D₃ in the liver.

2.1.4 Metabolism
As an endogenously occurring substance, calcium is not metabolised in the traditional pharmacokinetic sense.

The metabolism of vitamin D₃ starts in the liver with its conversion to calcifediol via the cytochrome P450 system. This is released into the circulation bound to alpha-globulin. It reaches the kidneys where it is further metabolised to the active form, calcitriol. This metabolism is balanced in the calcium homeostasis system, with further hydroxylation occurring dependent on the serum calcium concentration.

2.1.5 Excretion
Calcium is excreted primarily in the urine and faeces. In the kidney, 98% of the filtered calcium is reabsorbed, with only 2% lost as obligatory calcium loss. Unabsorbed calcium is excreted in the faeces, together with that secreted in the bile and pancreatic juices. Excretion of vitamin D₃ is mainly in the bile and faeces, with very little appearing in the urine.

2.1.6 Special populations
It is well-recognised that calcium absorption is dependant on body size, oestrogen status (post-menopausal women absorb much less), vitamin D status, age and genetic polymorphisms. Of particular interest is that in menopausal women, the ability to absorb calcium drops rapidly. There is also a similar effect seen with age in both men and women. The oestrogen loss associated with the menopause; along with the
changes associated with age indicate why supplementation with calcium and vitamin D₃ is required.

2.1.7 Overall conclusions on Pharmacokinetics

The pharmacokinetics of calcium and vitamin D₃ are well-established, as is their interaction within the calcium homeostasis system. Comparative dissolution data have been provided for Adcal-D3 Caplets, 750 mg/200 I.U, film-coated tablets and the previously approved Adcal-D3 Chewable tablets. It is accepted that the dissolution data indicate that the two formulations allow for similar levels of drug to be available for absorption.

2.2 Bioequivalence

Bioequivalence studies were not necessary to support this well-established use application.

2.3 Pharmacodynamics

2.3.1 Introduction

Calcium carbonate is given as a supplement for people who have either a deficiency or an increased need for calcium. The pharmacodynamics of calcium carbonate are based on its natural, biochemical requirement in the body. Calcium is mainly used in the mineralisation of bones and teeth, with 99% of the calcium in the body held in this way. The other 1% is involved as an essential ion in many physiological processes, such as: cell motility, muscle contraction, axonal flow, cytoplasmic streaming, chromosome movement, neurotransmitter release, endocytosis and exocytosis. Within the cells it is bound with high affinity to specific calcium binding proteins, which serve as calcium receptors. Calcium homeostasis is maintained by a number of hormones and feedback mechanisms.

Vitamin D₃ has a primary role in calcium homeostasis. It is metabolised to calcitriol, which enables uptake of calcium from the small intestine. Its levels are regulated by serum calcium levels, which in turn affect the PTH levels, which in turn alter the levels of calcitriol. Vitamin D₃ deficiency reduces the uptake of calcium from the intestine and in more advanced states can lead to osteomalacia. Treatment of vitamin D₃ deficiency with supplementation is well-established and will quickly restore calcium homeostasis.

2.3.2 Overall conclusions on Pharmacodynamics

The pharmacodynamics of calcium and vitamin D₃, as endogenous substances and as supplements, is well-known.

3. CLINICAL EFFICACY

Calcium and vitamin D₃ supplementation are well-established treatments where therapeutic supplementation of malnutrition states is required, in the prevention and treatment of deficiencies often seen in the elderly and housebound and also as an adjunct to treatment of osteoporosis. The level of supplementation provided by the applicant’s medicine is in line with what is generally recommended for treatment (1200mg calcium and 800 IU vitamin D₃).
The applicant has supplied efficacy data from 9 different meta-analyses along with other important studies, containing treatment with either calcium or vitamin D₃ or both, whilst looking at end-points relevant to the indications.

The first meta-analysis looked at post-menopausal women or men over the age of 65. The end points examined were fracture rates on treatment. The analysis looked at various combinations of treatments and various comparators. When it looked at vitamin D alone versus placebo, no significant differences were found. When it looked at vitamin D and calcium versus placebo, significant effects were seen on non-vertebral fracture rates. When it compared combination treatment to treatment with calcium alone, no significant differences were seen.

The second meta-analysis looked at older individuals of both sexes aged 65 and over. It looked at non-vertebral fracture rates of vitamin D with or without calcium. Significant differences were seen in both hip and non-vertebral fracture rates. When it looked at the fracture rate in patients treated with higher doses of vitamin D (>400 IU/day) this effect was even greater.

The third meta-analysis looked at treatment of older males and females (41-79 years old) with calcium only. No overall effect on fracture rate was seen.

The fourth meta-analysis looked at over 50s. It showed that treatment with vitamin D with calcium significantly reduced fracture rates, as was also the case with calcium treatment alone. It also showed that patients who were compliant with treatment showed a significantly greater risk reduction. Additionally, it showed that treatment with 1200 mg of calcium or with 800 IU or more of vitamin D per day gave the best treatment effect.

The fifth meta-analysis, in mainly post-menopausal women, looked at treatment with 300-800 IU/day of vitamin D or 100,000 IU every 4 months, with or without calcium supplementation. It showed a reduction in relative risk of falls and of non-vertebral fractures versus no supplementation.

The sixth meta-analysis looked at post-menopausal women and men of 50 years of age and over and examined the hip fracture rates. It showed no effect on fracture rates for vitamin D alone, but a reduction in rates when patients were given vitamin D with calcium.

The seventh meta-analysis looked at children, women of reproductive age, post-menopausal women and elderly men. It looked at vitamin D supplementation, either as a medicine or in fortified foods. It found that circulating levels of 25(OH) vitamin D may be inversely associated with falls and have a positive association with bone density. It found that bone density did increase with supplementation. Results looking at fracture rates and falls were inconsistent overall. However, looking at older and especially institutionalised individuals the fracture rate was significantly reduced.

The eighth meta-analysis looked at males and females over the age of 60 who were either ambulatory or institutionalised. This showed that hip and non-vertebral fracture rates were only affected by higher doses of vitamin D (700-800 IU/day) with calcium and that calcium and lower doses of vitamin D did not show any significant effects.
The ninth meta-analysis looked at post-menopausal women who received supplementation with both calcium and vitamin D. There were too few fracture events to assess the effect but bone density did increase in all sites except the lumbar spine.

One study on calcium and vitamin D supplementation was included separate to the meta-analyses. It found that the number of falls was decreased with supplementation in the elderly population studied. Fracture rates were not high enough to assess but muscle parameters did show a general increase in strength and a decrease in body sway.

3.1 Overall conclusions on Clinical Efficacy

The above data give good support for the indications requested in this application. The efficacy of calcium and vitamin D supplementation is well-established.

4. CLINICAL SAFETY

Calcium carbonate and vitamin D₃ are both well-known medicines and have been used on their own and as a combination for many years. They are marketed widely around the world and widely used and prescribed. The applicants range of Adcal D3 products have been marketed in the UK for many years and they have a good safety and tolerability profiles.

Safety data has been presented from the 9 meta-analyses discussed in the efficacy section. Only one meta-analysis of RCTs contained adverse event data. Another meta-analysis did contain 3 prospective cohort studies with about 140,000 patients in total. The adverse event data mainly concentrated on hypercalcaemia, hypercalcuria, renal stones and other types of calcification. Hypercalcaemia is generally associated with primary hyperparathyroidism or malignant disease but has also been seen with high serum concentrations of 25(OH) vitamin D₃ (above 220 nmol/l), which could be caused by vitamin D₃ supplementation. In the meta-analyses mentioned it was noted that hypercalcaemia was most frequently seen in patients given Vitamin D or its analogues and not on placebo or calcium supplementation. The hypercalcaemia was particularly high in patients supplemented with calcitriol. Hypercalcuria was seen rarely but did occur more frequently in those treated with vitamin D. Renal stones were also rarely reported, although in one study of 36,000 women, followed up for 7 years, they were seen significantly more frequently in patients who received vitamin D₃ and calcium combination supplementation. No other significant differences in AEs were seen (although calcium carbonate is recognised to cause gastro-intestinal effects, including constipation and flatulence) and overall mortality data showed no increase in patients receiving vitamin D₃ and calcium supplementation.

No ethnic or age-dependent changes in adverse event rates have been observed in any of the studies but calcium and vitamin D₃ supplementation is contra-indicated in hypercalcaemia, hypercalcuria and nephrolithiasis. It is also cautioned against in renal impairment, sarcoidosis and pregnancy. Extrinsic factors, such as the ingestion of foods containing oxalic acid (spinach, rhubarb, etc.) or phytic acid (seeds, nuts, soy, etc.), can also cause calcium to be poorly absorbed from food.
Drug Interactions

Drug Interactions with vitamin D are described below:

- **Diuretics, thiazide and related**: There is an increased risk of hypercalcaemia if vitamin D is given with thiazide diuretics, calcium, or phosphate. Plasma calcium concentrations should be monitored in such situations.
- **Carbamazepine**: Some anti-epileptics may increase vitamin D requirements (e.g. carbamazepine, phenobarbital, phenytoin, and primidone). Rifampicin and isoniazid may reduce the effectiveness of vitamin D. Corticosteroids may counteract the effect of vitamin D.
- **Primidone**: Vitamin D requirements possibly increased when given with primidone.
- **Phenytoin**: Vitamin D requirements possibly increased when given with phenytoin.
- **Ketoconazole**: The plasma concentration of paricalcitol (analogue of calcitriol) may be increased by ketoconazole.

Drug Interactions with calcium are described below:

- **Ciprofloxacin**: Concurrent administration of calcium carbonate reduces the total absorption and peak serum levels of ciprofloxacin.
- **Quinolones**: Concurrent administration of calcium reduces the bioavailability of quinolones.
- **Antacids**: Calcium carbonate and other antacids may interfere with the absorption of concomitantly administered tetracycline preparations.
- **Glycosides**: Calcium-containing salts should be used with caution in patients taking cardiac glycosides because hypercalcaemia, like hypokalaemia, increases the potency of these drugs. Calcium carbonate and other calcium salts may enhance the cardiac effects of digoxin and other cardiac glycosides if systemic hypercalcaemia occurs. Calcium may precipitate digitoxin intoxication; arrhythmias may occur if these drugs are given together.
- **Omeprazole**: In a study of 18 women over the age of 65, the use of omeprazole for a week significantly reduced the absorption of calcium from a calcium carbonate supplement given on an empty stomach. Fractional calcium absorption was reduced from 9.1% with placebo to 3.5% with omeprazole.
- **Bisphosphonates**: The oral absorption of bisphosphonates is reduced by antacids, calcium-rich foods, calcium supplements, iron preparations, magnesium-containing laxatives or milk.
- **Levothyroxine**: The efficacy of levothyroxine can be reduced by calcium carbonate, and a minimum period of four hours should be allowed before taking Adcal-D3.
- **Tetracyclines**: The serum levels and, therefore, the therapeutic effectiveness of the tetracyclines can be markedly reduced or even abolished by antacids containing aluminium, bismuth, calcium or magnesium. Other antacids, such as sodium bicarbonate, may also reduce the bioavailability of some tetracyclines. Even intravenous doxycycline levels can be reduced by antacids.
- **Verapamil**: An isolated report describes antagonism of the anti-arrhythmic effects of oral verapamil due to the use of oral calcium and calciferol.
Pregnancy and Lactation

No links with calcium supplementation or its use as an antacid have been found with foetal malformations. Vitamin D is distributed in breast milk and its concentration seems to follow that in the mother’s blood. It is recommended in the US that, if therapeutic doses are administered, the mother is followed up looking for signs and symptoms of vitamin D toxicity or hypercalcaemia.

Overdose

Overdose is a rare occurrence, with there being no cases reported in the literature of acute calcium carbonate overdose. Chronic overdose can lead to hypercalcaemia, with one case recorded in the literature. The patient’s condition returned to normal after rehydration and stopping the supplements. The applicant’s Periodic Safety Update Report (PSUR) notes 4 cases of overdose in infants and children, all of whom recovered without sequelae.

PSUR for other Adcal D₃ products

There are over 1,320,000 patient years of exposure to the chewable formulation of Adcal D₃ in the 5 years of the last PSUR cycle. From this record only 85 adverse events have been reported that could be linked to Adcal D₃. Of these, only 4 were serious and unlisted. There was 1 case of small bowel obstruction secondary to hypercalcaemia, a fatal haemorrhage associated with a gastric ulcer and hypercalcaemia, blisters and injection site reactions after etanercept injections. Confounding factors were present in all of these. In this time the SmPC was amended to include tooth decay as there were 3 non-serious reports made.

4.1 Overall conclusions on Clinical Efficacy

The safety profile of combination vitamin D₃ and calcium supplementation is well-recognised. The applicant’s presentation of the safety data above is adequate for the application.

5. CLINICAL OVERVIEW

A satisfactory clinical overview is provided and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

6. PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPC is satisfactory. It is consistent with the SmPC for the previously approved Adcal-D₃ Chewable tablets (PL 16508/0001).

Patient Information Leaflet (PIL)

The final PIL is in line with the approved SmPC and is satisfactory.

Labelling

The labelling artwork is satisfactory.
7. CONCLUSION

As a ‘well-established use’ application submitted under Article 10a of Directive 2001/83/EC (as amended), no new clinical data have been included, nor are they required. The pharmacodynamics and pharmacokinetics of the active substances are well-documented in the literature and their clinical use in combination is established. The pharmacodynamic, efficacy and safety summaries are satisfactory. Sufficient clinical information has been submitted to support this application. The product literature is approved. The grant of a Marketing Authorisation was, therefore, recommended.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Adcal-D3 Caplets, 750 mg/200 I.U, film-coated tablets 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 and none are required for an application of this type.

CLINICAL
No new data are submitted and none are required for this type of application.

The published literature supports the efficacy of this product in the proposed indications. The safety and efficacy of calcium and vitamin D₃ in combination is well-known. The presented evidence for well-established use of the product is sufficient.

The literature review identifies no new safety issues or concerns.

PRODUCT LITERATURE
The approved SmPC is consistent with the SmPC for Adcal-D₃ Chewable tablets (PL 16508/0001) and is satisfactory.

PIL user-testing has been accepted based on a bridging statement provided by the applicant making reference to the successful user-testing of the PIL for Adcal-D₃ Chewable tablets (PL 16508/0001).

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label. The MAH has committed to submitting mock-ups for unmarketed pack sizes to the MHRA for approval before those packs are marketed.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Calcium and vitamin D₃ are active substances of well-known safety and efficacy. Extensive clinical experience with calcium and vitamin D₃ in combination is considered to have demonstrated the therapeutic value of the product. The benefit: risk ratio is considered to be positive.
Adcal-D3 Caplets, 750 mg/200 I.U, film-coated tablets
(calcium carbonate, vitamin D₃)

PL 16508/0039

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation application on 6th May 2010.

2 Following standard checks and communication with the applicant the MHRA considered the application valid on 27th May 2010.

3 Following assessment of the application the MHRA requested further information relating to the quality dossier on 20th August 2010; and further information relating to the clinical dossier on 6th December 2010 and 10th May 2011.

4 The applicant responded to the MHRA’s requests, providing further information for the quality sections on 21st January 2011; and further information for the clinical sections on 10th May 2011 and 27th May 2011 respectively

5 The application was determined 13th July 2011
Adcal-D3 Caplets, 750 mg/200 I.U, film-coated tablets
(calcium carbonate, vitamin D₃)

PL 16508/0039

STEPS TAKEN AFTER AUTHORISATION

Not applicable
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Adcal-D3 Caplets, 750 mg/200 I.U, film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Per tablet:
- Calcium carbonate: 750 mg equivalent to 300 mg of elemental calcium.
- Colecalciferol: 200 I.U. equivalent to 5 μg vitamin D₃.

This product also contains sucrose (part of the vitamin D₃ concentrate: approximately 0.4 milligrams per tablet).

For full list of excipients see 6.1.

3 PHARMACEUTICAL FORM
Pale orange capsule-shaped film-coated tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
As an adjunct to specific therapy for osteoporosis and in situations requiring therapeutic supplementation of malnutrition e.g. in pregnancy and established vitamin D dependent osteomalacia.

The prevention and treatment of calcium deficiency/vitamin D deficiency especially in the housebound and institutionalised elderly subjects. Deficiency of the active moieties is indicated by raised levels of PTH, lowered 25-hydroxy vitamin D and raised alkaline phosphatase levels which are associated with increased bone loss.

4.2 Posology and method of administration
Oral.

Adults and Elderly and children above 12 years of age:
Two tablets to be taken twice a day, preferably two tablets each morning and two tablets each evening.

Children:
Not recommended for children under 12 years.

4.3 Contraindications
Absolute contra-indications are hypercalcaemia resulting for example from myeloma, bone metastases or other malignant bone disease, sarcoidosis, primary hyperparathyroidism and vitamin D overdosage. Severe renal failure. Hypersensitivity to any of the tablet ingredients.

Relative contra-indications are osteoporosis due to prolonged immobilisation, renal stones, severe hypercalciuria.

4.4 Special warnings and precautions for use
Patients with mild to moderate renal failure or mild hypercalciuria should be supervised carefully including periodic checks of plasma calcium levels and urinary calcium excretion.

In patients with a history of renal stones, urinary calcium excretion should be measured to exclude hypercalciuria.
With long-term treatment it is advisable to monitor serum and urinary calcium levels and kidney function, and reduce or stop treatment temporarily if urinary calcium exceeds 7.5 mmol/24 hours (300 mg/24 hours).

Caution is required in patients receiving treatment for cardiovascular disease (see Section 4.5 – thiazide diuretics and cardiac glycosides including digitalis).

Adcal-D3 should also be used with caution in other patients with increased risk of hypercalcaemia e.g. patients with sarcoidosis or those suffering from malignancies.

This product contains small quantities of sucrose.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Allowances should be made for calcium and vitamin D supplements from other sources.

Adcal should be used cautiously in immobilised patients with osteoporosis due to increased risk of hypercalcaemia.

### 4.5 Interaction with other medicinal products and other forms of interaction

The risk of hypercalcaemia should be considered in patients taking thiazide diuretics since these drugs can reduce urinary calcium excretion. Hypercalcaemia must be avoided in digitalised patients.

Certain foods (e.g. those containing oxalic acid, phosphate or phytinic acid) may reduce the absorption of calcium.

Concomitant treatment with phenytoin or barbiturates can decrease the effect of vitamin D because of metabolic activation. Concomitant use of glucocorticoids can decrease the effect of vitamin D.

The effects of digitalis and other cardiac glycosides may be accentuated with the oral administration of calcium combined with Vitamin D. Strict medical supervision is needed and, if necessary, monitoring of ECG and calcium.

Calcium salts may reduce the absorption of thyroxine, bisphosphonates, sodium fluoride, quinolone or tetracycline antibiotics and iron. It is advisable to allow a minimum period of four hours before taking calcium.

### 4.6 Pregnancy and lactation

During pregnancy and lactation, treatment with Adcal-D3 Caplets should always be under the direction of a physician. Requirements for calcium and vitamin D are increased during pregnancy and lactation, but, in deciding on the required supplementation, allowances should be made for availability of these agents from other sources. If the patient requires administration of both Adcal-D3 Caplets and iron supplements, they should be taken at different times (see Section 4.5).

Overdoses of vitamin D have shown teratogenic effects in pregnant animals. However, there have been no studies on the use of this medicinal product in human pregnancy and lactation. In humans, long term hypercalcaemia can lead to physical and mental retardation, aortic stenosis and retinopathy in a new born child. Vitamin D and its metabolites pass into the breast milk.

### 4.7 Effects on ability to drive and use machines

None known.
4.8 Undesirable effects
The use of calcium supplements has, rarely, given rise to mild gastro-intestinal disturbances, such as constipation, flatulence, nausea, gastric pain or diarrhoea. Following administration of vitamin D supplements occasional skin rash has been reported. Hypercalciuria, and in rare cases hypercalcaemia, have been seen with long term treatment at high dosages.

4.9 Overdose
The most serious consequence of acute or chronic overdose is hypercalcaemia due to vitamin D toxicity. Symptoms may include nausea, vomiting, polyuria, anorexia, weakness, apathy, thirst and constipation. Chronic overdoses can lead to vascular and organ calcification as a result of hypercalcaemia. Treatment should consist of stopping all intake of calcium and vitamin D and rehydration.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
A12AX01; Calcium carbonate and colecalciferol

Strong evidence that supplemental calcium and vitamin D3 can reduce the incidence of hip and other non-vertebral fractures derives from an 18 month randomised placebo controlled study in 3270 healthy elderly women living in nursing homes or apartments for elderly people. A positive effect on bone mineral density was also observed.

In patients treated with 1200mg elemental calcium and 800IU vitamin D3 daily, i.e. the same dose delivered by the twice daily administration of two Adcal-D3 Caplets, the number of hip fractures was 43% lower (p=0.043) and the total number of non vertebral fractures was 32% lower than among those who received placebo. Proximal femur bone mineral density after 18 months of treatment increased 2.7% in the calcium/vitamin D3 group and decreased 4.6% in the placebo group (p < 0.001). In the calcium/vitamin D3 group, the mean serum PTH concentration decreased by 44% from baseline at 18 months and serum 25-hydroxy-vitamin D concentration had increased by 162% over baseline.

Analysis of the intention-to-treat results showed a decreased probability of both hip fractures (p = 0.004) and other fractures (p < 0.001) in the calcium/vitamin D3 treatment group. Analysis of the other two populations (active treatment and those treated and followed for 18 months) revealed comparable results to the intention-to-treat analysis. The odds ratio for hip fractures among women in the placebo group compared with those in the calcium/vitamin D3 group was 1.7 (95% CI 1.0 to 2.8) and that for other nonvertebral fractures was 1.4 (95% CI 1.4 to 2.1). In the placebo group, there was a marked increase in the incidence of hip fractures over time whereas the incidence in the calcium/vitamin D3 group was stable. Thus treatment reduced the age-related risk of fracture at 18 months (p = 0.007 for hip fractures and p = 0.009 for all non-vertebral fractures). At 3 years follow-up, the decrease in fracture risk was maintained in the calcium/vitamin D3 group.

5.2 Pharmacokinetic properties
The pharmacokinetic profiles of calcium and its salts are well known. Calcium carbonate is converted to calcium chloride by gastric acid. Calcium is absorbed to the extent of about 15-25% from the gastro-intestinal tract while the remainder reverts to insoluble calcium carbonate and calcium stearate, and is excreted in the faeces.

The pharmacokinetics of vitamin D is also well known. Vitamin D is well absorbed from the gastro-intestinal tract in the presence of bile. It is hydroxylated in the liver to form 25-hydroxycholecalciferol and then undergoes further hydroxylation in the kidney to form the active metabolite 1, 25 dihydroxycholecalciferol (calcitriol). The metabolites circulate in the blood bound to a specific α - globin. Vitamin D and its metabolites are excreted mainly in the bile and faeces.
5.3 Preclinical safety data
Calcium carbonate and vitamin D are well known and widely used materials and have been used in clinical practice for many years. As such, toxicity is only likely to occur in chronic overdosage where hypercalcaemia could result.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet Core:
- Colloidal silicon dioxide
- Microcrystalline cellulose
- Croscarmellose sodium
- Magnesium stearate
- Modified food starch
- Sucrose
- Sodium ascorbate cryst.
- Medium chain triglycerides
- Silicon dioxide
- DL-alpha-tocopherol
- Pregelatinized starch

Film-coat:
- Hypromellose
- Polydextrose
- Acacia
- Talc
- Titanium dioxide
- Iron oxide yellow
- Iron oxide red

6.2 Incompatibilities
Not applicable, oral preparation.

6.3 Shelf life
18 months in HDPE bottle.

6.4 Special precautions for storage
Do not store above 25°C.

6.5 Nature and contents of container
HDPE bottle with polyethylene cap and silica gel dessicant: Pack sizes 112 or 224 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special conditions.

7 MARKETING AUTHORISATION HOLDER
ProStrakan Limited
Galabank Business Park
Galashiels
TD1 1QH
UK
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UKPAR Adcal-D3 Caplets, 750 mg/200 LU, film-coated tablets

PRODUCT INFORMATION LEAFLET

Patient Leaflet: Information for the user

Adcal-D3® Caplets
Calcium carbonate (750 mg) and vitamin D3 (200 I.U.)
Film-coated tablets

In this leaflet:
1. What Adcal-D3 Caplets are and what they are used for
2. Before you take Adcal-D3 Caplets
3. How to take Adcal-D3 Caplets
4. Possible side effects
5. How to store Adcal-D3 Caplets
6. Further information

Read all of this leaflet carefully before you start taking this medicine
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects worsen, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

1. WHAT ADCAL-D3 CAPLETS ARE AND WHAT THEY ARE USED FOR
Adcal-D3 Caplets contain calcium and vitamin D3 which are both essential for healthy bones and teeth. Adcal-D3 Caplets provide extra calcium and vitamin D3 to your diet. It is therefore used in conditions where your body's calcium and vitamin D levels need to be increased.
Adcal-D3 Caplets can be prescribed by doctors for certain bone conditions, for example, osteoporosis.
Studies show that taking calcium and vitamin D3 over a long time can prevent hip and other non-vertebral bone fractures in later life.

2. BEFORE YOU TAKE ADCAL-D3
Do not take Adcal-D3
- If you are allergic (hypersensitive) to calcium carbonate, vitamin D3, or any of the other ingredients in Adcal-D3 Caplets (see Section 6 Further Information).
- If you have higher than normal levels of calcium in your blood (hypercalcaemia). Your doctor will be able to tell you if you do.
- If you have severe kidney failure

Take special care with Adcal-D3 Caplets
- If you have osteoporosis (thinning of the bones) due to long periods of inactivity, such as long-term bed rest.
- If you have problems with your kidneys, for example kidney stones.
- If you have higher than normal levels of calcium in your urine (hypercalciuria). If you are unsure your doctor will advise you.
- If you have sarcoidosis (inflammation that produces lumps of cells in various organs in the body). Your doctor will be able to tell you if you do.
- If you have previously been told by your doctor that you have an intolerance to some sugars.
- If you are taking any other medication, even those you may have bought for yourself without prescription.

Taking other medicines
Tell your doctor if you are taking calcium supplements or antacids for indigestion, diuretics or corticosteroids.
If you are taking thyroxine, bisphosphonates, ion or fluoride medicines, tetracycline or quinolone antibiotics make sure your doctor knows this. When taking these medicines leave a period of about 4 hours before taking your Adcal-D3 Caplets. Do not take any of these listed medicines at the same time as your Adcal-D3 Caplets.
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines including medicines taken without a prescription.

Pregnancy and breastfeeding
In pregnancy or when breast feeding, Adcal-D3 Caplets should only be used under medical supervision. Ask your doctor or pharmacist for advice before taking any medicine.
3. HOW TO TAKE ADCAL-D3 CAPLETS
Always take Adcal-D3 Caplets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Adults, elderly and children over 12 years of age - Swallow 2 caplets twice daily, ideally two caplets in the morning and two in the evening.

Children under 12 - Do not give Adcal-D3 Caplets to children under 12 years.

If you take more Adcal-D3 Caplets than you should - You should only take what your doctor recommends. If you take too many caplets contact your doctor or pharmacist if you can do so. If not, go to the nearest hospital casualty department immediately, taking the pack and remaining tablets with you.

If you forget to take Adcal-D3 Caplets - If you forget to take your caplets, take them as soon as possible and then continue to take them as normal. Do not take a double dose to make up for forgotten caplets.

If you stop taking Adcal-D3 Caplets - Always talk to your doctor or pharmacist before you stop taking the caplets.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Adcal-D3 Caplets can cause side effects, although not everybody gets them.

Rare Side Effects (affecting less than 1 in 1,000 people):
- Constipation, wind, feeling sick, stomach ache, diarrhoea
- Skin rash
- Hypercalcaemia (too much calcium in your blood) or hypercalciuria (too much calcium in your urine)

If you are on long term treatment your doctor may from time to time wish to check the level of calcium in your blood and take urine samples to monitor kidney function.

If any of the side effects worsen, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ADCAL-D3 CAPLETS
- Keep out of reach and sight of children.
- Do not store above 25°C. Store in the original package.
- Do not use Adcal-D3 Caplets after the expiry date that is printed on the carton label has passed.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION
What Adcal-D3 Caplets contain
- The active substances are calcium carbonate (750 mg equivalent to 300 mg calcium) and vitamin D3 (200 I.U. equivalent to 5 micrograms of cholecalciferol).
- The other ingredients in the tablet core are colloidal silicon dioxide, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, modified food starch, sucrose, sodium ascorbate, medium chain triglycerides, silicon dioxide, DL-alpha-tocopherol and pregelatinized starch.
- The orange film-coat contains hypromellose, polydextrose, acacia, talc, titanium dioxide, iron oxide yellow and iron oxide red.

What Adcal-D3 Caplets looks like and contents of the pack
Adcal-D3 Caplets are pale orange capsule-shaped film-coated tablets (caplets) provided in bottles of 112 or 224 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder: ProStrakan Limited
Galabank Business Park
Galashiels
Scotland
TD1 1QH

Manufacturer: NexiPharma
siblings PharmArzneimittel GmbH
Hildebrandstrasse 12
D-37071 Göttingen
Germany

Additional information
If you have been prescribed Adcal-D3 Caplets for the treatment or prevention of osteoporosis and would like further information you should speak to your doctor or contact the National Osteoporosis Society on 0845 450 0230. The National Osteoporosis Society is a national charity dedicated to offering advice, information and support to all osteoporosis sufferers and those at risk of the disease.

This leaflet was last approved in MM/YYYY
LABELLING

Carton
Carton showing Braille
Each caplet contains 750 mg calcium carbonate (equivalent to 300 mg calcium) and 200 i. U. colcalciferol (equivalent to 5 micrograms vitamin D3).
Also contains small quantities of sucrose.
See enclosed leaflet for further information.
Swallow the caplets with a glass of water.
Read the package leaflet before use.
Do not store above 25°C.
Store in the original container.
Keep out of the reach and sight of children.