

**ADCAL D₃ DISSOLVE 1500 MG/400IU EFFERVESCENT
TABLETS
PL 16508/0026**

UKPAR

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**ADCAL D₃ DISSOLVE 1500 MG/400IU EFFERVESCENT
TABLETS
PL 16508/0026**

LAY SUMMARY

The MHRA granted ProStrakan Limited a Marketing Authorisation (licence) for the medicinal product Adcal D₃ Dissolve 1500 mg/400IU Effervescent Tablets (PL 16508/0026). This pharmacy-only medicine (P) is used as a dietary supplement to increase calcium and vitamin D levels in the body and can be prescribed by doctors to treat certain bone conditions such as osteoporosis.

Adcal D₃ Dissolve 1500 mg/400 IU Effervescent Tablets contain the active ingredients calcium carbonate and colecalciferol.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Adcal D₃ Dissolve 1500 mg/400IU Effervescent Tablets outweigh the risks, hence Marketing Authorisations have been granted.

**ADCAL D₃ DISSOLVE 1500 MG/400IU EFFERVESCENT
TABLETS
PL 16508/0026**

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Adcal D₃ Dissolve 1500 mg/400IU Effervescent Tablets (PL 16508/0026) on 22nd November 2007. The product is a pharmacy-only medicine.

This application was for a line extension to the marketing authorisation for Adcal-D₃ Chewable Tablets (PL 16508/0001) first authorised in the UK in December 1999 to add the pharmaceutical form, effervescent tablets. The application was submitted under Article 10a of Directive 2001/83 (as amended), so called well-established use application, as such the application relies solely on bibliographic data with respect to the clinical aspects.

The product contains the active ingredients calcium carbonate and colecalciferol and is used as a dietary supplement in the treatment of calcium/vitamin D₃ deficiencies. Its intended use is to complement specific treatments for osteoporosis and in situations requiring therapeutic supplementation of malnutrition.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE (1)

Calcium Carbonate

INN: Calcium Carbonate

CAS No: 471-34-1

Molecular formula: CaCO₃

Relative molecular weight: 100.1

Physical form: White or almost white powder.

Solubility: Practically insoluble in water.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Calcium carbonate is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a retest period of 36 months, with no specific storage instructions.

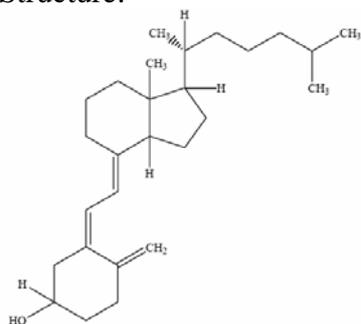
DRUG SUBSTANCE (2)

Colecalciferol

INN: Colecalciferol

CAS No: 67-97-0

Structure:



Molecular formula: C₂₇H₄₄O

Relative molecular weight: 384.6

Physical form: White or yellowish-white powder.

Solubility: Disperses in water.

An appropriate specification based on the European Pharmacopoeia has been provided. The other components in the colecalciferol concentrate namely, All-rac-alpha-tocopherol, hydrogenated soyabean oil, sucrose, maize starch and gelatin are also all

controlled according to the specification of their individual Ph Eur monographs. A European Pharmacopoeial TSE certificate of suitability for gelatin has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Colecalciferol is stored in laminated aluminium foil bags. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a retest period of 12 months, when stored in laminated aluminium foil bags with a specific storage instruction of "Do not store above 25°C".

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely citric acid anhydrous, malic acid, sodium hydrogen carbonate, sodium cyclamate, lemon flavour "BSL 119", sodium carbonate anhydrous, maltodextrin and saccharin sodium. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeial monograph, with the exception of lemon flavour "BSL 119" which complies with an in-house specification and this is acceptable. Satisfactory certificates of analysis have been provided for all excipients.

A stability overage for the drug substance colecalciferol is incorporated in the finished product to cover its losses over the 3-year shelf-life to allow the product to contain at least 90% of the label claim. The suitability of the overage is demonstrated by the production batch stability data. As the proposed stability overage is attributed to colecalciferol which is a vitamin that has a well known degradation process and which poses no safety problem; this is therefore a suitable justification.

An overage for citric acid and sodium hydrogen carbonate is incorporated into the finished product. The overage was justified in terms of minor weight losses due to acid-base reaction between these two components which occurs during granulation with water. The overage is required to compensate for the loss of these two components which causes an increase in the calcium content in the final effervescent tablet. The adequacy and suitability of the overages was demonstrated by the results of manufacturing process validation on three production scale batches. The justification is acceptable.

Physicochemical properties

No dissolution test is required for effervescent tablets according to the Ph Eur and this is replaced with the disintegration test. Data have demonstrated that disintegration is achieved within 5 minutes and is in compliance with Ph.Eur for effervescent tablets.

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 has been carried out on three production-scale batches. The results are satisfactory.

Finished product specification

The finished product specification is 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. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

Product is packaged in an aluminium or polypropylene tube closed with polyethylene stoppers with desiccant material. Specifications and certificates of analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food. The product is packaged in sizes of 4 x 14 effervescent tablets in a carton packs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. Storage conditions are "Do not store above 25 degrees" and "Keep container tightly closed".

Summary of Product Characteristics

This is acceptable.

Patient Information Leaflet

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. 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.

Label

This is acceptable.

Conclusion

It is recommended that a Marketing Authorisation is granted for this application.

PRECLINICAL ASSESSMENT

INTRODUCTION

This is an abridged application to add a new formulation to the currently licensed and marketed Adcal-D₃ chewable tablets (PL 16508/0001). Adcal-D₃ is used for the prevention and treatment of calcium and vitamin D deficiency and adjunctive therapy in the treatment of osteoporosis.

This line extension application is presented in accordance with reference to Annex II of Community Regulations 1084/2003/EC and 1085/2003/EC. Cross reference is made to relevant data in Adcal D₃ chewable tablets in respect of non-clinical data.

NON-CLINICAL ASPECTS

There is no new non-clinical data and cross reference is made to previous Expert Report presented in respect of Adcal D₃ chewable tablets.

The product contains a combination of well established active substances. Adcal-D₃ chewable tablets have been licensed in the UK since December 1999 and are currently marketed. Adcal-D₃ Dissolve effervescent tablets have the same qualitative and quantitative composition in terms of the active ingredients as Adcal D₃ chewable tablets. Adcal D₃ Dissolve effervescent tablets will have the same indications as Adcal D₃ chewable tablets, that is, the prevention and treatment of calcium and Vitamin D₃ deficiency and as adjunctive therapy in the treatment of osteoporosis.

NON-CLINICAL OVERVIEW

The Expert overview has been written by a suitably qualified and experienced person. The Expert has stated that there are no new safety data relating to either active moiety which would materially affect the safety profile of the combined administration at the dosages proposed for Adcal D₃ Dissolve effervescent tablets.

SUMMARY OF PRODUCT CHARACTERISTICS

This is acceptable.

CONCLUSIONS

There are no non-clinical objections to the grant of this line extension.

CLINICAL ASSESSMENT

1. 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. These are identical to that for the original product and are acceptable.

2. DOSE & DOSE SCHEDULE

Oral.

Adults, and elderly and children over 12 years of age:	Take 2 effervescent tablets daily, preferably one tablet each morning and evening. The effervescent tablets should be dissolved in a glass of water (approx. 200ml) and drunk immediately
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Children :	Not recommended for children under 12 years.
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This is consistent with that of the original product and is acceptable.

3. TOXICOLOGY

There is a separate pre-clinical assessment report.

There is a pre-clinical overview written by an appropriately qualified expert.

4. CLINICAL PHARMACOLOGY

The clinical pharmacology of calcium and vitamin D has been documented in published papers.

4.1 Pharmacodynamic Properties

Calcium intake corrects a lack of calcium in the diet. The commonly accepted requirement of calcium in the elderly is 1500mg/day. Vitamin D corrects an insufficient intake of vitamin D. It increases intestinal absorption of calcium. The optimal amount of vitamin D in the elderly is 500-1000 I.U./day. Vitamin D and calcium correct secondary senile hyperparathyroidism.

4.2 Pharmacokinetic Properties

Calcium Carbonate

In the stomach, calcium carbonate releases calcium ions as a function of pH. Calcium administered as calcium carbonate is absorbed to 20-30% and the absorption takes place mainly in the duodenum through vitamin D-dependent, saturable, active

transport. Calcium is eliminated in urine, faeces and sweat. The urinary calcium excretion is a function of glomerular filtration and tubular reabsorption of calcium.

Vitamin D

Vitamin D is absorbed in the small intestine and bound to specific alpha globulins and transported to the liver where it is metabolised to 25-hydroxy-cholecalciferol. A second hydroxylation to 1,25-dehydroxy-cholecalciferol occurs in the kidney. This metabolite is responsible for the vitamin's ability to increase the absorption of calcium. Non-metabolised vitamin D is stored in tissues such as fat and muscle. Vitamin D is eliminated via faeces and urine.

5. EFFICACY

The following tables outline the studies used to support the efficacy and safety of the product.

Study ID	Design Control type	Study & Ctrl Drugs Dose, Route & Regimen	Study Objective	Study Population	Duration	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)
Dawson-Hughes et al (1991) ¹²²	Randomised, double-blind, placebo controlled	Mean 377mg Ca ²⁺ plus 400I.U. vitamin D ₃ vs mean 377mg Ca ²⁺ plus placebo over one year, dietary calcium intake: <650mg Ca ²⁺ Dietary vitamin D ₃ intake: 100I.U. period 1: month VI/VII to XII/I to VI/VII	Effect of Vitamin D Supplementation on Wintertime and Overall Bone Loss in Healthy Postmenopausal Women	n=249 healthy ambulatory postmenopausal women with low dietary calcium and vitamin D ₃ intake.	One year	F	Whole body and spine bone mineral density (dexa, serum 25-OH-D, PTH)	Overall active treatment with 400I.U. vitamin D/day together with an improvement of daily calcium ingestion reduces late wintertime bone loss compared with placebo group in which only calcium supplementation was given. It is thought that the raised 25-OH-D serum concentrations seen in the active group resulted in low PTH levels leading to the results seen.
Dawson-Hughes et al (1997) ¹²³	Double-blind, randomised, placebo controlled	Active group: 500mg calcium and 700I.U. vitamin D ₃ /day. Placebo group: microcrystalline cellulose containing tablets.	Effect of Calcium and Vitamin D Supplementation on Bone Density in Men and Women 65 years of Age or Older	n=389 subjects assigned to active and placebo groups. Active group: n=86 men, mean age 70 ± 4y, n=101 women, mean age 71 ± 4y. Placebo group: n=90 men, mean age 71 ± 5y, n=112 women, mean age 72 ± yrs	3 years	MF	BMD, biochemical measures of bone metabolism, incidence of fractures (non-vertebral).	Calcium and vitamin D dietary supplementation moderately reduced bone loss in femoral neck, spine and total body over a 3 year period. A reduction in the incidence of non-vertebral fractures was seen.

Study ID	Design Control type	Study & Ctrl Drugs Dose, Route & Regimen	Study Objective	Study Population	Duration	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)
Heikinheimo et al, (1992) ¹³⁰	Open age matched controlled study	Active group 1 and 2: annual vitamin D ₂ injection: 150,000I.U. (one year only: 300,000)	Annual Injection of Vitamin D and Fractures of Aged Bones	Group 1: n=199 subjects living at home, mean age 86.6 years; Group 2: n=142 institutionalised subjects mean age 79.3 years; Control 1: n=280, mean age 86.1 years; Control 2: n=178, mean age 79.4 years	Group 1: 3.49 yrs Group 2: 3.27 yrs Control 1: 3.41yrs Control 2: 3.30yrs	MF	Fracture, rate, laboratory parameters, vitamin D levels, possible side effects, mortality.	Supplementing reduced vitamin D levels in elderly people (who generally have insufficient vitamin D intake) by annual vitamin D injections (corresponding to numerically about 400I.U./day) decrease the number of new fractures especially in women who have a lower bone mass than men.
Chapuy et al (1992) ¹³²	Randomised, double-placebo, double blind	1200mg Ca ²⁺ plus 800I.U. vitamin D ₃ vs double placebo	Vitamin D ₃ and Calcium to Prevent Hip Fractures in Elderly Women	n=3270 ambulatory institutionalised women	18 months	F 84 ± 6y	Hip fractures, non-vertebral fractures; sub group: bone mineral density of femoral neck, serum 25-OH-D, PTH	In elderly ambulatory women living in nursing or apartment houses a calcium and vitamin D supplement in daily doses as in Adcal-D ₃ i.e. 1200mg elemental calcium and 800I.U. vitamin D ₃ , secondary hyperparathyroidism disappeared, bone mineral density of the proximal femur increased and hip and other non-vertebral fractures can be reduced in comparison with double placebo by 43% and 32% respectively within an 18 month period.
Chapuy et al (1994) ¹³³	Randomised, double-placebo, single blind	Continuation of study, Ref. No. IVB 4, further 18 months	Effect of Calcium and Cholecalciferol Treatment for Three Years on Hip Fractures in Elderly Women.	Continuation of study, Ref. No. IVB 4	3 years	F	As in Ref. No. IVB4	The therapeutic efficacy of calcium plus vitamin D supplementation in elderly institutionalised ambulatory women followed for an initial observation period of 18 months is documented for an additional 18 months of therapy. The preventative effect in reducing the incidence of hip and other non-vertebral fractures is shown to continue.

Study ID	Design Control type	Study & Ctrl Drugs Dose, Route & Regimen	Study Objective	Study Population	Duration	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)
Chevalley et al (1994) ¹³⁴	Randomised, double-blind, placebo controlled	2x400mg Ca ²⁺ (as Calcium carbonate or calcium osseino mineral complex) vs placebo. All participants: 1x300,000IU. vitamin D ₃ at entry	Effects of Calcium Supplements on Femoral Bone Density and Vertebral Fracture Rate in Vitamin-D Replete Elderly Patients	n=93 healthy subjects, 72 ± 0.6y (vs placebo); n=63 patients with recent osteoporotic hip fracture, 78.4 ± 1.0y, vs baseline characteristics	18m	F	BMD: femoral shaft/neck, lumbar spine, incidence of vertebral fractures (height reduction of ≥20%)	An 18 month calcium supplementation of 800mg/day together with a single vitamin D supplement of 300,000IU. at the beginning resulted in the prevention of femoral bone mineral decrease and a significant decrease of vertebral fracture rate in elderly healthy women compared to placebo plus vitamin D.
Aloia et al, (1994) ¹³⁵	Randomised, three-armed, placebo controlled parallel study	Group 1: vitamin D ₃ 400I.U./ day double placebo; Group 2: vitamin D ₃ 400I.U./day plus 1700mg Ca ²⁺ (nutritional plus supplement) plus placebo; Group 3: as group 2 plus HRT (0.625mg equine oestrogens, day 1-25/10mg progesterone, day 16-25)	Calcium Supplementation with and without Hormone Replacement Therapy to Prevent Postmenopausal Bone Loss	n=118 healthy 3-6 years postmenopausal women	2.9 ± 1.1y	F	BMD: lumbar spine, radius, Ward triangle, femoral neck, femoral trochanter, total body calcium	The results document that over an almost three year observation period, the addition of calcium 1700mg/day (and vitamin D 400I.U.) alone significantly retards bone loss from the femoral neck and improves calcium balance in recently menopausal women. Calcium (and vitamin D) therapy when combined with HRT gives superior results.
Ooms et al, (1995) ¹³⁶	Randomised, placebo controlled, double-blind	1x400I.U. vitamin D ₃ or placebo/day Nutritional median calcium intake: 876mg (active), 859mg (placebo).	Prevention of Bone Loss by Vitamin D Supplementation in Elderly Women: A Randomised Double-Blind Trial	n=348 elderly women, active: n=177, mean: 80.1 ± 5.6 years, placebo: n=171, mean: 80.6 ± 5.5 years.	2 years	F	BMD: at different sites, laboratory parameters	Supplementation with 400I.U. per day vitamin D in elderly women has beneficial effects on circulating PTH levels and increases bone mineral density at the femoral neck. It is not clear in what way the higher mortality levels seen in the placebo group may have affected the result.

Study ID	Design Control type	Study & Ctrl Drugs Dose, Route & Regimen	Study Objective	Study Population	Duration	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)
Dawson-Hughes et al, (1995) ¹³⁷	Randomised, double-blind, parallel group	Group 1: 100I.U. vitamin D/day Group 2: 700I.U. vitamin D/day Both groups: 500mg Ca ²⁺ /day	Rates of bone loss in postmenopausal women randomly assigned to one of two dosages of vitamin D	n=261 healthy, ambulatory late postmenopausal white women with vitamin D intake: 100I.U./day, calcium intake: below 500mg/day	2 years	F	BMD: total body, femoral neck, spine in 6 month intervals (dexa method)	These results indicate that in healthy late postmenopausal women a vitamin D intake of 200I.U./day is not sufficient to limit bone loss at femoral neck site even when calcium intake is elevated up to 1000mg/day. A total of 800I.U. vitamin D per day reduces bone loss from femoral neck. The supplemented daily dose of 700I.U. vitamin D and 500mg Ca ²⁺ was safe and well tolerated.
Lips et al, (1996) ¹³⁸	Randomised, double-blind, placebo controlled	1x400I.U. vitamin D vs placebo	Vitamin D Supplementation and Fracture Incidence in Elderly Persons. A Randomised, Placebo-Controlled Clinical Trial	n=2578 independently living, healthy participants aged 70-97 years (n=1916 women, n=662 men)	3-3.5 years, additional 6 month follow-up	F/M 70-97 yrs	Number of new hip and other peripheral fractures.	Supplementation with 400I.U. vitamin D had no effect on the incidence of hip fracture in elderly and old people with an average nutritional calcium intake of 850-900mg/day.

Author/ Year	Study Details			Results			Quality/Comments	
	End-points: P – primary S – secondary T – tertiary	Methods Length study ^{2/}	Population ^{1/} /Average age /Setting	Baseline 25(OH)D ^{3/} Nmol/L	Change 25(OH)D	Change PTH	Outcome	
Chapuy ¹⁴¹ 2002	P: bone biochemistry S: hip fractures T: Falls no definition; no diary	RCT DB 24m Placebo control	583 women 85y Ambulatory in homes for elderly	Insufficient 21	+252% P<0.0001	-57% P<0.0001	BMD maintained by treatment, decreased in placebo by 2.65%	Randomisation unclear; Drop-out 31%; ITT; definition and data for falls not presented
Porthouse ¹⁴² 2005	P: clinical fractures; S: falls, adherence, QoL; no diary, no definition; Q/6m	Factorial RCT 25m; 1321 women with >1 risk factor for hip fracture; leaflet on prevention of falls and fractures. Dietary Ca est 1075mg	1321 women 77y with >1 risk for fracture community	Not measured	Not measured	Not measured	No change in risk of fractures OR 1.6 (0.75-3.40); compliance declined to 45% after 2y when non-responders included;	No placebo, drop-out 40%; underpowered for fracture reduction of <30%; lower than expected fracture rate may indicate confounding; all participants received advisory leaflet on Ca intake & prevention of falls
Grant ¹⁴³ 2005	P: fracture rate; S: falls; no definition; no diary – postal Q every 4m asking for falls in previous week	RCT factorial 24-62m comparison vitamin D alone, Ca alone	1110 women + 196 men >70y with previous fracture, community	Insufficient 38 (60pts only)	+63% to 62 sig n/a Measured in only 1.1% of subjects	-34.5% Measured in only 1.1% of subjects	Risk of Fracture (NS): Vit D + Ca: 13.7% Vit D: 15.5% Ca: 14.1% Placebo: 14.4%	Compliance 60% @ 4m, 46% @ 12m; 25(OH)D & PTH only measured in 60 participants at baseline & 12m ITT; dietary Ca not estimated

1/ of the treatment group; 2/ RCT = randomised controlled trial; 1 = intervention; FU = follow-up period, no treatment; Q = questionnaire, or interview; ITT – intention to treat; 3/ <15nmol = deficient, 15-75nmol = insufficient; >75 = sufficient; sig = statistically significant effect; NS = not statistically significant at 95% level or less

Author/ Year	Study Details			Results			Quality/Comments	
	End-points: P – primary S – secondary T – tertiary	Methods Length study ^{2/}	Population ^{1/} /Average age /Setting	Baseline 25(OH)D ^{3/} Nmol/L	Change 25(OH)D	Change PTH	Outcome	
Harwood ¹³⁹ 2004	P: Bone biochem, BMD S: Fracture, Falls, no diary, Qs at 3, 6, 12m	RCT 12m comparisons vitamin D injection 300,000IU, vitamin D injection +Ca oral, oral vitamin D + 1000mg Ca, no treatment	39 women 87y, recruited 7 days after hip replacement, previously community	Insufficient 27	+85% to 50 P<0.0005	-28% P=0.003	25(OH)D fell BMD increased by up to 4.6 (no P); fracture rate halved at 12m in treated group	No blinding, no masking, no placebo;
Larsen ¹⁴⁰ 2004	P: prevention of fractures S: 25(OH)D + PTH	Vit D 400IU + 1000mg Ca; factorial, pragmatic in 4 blocks; 24m; comparison programme for domestic improvements	2983 women + 1974 men 74y community	Insufficient 80%<50	+ data n/a p<0.001	Decreased significantly at 1m and maintained at 24m (P<0.001)	16% reduction in fracture incidence rate (RR 0.84; CI, 0.72-0.98; p<0.025) among male and female residents taking Ca & vitamin D	Randomised in blocks only, not participants; no blinding, no placebo ITT; falls underestimated compared to other studies due to definition
Trivedi ¹⁴⁴ 2003	P: fractures S: mortality T: falls, not defined; postal Q at last study visit for previous 12m	Vitamin D 100,000 oral x1 per 4m, no Ca, but 742mg dietary; placebo; RCT DB; 12m; trial 60m,	326 women + 1019 men 75y community ambulatory	Insufficient 53 ³	+40% P<0.001	-6% NS	Positive for fractures: RR in the vitamin D group were 0.78 (0.61 to 0.99, P=0.04) for any first fracture and 0.67 (0.48 to 0.93, P=0.02) for first hip, wrist or forearm, or vertebral fracture	Randomisation unclear Drop-out 35% ITT
Jackson ¹³⁸ 2006	P: Fractures	Vitamin D 400IU calcium 1000mg double blind placebo controlled, randomly assigned; 7y	36,282 women, healthy 50-79y	Measured in 357 cases:	n/a	n/a	12% reduction in hip fracture not statistically significant, in those taking >80% medication, hazard risk of fractures reduced by 29% (P=0.05)	No significant interaction between baseline 25(OH)D and supplementation; analysis ITT and planned sub-group. Patient population not elderly enough. Dose too low. Patient population taking additional supplements + HRT uncontrolled

1/ of the treatment group; 2/ RCT = randomised controlled trial; 1 = intervention; FU = follow-up period, no treatment; Q = questionnaire, or interview; ITT – intention to treat; 3/ <15nmol = deficient, 15-75nmol = insufficient; >75 = sufficient; sig = statistically significant effect; NS = not statistically significant at 95% level or less

A 2005 Cochrane collaboration review undertook a meta-analysis to determine the efficacy of supplementation with vitamin D or a vitamin D analogue in the prevention of fractures of the axial and appendicular skeleton.

The reviewers concluded that in frail older people confined to institutionalised care calcium and vitamin D supplements may sustain fewer hip and other non-vertebral fractures. They further stated that the effectiveness of vitamin D alone in fracture prevention is unclear and that there is no evidence of advantage of vitamin D analogues compared with vitamin D. The authors indicated that route of administration of vitamin D, dose and frequency of dosing in older people requires further investigation.

Efficacy data have been derived from published papers. The use of calcium and vitamin D has been well established for many years for use in correcting these deficiencies and as adjunctive therapy for osteoporosis. The use of a fixed combination of calcium and vitamin D in a single effervescent tablet represents a simplification of therapy (improvement in compliance, especially for elderly patients). Daily intakes of 1000-1500mg calcium and 800 I.U. vitamin D₃ have been recommended particularly for elderly people.

6. SAFETY

Safety data have been derived from published papers and from ADROIT data for the marketed product. The most commonly reported undesirable effects are gastrointestinal disturbances together with hypercalcaemia and hypercalciuria. All the expected adverse events have been documented in the Summary of Product Characteristics.

7. CLINICAL EXPERT REPORT

There is an adequate clinical overview written by an appropriately qualified expert.

8. SUMMARY OF PRODUCT CHARACTERISTICS

This is satisfactory

9. PATIENT INFORMATION LEAFLET

User testing has been undertaken and has been assessed as satisfactory.

10. LABELLING

Clinically Satisfactory

11. DISCUSSION

This line extension application is for a combination of calcium and vitamin D as effervescent tablets for the treatment of calcium and vitamin D deficiencies particularly in the elderly and as adjunctive therapy for osteoporosis.

The application has been submitted under article 10a of EC Directive 2003/83 (as amended) and references from the literature are cited to establish the daily requirements of calcium and vitamin D in the proposed indications. The clinical pharmacology of calcium and vitamin D has been well documented in published papers. The efficacy and safety data have been derived from published papers, and the ADROIT database for the original product the use of the product in the proposed doses in the requested indications has been established over many years' clinical study and use.

The clinical expert has made an adequate appraisal of the data derived from the published papers. The data presented here are sufficient to establish the efficacy and safety of the product for use in the proposed indications.

12. RECOMMENDATIONS

The efficacy and safety of the product is satisfactory for the grant of a product licence.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT**QUALITY**

The important quality characteristics of Adcal D₃ Dissolve 1500 mg/ 400 IU Effervescent 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.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

Calcium carbonate and colecalciferol are well known dietary supplements and have been used to treat calcium/vitamin D₃ deficiencies for many years.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with calcium carbonate and colecalciferol is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

**ADCAL D₃ DISSOLVE 1500 MG/400IU EFFERVESCENT
TABLETS
PL 16508/0026**

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 15 th June 2006.
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 30 th June 2006.
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 21 st March 2007, and further information relating to the quality dossiers on 27 th April 2007 and 24 th October 2007.
4	The applicant responded to the MHRA's requests, providing further information on 27 th April 2007 for the clinical sections, and again on 20 th September 2007 and 6 th November 2007 for the quality sections.
5	The applications were determined on 22 nd November 2007.

**ADCAL D₃ DISSOLVE 1500 MG/400IU EFFERVESCENT
TABLETS
PL 16508/0026**

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Adcal-D₃ Dissolve 1500mg/400IU Effervescent Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One effervescent tablet contains:

1500 mg calcium carbonate (equivalent to 600 mg or 15 mmol elemental calcium)

400 I.U. or 10 micrograms colecalciferol (vitamin D₃) as colecalciferol concentrate 'powder form'

This product also contains sucrose (part of the vitamin D₃ concentrate: approximately 1.5 micrograms per tablet) and soya oil (also part of the vitamin D₃ concentrate: approximately 0.3 milligrams per tablet).

For a full list of excipients see Section 6.1

3 PHARMACEUTICAL FORM

White, round, lemon flavoured effervescent tablets.

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 over 12 years of age:	Take 2 effervescent tablets daily, preferably one tablet each morning and evening. The effervescent tablets should be dissolved in a glass of water (approx. 200ml) and drunk immediately
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 excipients.

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

Adcal-D₃ Dissolve contains a small quantity of soya oil and is therefore contraindicated in patients who are allergic to peanuts or soya.

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 7.5mmol/24 hours (300mg/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 Dissolve should also be used with caution in other patients with increased risk of hypercalcaemia e.g. patients with sarcoidosis or those suffering from malignancies.

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.

Information for diabetics:

Patients who have diabetes mellitus or require a low-sugar diet should take account of the sucrose content of this medicinal product.

One effervescent tablet contains 1.672mg of sucrose.

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 or iron. It is advisable to allow a minimum period of four hours before taking the calcium.

4.6 PREGNANCY AND LACTATION

During pregnancy and lactation treatment with Adcal-D₃ Dissolve should always be under the direction of a physician. During pregnancy and lactation, requirements for calcium and vitamin D are increased but in deciding on the required supplementation allowances should be made for availability of these agents from other sources. If Adcal-D₃ Dissolve and iron supplements are both required to be administered to the patient, 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

No studies on the effects on the ability to drive and use machines have been performed.

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, 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**

Pharmacotherapeutic group: 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 two tablets of Adcal-D₃ Dissolve, 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-hydroxycolecalciferol and then undergoes further hydroxylation in the kidney to form the active metabolite 1, 25 dihydroxycolecalciferol (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**

citric acid anhydrous
malic acid
sodium hydrogen carbonate (E500)
sodium cyclamate (E953)
sodium carbonate anhydrous (E500)
maltodextrin

saccharin sodium (E954)
sucrose
gelatine
maize starch
hydrogenated soyabean oil
 α -tocopherol
lemon flavour BSL Code 119 *containing* lemon oil, lime flavouring, sorbitol (E420), mannitol (E421), gluconolactone, maltodextrin and acacia

6.2 INCOMPATIBILITIES

None

6.3 SHELF LIFE

3 Years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C.

Keep the container tightly closed.

6.5 NATURE AND CONTENTS OF CONTAINER

Packs of 4 x 14 effervescent tablets in a carton.

Each unit of 14 effervescent tablets is in an aluminium or polypropylene tube with a polyethylene stopper.

Contains a desiccant.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements

7 MARKETING AUTHORISATION HOLDER

ProStrakan Limited

Galabank Business Park

Galashiels

Scotland

TD1 1QH

8 MARKETING AUTHORISATION NUMBER(S)

PL 16508/0026

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/11/2007

10 DATE OF REVISION OF THE TEXT

22/11/2007

11 DOSIMETRY (IF APPLICABLE)**12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)**

PATIENT INFORMATION LEAFLET

Patient Information Leaflet



Adcal-D₃[®] Dissolve 1500mg/400IU Effervescent Tablets Calcium carbonate and Colecalciferol

In this leaflet:

1. What these tablets do
2. Check before you take...
3. How to take these tablets
4. Possible side effects
5. Storing your medicine
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 further questions, please 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 get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

1. What these tablets do

Adcal-D₃ Dissolve contains calcium and vitamin D₃ which are both essential for healthy bones and teeth. Adcal-D₃ Dissolve provides 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 Dissolve 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. Check before you take

X Do not take if you:

- Are allergic (hypersensitive) to calcium carbonate, vitamin D₃ or any of the other ingredients in Adcal-D₃ Dissolve (see Section 6 Further Information)
- Are allergic to peanut or soya. Adcal-D₃ Dissolve contains soya oil.

? Take special care:

Tell your doctor or pharmacist if you:

- Have high levels of calcium in your blood (hypercalcaemia) or high levels of calcium in your urine (hypercalciuria). If you are unsure your doctor will advise you
- Have problems with your kidneys, for example kidney stones
- Have sarcoidosis (inflammation that produces lumps of cells in various organs in the body). If you are unsure your doctor will advise you
- Have previously been told by your doctor that you have an intolerance to some sugars
- Are taking any other medication, even those you may have bought for yourself without prescription.
- Have diabetes mellitus or require a low-sugar diet, each tablet contains 1.672 mg of sucrose.

! Taking other medicines with Adcal-D₃ Dissolve

Tell your doctor if you are taking calcium supplements or antacids for indigestion, digitalis drugs (e.g. Lanoxin), diuretics or corticosteroids.

If you are taking thyroxine, bisphosphonates, iron 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 Dissolve tablets. Do not take them at the same time.

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 breast-feeding

In pregnancy or when breast-feeding, Adcal-D₃ Dissolve should only be used under medical supervision. Ask your doctor or pharmacist for advice before taking any medicine.

Important information about some of the ingredients of Adcal-D₃ Dissolve

- The tablets contain a small amount of sugar and may be harmful to the teeth if used for a prolonged period
- If you have been told by your doctor you have an intolerance to some sugars, contact your doctor before taking this medicine.
- Adcal-D₃ Dissolve contains soya oil. If you are allergic to peanut or soya, do not use this medicine.
- This medicine contains 52 mg of sodium per tablet. To be taken into consideration by patients on a controlled sodium diet.

3. How to take your tablets

Always take Adcal-D₃ Dissolve exactly as your doctor or pharmacist 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 - 2 tablets daily, ideally one taken in the morning and one tablet in the evening. Dissolve one tablet in a glass of water (approximately 200ml) and drink immediately, do not chew or swallow the tablets whole.

X Children under 12 – Adcal-D₃ Dissolve must not be given to children under 12 years.

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

If you forget to take Adcal-D₃ Dissolve - If you forget to take your tablet, take it as soon as possible and continue to take the tablets as normal. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Adcal-D₃ Dissolve - Always talk to your doctor or pharmacist before stopping Adcal-D₃ Dissolve.

? 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 Dissolve can have side effects, although not everybody gets them.

Rare side effects (affecting fewer than 1 in 1,000 people)

- Constipation, wind, feeling sick, stomach ache, diarrhoea
- Skin rash
- Hypercalcaemia (too much calcium in your blood) and 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. Storing your medicine

- Keep out of the sight and reach of children
- Do not store above 25°C
- Keep the container tightly closed
- Do not use Adcal-D₃ Dissolve after the expiry date (Exp) which is stated on the tube/label. The expiry date refers to the last day of that month.
- 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

- Each tablet contains 1500 mg calcium carbonate (equivalent to 600 mg calcium) and 400 iu vitamin D₃ (equivalent to 10 µg of colecalciferol). It also contains citric acid anhydrous, malic acid, sodium hydrogen carbonate (E500), sodium cyclamate (E953), lemon flavour (BSL Code 119: containing lemon oil, lime flavouring, sorbitol (E420), mannitol (E421), gluconolactone, maltodextrin, and acacia), sodium carbonate anhydrous (E500), maltodextrin and saccharin sodium (E954). The dry vitamin D₃ type 100 CWS contains α-tocopherol, hydrogenated soyabean oil, gelatin, sucrose and maize starch.
- The tablets are white, round and lemon flavoured
- Adcal-D₃ Dissolve is provided in tubes containing 14 effervescent tablets, and is supplied in cartons of 4 tubes (total of 56 effervescent tablets).

Marketing Authorisation Holder:

ProStrakan Limited
Galabank Business Park
Galashiels, Scotland, TD1 1QH

Manufacturer:

Hermes Arzneimittel GmbH
82049 Grosshesselohe
Germany

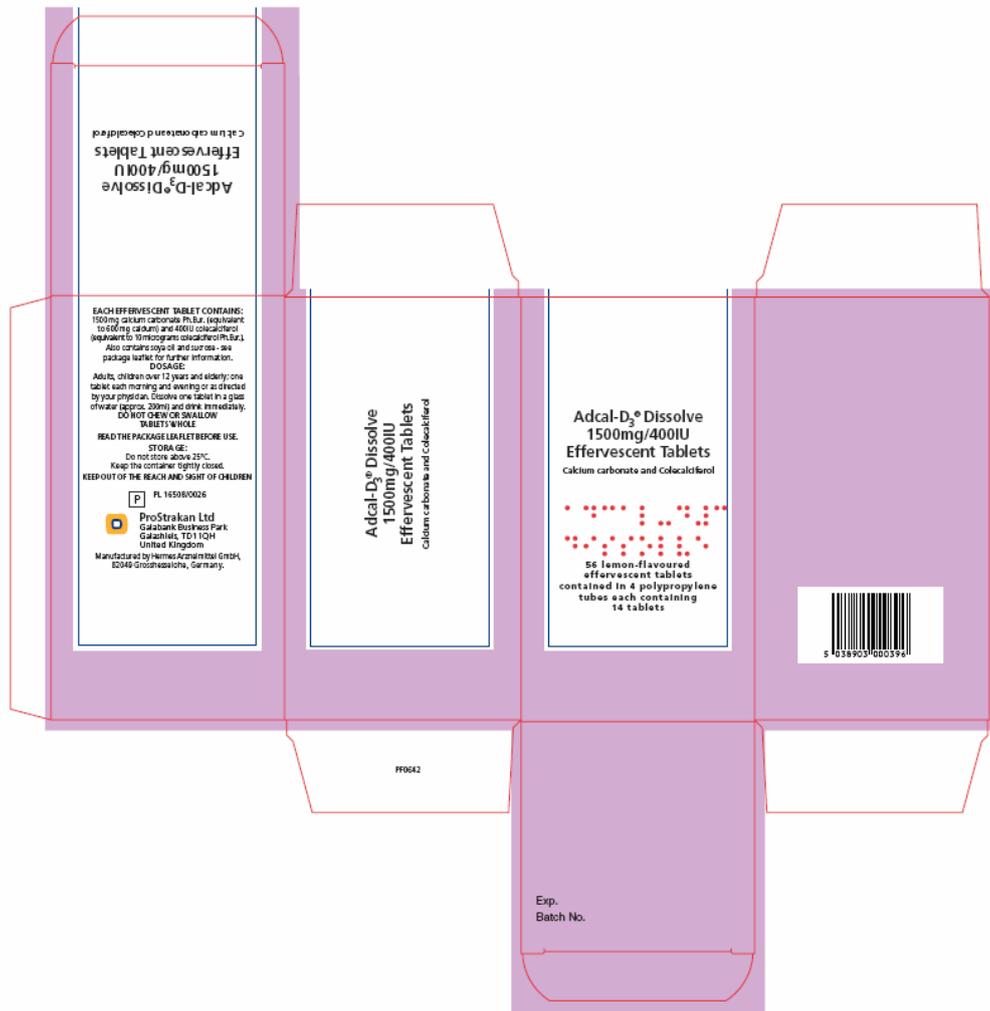
Additional information

If you have been prescribed Adcal-D₃ Dissolve effervescent tablets 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 1303076. 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 12/2007

PG0644

LABELLING



Adcal-D₃® Dissolve 1500mg/400IU Effervescent Tablets

Calcium carbonate and Colecalciferol

EACH EFFERVESCENT TABLET CONTAINS :

1500 mg calcium carbonate Ph.Eur. (equivalent to 600 mg calcium) and 400iu colecalciferol (equivalent to 10 micrograms colecalciferol Ph.Eur.). Also contains soya oil and sucrose - see package leaflet for further information.

14 lemon-flavoured effervescent tablets.

DOSAGE:

Adults, children over 12 years and elderly:
One tablet morning and evening or as directed by your physician.

Dissolve one tablet in a glass of water (approx. 200ml) and drink immediately.
DO NOT CHEW OR SWALLOW THE TABLET WHOLE.
Read the package leaflet before use.

STORAGE:

Do not store above 25°C.
Keep the container tightly closed.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

PL 16508/0026



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