ADCAL-D_3 LEMON CHEWABLE TABLETS
PL 16508/0028

UKPAR

TABLE OF CONTENTS

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PL 16508/0028

LAY SUMMARY

The MHRA granted ProStrakan a Marketing Authorisation (licence) for the medicinal product Adcal-D_3 Lemon Chewable Tablets (PL 16508/0028) on 19th July 2007. 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-D_3 Lemon Chewable Tablets contain the active ingredients calcium carbonate and colecalciferol.

This application is identical to a previously granted application for Adcal-D_3 Chewable Tablets (PL 16508/0001) granted to the same Marketing Authorisation Holder on 1st December 1998.

No new or unexpected safety concerns arose from this simple application and it was, therefore, judged that the benefits of taking Adcal-D_3 Lemon Chewable Tablets outweigh the risks; hence a Marketing Authorisation has been granted.

ADCAL-D_3 LEMON CHEWABLE TABLETS
PL 16508/0028

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

INTRODUCTION

The UK granted a marketing authorisation for the medicinal product Adcal-D_3 Lemon Chewable Tablets (PL 16508/0028) to ProStrakan Limited on 19th July 2007. The product is a pharmacy-only medicine.

The application was submitted as a simple abridged application according to Article 10c of Directive 2001/83/EC, cross-referring to Adcal-D_3 Chewable Tablets (PL 16508/0001), approved on 1st December 1998.

No new data was submitted nor was it necessary for this simple application, as the data are identical to that of the previously granted cross-reference product. As the cross-reference product was granted prior to the introduction of current legislation, no Public Assessment Report (PAR) was generated for it.

The product contains the active ingredients calcium carbonate and colecalciferol and is used as a dietary supplement in the treatment of calcium/vitamin D_3 deficiencies and to complement specific treatments for osteoporosis.

PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 16508/0028
PROPRIETARY NAME: Adcal-D_3-Lemon Chewable Tablets
ACTIVE(S): Calcium carbonate 1500mg (600mg elemental calcium) colecalciferol 400i.u (10µg vitamin D_3)
COMPANY NAME: ProStrakan
E.C. ARTICLE: Article 10c of EC Directive 2004/27 (previously 10.1(a)(i) of Directive 2001/83/EC
LEGAL STATUS: P

1. INTRODUCTION

This is a simple, informed consent application for Adcal-D_3 Lemon Chewable Tablets submitted under Article 10c of Directive 2001/83/EC (formerly Article 10.1(a)(i)) of Directive 2001/83/EC). The proposed MA holder is ProStrakan Limited, Galabank Business Park, Galashiels, TD1 1QH, Scotland.

This application cross refers to a complex abridged application for Adcal-D_3 Chewable Tablets held by the same MA Holder (PL 16508/0001) which is currently registered in the UK. This application is considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The proposed name of the product is Adcal-D_3 Lemon Chewable Tablets. The product has been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

The product contains calcium carbonate 1500mg, equivalent to 600mg of elemental calcium and colecalciferol 4.4mg, equivalent to 10µg vitamin D_3. The product is to be stored in blister packs of 30, 56, 60, 90, 100 and 112 tablets. The proposed shelf-life (18 months) and storage conditions ("Do not store above 25^{o}C") are consistent with the details registered for the cross-reference product.

2.3 Legal status

On approval, the product will be available as pharmacy-only (P) medicine.

2.4 Marketing authorisation holder/Contact Persons/Company

The proposed Marketing Authorisation holder is ProStrakan Limited, Galabank Business Park, Galashiels, TD1 1QH, Scotland.

The QP responsible for pharmacovigilance is stated and his CV is included.

2.5 Manufacturers

The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition
The proposed composition is consistent with the details registered for the cross-reference product.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

2.8 Finished product/shelf-life specification
The proposed finished product specification is in line with the details registered for the cross-reference product.

2.9 Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference product.

2.10 TSE Compliance
No materials of animal or human origin are included in the product. This is consistent with the cross reference product.

3. EXPERT REPORTS
The applicant has included detailed expert reports in Module 2 of the application. Signed declarations and copies of the experts' CVs are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product name. The appearance of the product is identical to the cross-reference product.

5. SUMMARY OF PRODUCT CHARACTERISTICS
The proposed SmPC is consistent with the details registered for the cross-reference product.

6. PATIENT INFORMATION LEAFLET/CARTON
PIL

The patient information leaflet has been prepared in-line with the details registered for the cross-reference product.

Carton and blister

The proposed artwork is comparable to the artwork registered for the cross-reference product and complies with statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSIONS
The data submitted with the application is acceptable. A Marketing Authorisation should be granted.

PRECLINICAL ASSESSMENT

No new preclinical data has been supplied with this application and none is required for an application of this type.

CLINICAL ASSESSMENT

No new clinical data has been supplied with this application and none is required for an application of this type.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The data for this application is consistent with that previously assessed for the cross-reference product and as such has been judged to be satisfactory.

PRECLINICAL

No new preclinical data was submitted and none is 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 D_3 deficiencies for many years. This application is identical to the previously granted application for Adcal-D_3 Chewable Tablets (PL 16508/0001). 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. The applicant's product is identical to the cross-reference product except for flavour. Extensive clinical experience with calcium carbonate and colecalciferol is considered to have demonstrated the therapeutic value of the compounds. The risk benefit is therefore considered to be positive.

ADCAL-D_3 LEMON CHEWABLE TABLETS
PL 16508/0028

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 13th March 2006.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 31st March 2006.
3	Following assessment of the application the MHRA requested further information relating to the quality dossier on 5th September 2006, 15th February 2007, 12th April 2007 and 19th June 2007.
4	The applicant responded to the MHRA's requests, providing further information on 22nd December 2006, 07th March 2007, 22nd May 2007 and 21st June 2007
7	The application was determined on 19th July 2007

ADCAL-D_3 LEMON CHEWABLE TABLETS
PL 16508/0028

STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome
10th August 2007	PIQ- Label and Leaflet	Label and Leaflet –Self Certification- To change the dimensions of the leaflet.	Approved

ADCAL-D_3 LEMON CHEWABLE TABLETS
PL 16508/0028

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Adcal-D_3 Lemon Chewable tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Per tablet:
Calcium carbonate: 1500mg, equivalent to 600mg of elemental Calcium
Colecalciferol: 400iu, equivalent to 10µg vitamin D_3

This product also contains sucrose (part of the vitamin D_3 concentrate: approximately 1.5 micrograms per tablet) and soya oil (also part of the vitamin D_3 concentrate: approximately 0.3 milligrams per tablet).

For full list of excipients see 6.1

3 PHARMACEUTICAL FORM
Chewable 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:

2 chewable tablets per day, preferably one tablet each morning and 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..

Adcal-D_3 Lemon 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-D_3 Lemon 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.

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-D_3 Lemon 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-D_3 Lemon 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

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, 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

Strong evidence that supplemental calcium and vitamin D_3 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 D daily, i.e. the same dose delivered by two tablets of Adcal-D_3 Lemon, 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 D_3 group and decreased 4.6% in the placebo group ($p < 0.001$). In the calcium/vitamin D_3 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 D_3 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 D_3 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 D_3 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 D_3 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

Xylitol, modified maize starch, sodium saccharin, magnesium stearate, DL-α-tocopherol, edible fats, gelatin, soya oil, sucrose, corn starch and lemon flavour.

6.2 Incompatibilities

Not applicable, oral preparation.

6.3 Shelf life

18 months

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Blister packs of 10 (physicians sample), 30, 56, 60, 90, 100 and 112 tablets in a cardboard carton.

6.6 Special precautions for disposal and other handling

No special conditions.

7 MARKETING AUTHORISATION HOLDER

ProStrakan Limited
Galabank Business Park
Galashiels
TD1 1QH
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 16508/0028

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/07/2007

10 DATE OF REVISION OF THE TEXT

19/07/2007

PATIENT INFORMATION LEAFLET

ADCAL-D_3 LEMON CHEWABLE TABLETS
PL 16508/0028

Patient Information Leaflet

Adcal-D_3® Lemon

ProStrakan

Chewable Tablets

Calcium carbonate (1500 mg) and Vitamin D_3 (400 I.U.)

In this leaflet:

Read all of this leaflet carefully before you start using this medicine

- Keep this leaflet. You may need to read it again.
- If you have any 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-D_3 Lemon contains calcium and vitamin D_3 which are both essential for healthy bones and teeth. Adcal-D_3 Lemon provides extra calcium and vitamin D_3 to your diet. It is therefore used in conditions where your body's calcium and vitamin D levels need to be increased.

Adcal-D_3 Lemon can be prescribed by doctors for certain bone conditions, for example, osteoporosis.

Studies show that taking calcium and vitamin D_3 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 D_3 or any of the other ingredients in Adcal-D_3 Lemon Chewable Tablets (see Section 6 Further Information)
- Are allergic to peanut or soya. Adcal-D_3 Lemon 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), your doctor will be able to tell you if you do
- 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.

! Taking other medicines with Adcal-D_3 Lemon

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-D_3 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-D_3 Lemon 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-D_3 Lemon

- The tablets contain a small amount of sugar and may be harmful to the teeth if used for a prolonged period
- Adcal-D_3 Lemon contains soya oil. If you are allergic to peanut or soya, do not use this medicine.

3. How to take the tablets

Always take Adcal-D_3 Lemon 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 - 2 tablets daily, ideally one tablet taken in the morning and one in the evening. Adcal-D_3 Lemon tablets should be chewed. Do not swallow whole.

X **Children under 12** – Adcal-D_3 Lemon must not be given to children under 12 years.

If you take more Adcal-D_3 Lemon than you should - You should only take what your doctor recommends. If you take too many Adcal-D_3 Lemon tablets contact your doctor or pharmacist if you can do so. If not, go to the nearest hospital casualty department immediately, taking the Adcal-D_3 Lemon pack and remaining tablets with you.

If you forget to take Adcal-D_3 Lemon - 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-D_3 Lemon - Always talk to your doctor or pharmacist before stopping using Adcal-D_3 Lemon.

? 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-D_3 Lemon can cause 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) 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. Storing your medicine

- Keep out of the reach and sight of children.
- Do not store above 25°C.
- Keep the container tightly closed.
- Do not use Adcal-D_3 Lemon 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

- Each tablet contains 1500 mg calcium carbonate, equivalent to 600 mg calcium and 400 iu vitamin D_3 (equivalent to 10 µg of colecalciferol). It also contains xylitol (E967), modified maize starch, sodium saccharin (E954), magnesium stearate and lemon flavouring. The dry vitamin D_3 type 100 CWS contains DLα-tocopherol, edible fats (including soya oil), gelatin, sucrose and corn starch
- The tablets are white, flat faced and circular in shape
- Adcal-D_3 Lemon tablets are provided in packs of 56 or 112 tablets.

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

Manufacturer:
Biokirch GmbH
21220 Seevetal
Germany

Additional information
If you have been prescribed Adcal-D_3 Lemon 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 09/2006

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ADCAL-D_3 LEMON CHEWABLE TABLETS
PL 16508/0028

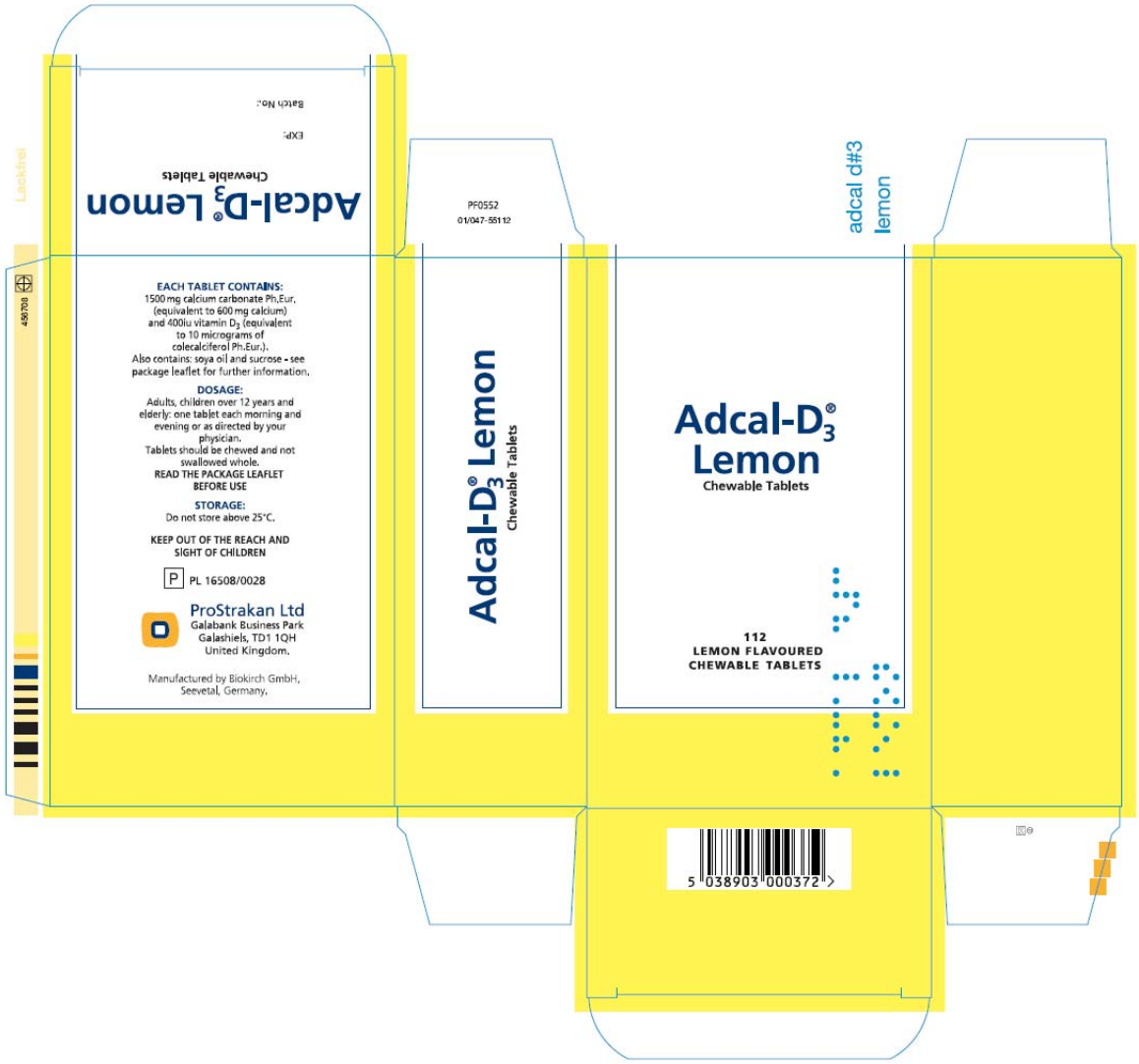
LABELLING

CARTON

Adcal-D_3 Lemon Chewable Tablets (56)

CARTON

Adcal-D_3 Lemon Chewable Tablets (112)



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