ALFACALCIDOL 1 MICROGRAM CAPSULES
ALFACALCIDOL 0.25 MICROGRAM CAPSULES

PL 12762/0185-6

UKPAR

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Goldshield Pharmaceuticals Limited Marketing Authorisations for the medicinal products Alfacalcidol 1 and 0.25 microgram Capsules (PL 12762/0185-6) on 20 September 2011. These are prescription-only medicines (POM).

Alfacalcidol 1 and 0.25 microgram Capsules are used in conditions where there is a disturbance in the body's calcium levels, for example in kidney disorders. They are mainly used to treat the following conditions:

- changes in bone caused by kidney failure
- disorders of the parathyroid glands
- low blood calcium in newborn babies
- softening and deformity of the bones due to lack of calcium

Alfacalcidol is a biologically active form of vitamin D, which belongs to a group of medicines called vitamin D analogues. Alfacalcidol promotes the uptake of calcium from food and assists in growth of healthy bones.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Alfacalcidol 1 and 0.25 microgram Capsules outweigh the risks; hence Marketing Authorisations were granted.

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ALFACALCIDOL 0.25 MICROGRAM CAPSULES
PL 12762/0185-6

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Goldshield Pharmaceuticals Limited Marketing Authorisations for the medicinal products Alfacalcidol 1 and 0.25 microgram Capsules (PL 12762/185-6) on 20 September 2011. These products are prescription-only medicines (POM).

Alfacalcidol is indicated in all conditions where there is a disturbance of calcium metabolism due to impaired 1-α hydroxylation, such as when there is reduced renal function. Alfacalcidol 1 and 0.25 microgram Capsules are used for the treatment of:

- renal osteodystrophy
- hyperparathyroidism (with bone disease)
- hypoparathyroidism
- neonatal hypocalcaemia
- nutritional and malabsorptive rickets and osteomalacia
- pseudo-deficiency (D-dependent) rickets and osteomalacia
- hypophosphataemic vitamin D resistant rickets and osteomalacia.

These applications were submitted under Article 10.1 (a) (iii) of Directive 2001/83/EC, claiming to be generic medicinal products of One-Alfa Capsules 1 and 0.25 microgram (PL 00043/0050 and PL 00043/0052; Leo Laboratories Limited, UK), which were first authorised on 26 January 1978.

The active ingredient, alfacalcidol is a non-peptide vitamin D analogue. Alfacalcidol chemically known as 1α-hydroxy vitamin D3 is fat soluble and up to 100% absorbed. After absorption, alfacalcidol is rapidly hydroxylated at 2-position, predominately in the liver to calcitriol (1,25-dihydroxy vitamin D3) which acts as a regulator of calcium and phosphate metabolism. The biological half-life is approximately 35 hours in the presence of renal insufficiency.

No new non-clinical data have been submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

A single-dose, bioequivalence study carried out under fasting conditions.was submitted to support these applications, comparing the pharmacokinetic profile of the test product, Alfacalcidol 1 microgram Capsules (Goldshield Pharmaceuticals Limited), versus the reference product, One-Alfa Capsules 1 microgram, (Leo Laboratories Limited, UK). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new clinical studies were performed, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Alfacalcidol 1 and 0.25 microgram Capsules outweigh the risks; hence Marketing Authorisations were granted.

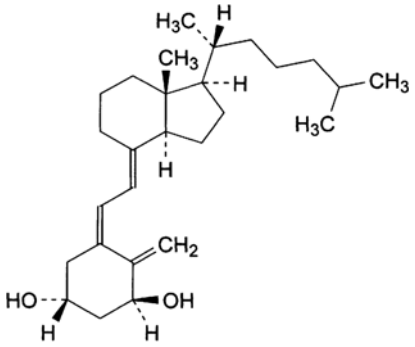
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

INN: Alfacalcidol

Chemical Name: 5*Z*,7*E*)-9,10-secocholesta-5,7,10(19)-triene-1α,3β-diol

Structure:



Molecular Formula: $C_{27}H_{44}O_2$

Molecular weight: 400.6

Appearance: A white or almost white crystals, practically insoluble in water, freely soluble in alcohol and soluble in fatty oils.

Alfacalcidol is the subject of a European Pharmacopoeia monograph.

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

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

Appropriate stability data have been generated to support a suitable retest period for the active substance when stored in the proposed packaging.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients namely, butylhydroxyanisole, butylhydroxytoluene, medium-chain triglycerides, gelatin, glycerol, sorbitol 70% solution, titanium dioxide (E171 – 0.25 microgram strength only), black iron oxide (E172 – 1 microgram strength only), red iron oxide (E172 – 1 microgram strength only) and purified water. Appropriate justifications for the inclusion of each excipient have been provided.

All excipients comply with their respective European Pharmacopoeia monographs, with the exception of black iron oxide (E172) and red iron oxide (E172), which are controlled to their respective National Formulary specifications. Black iron oxide (E172) and red iron oxide (E172) are in compliance with current European Directives concerning use of colouring agents in foodstuff. Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

With the exception of gelatin, no materials of animal or human origin are included in the products. The suppliers of gelatin have provided TSE Certificates of Suitability to show that appropriate measures are taken to reduce the risk of transmission of BSE/TSE, in line with current EU regulations.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious, stable products that could be considered generic medicinal products of the reference products, One-Alfa Capsules 0.25 microgram and 1 microgram (Leo Laboratories Limited, UK).

Suitable pharmaceutical development data have been provided for these applications.

Comparative disintegration and impurity profiles have been provided for these products and their respective reference products. As these are liquid-filled capsules, no dissolution testing was necessary.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of all strengths of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

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

Container Closure System
The finished products are packaged in polyvinylchloride (PVC)/polyvinylidene chloride (PVDC)/aluminium blisters. The blister strips are packed in cardboard boxes in pack sizes of 30 (3x10) capsules.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf life of 2 years with the storage conditions ‘Do not store above 25ºC. Keep blisters in the outer carton in order to protect from light.’ has been accepted.

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are satisfactory.

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

MAA Forms
The MAA forms are satisfactory.

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

Conclusion
The grant of Marketing Authorisations is recommended.

NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY

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

NON-CLINICAL EXPERT REPORT

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

ENVIRONMENTAL RISK ASSESSMENT

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the products are intended for generic substitution with products that are already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION

The grant of Marketing Authorisations is recommended.

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

The clinical pharmacology of alfacalcidol is well-known. With the exception of data from the below bioequivalence study, no new pharmacodynamic or pharmacokinetic data are provided or required for these applications.

Pharmacokinetics

In support of the applications, the Marketing Authorisation Holder submitted the following bioequivalence study:

A randomised, two-treatment, two-period, two-sequence, single-dose, crossover 2-way study to compare the pharmacokinetics of the test product One-Alfa Capsules 1 microgram, (Leo Laboratories Limited, UK) in healthy adult male subjects under fasted conditions.

All volunteers received a single oral dose of either the test or the reference product with 240 ml of water, under fasted conditions. Blood samples were taken for the measurement of pharmacokinetic parameters pre-dose and up to 72 hours post dose. The washout period between the two treatment arms was 14 days.

The pharmacokinetic results for the metabolite calcitriol are presented below:

Parameter	**Arithmetic mean**	
	Test mean (SD)	**Reference mean (SD)**
C_{max} (pg/ml)	67.492 (21.68)	71.901 (20.63)
AUC_{0-t} (pg/ml/h)	3296.928 (772.38)	3247.513 (1047.29)
T_{max} (h)	15.897 (22.76)	7.501 (3.38)

90% Confidence Intervals (ln-transformed) for primary parameters of calcitriol (test versus reference):

Parameter	**Geometric Mean**		**90% Confidence Interval (CI)**
	Test	Reference	
C_{max}(pg/ml)	4.159	4.227	81.58-107.17%
AUC_{0-t} (pg/ml/h)	8.068	8.021	87.90-124.03%

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
T_{max} time to maximum plasma concentration
90% geometric CI calculated from ln-transformed data
SD Standard Deviation

The 90% confidence intervals for AUC and C_{max} for test versus reference product for alfacalcidol are within predefined acceptance criteria specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98). Thus, the data support the claim that the test product Alfacalcidol 1 microgram Capsules (Goldshield Pharmaceuticals Limited) is bioequivalent to the reference product One-Alfa Capsules 1 microgram, (Leo Laboratories Limited, UK).

As the 0.25 microgram and 1 microgram strength products meet the biowaiver criteria specified in the *Guidance on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98), the results and conclusions from the bioequivalence study with the 1 microgram strength can be extrapolated to the 0.25 microgram strength.

EFFICACY

The efficacy of alfacalcidol is well-known. No new efficacy data have been submitted and none are required for applications of this type.

SAFETY

With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for applications of this type. No new or unexpected safety issues were raised by the bioequivalence data.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING

The SmPCs, PIL and labelling are clinically acceptable. The SmPCs are consistent with those for the reference products. The PIL is consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

CLINICAL EXPERT REPORT

The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN

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

Suitable justification has been provided for not submitting a risk management plan for these products.

CONCLUSION

The grant of Marketing Authorisations is recommended.

OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Alfacalcidol 1 and 0.25 microgram Capsules are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

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

EFFICACY
With the exception of the bioequivalence study, no new efficacy data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant's 1 microgram capsule strength and the reference product. As the 0.25 microgram strength of the product meet the biowaiver criteria specified in the *Guidance on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98), the results and conclusions from the bioequivalence study with the 1 microgram capsule strength can be extrapolated to the 0.25 microgram strength.

SAFETY
With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for applications of this type. No new or unexpected safety concerns arose from the bioequivalence study

PRODUCT LITERATURE
The SmPCs, PIL and labelling are acceptable. The SmPCs are consistent with those for the reference products. The PIL is consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data provided support the claim that these products are generic medicinal products of the reference products, One-Alfa Capsules 1 and 0.25 microgram (Leo Laboratories Limited, UK). Extensive clinical experience with alfacalcidol is considered to have demonstrated the therapeutic value of the products. The benefit/risk is, therefore, considered to be positive.

ALFACALCIDOL 1 MICROGRAM CAPSULES
ALFACALCIDOL 0.25 MICROGRAM CAPSULES
PL 12762/0185-6

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation applications on 06 January 2004.

2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 25 February 2004.

3 Following assessment of the applications the MHRA requested further information relating on the quality dossier on 10 December 2004, 23 April 2007, 26 March 2008, 20 April 2009 and 30 December 2009 and the clinical dossier on 01 April 2005, 22 April 2009 and 25 March 2011.

4 The applicant responded to the MHRA's requests, providing further information on the quality dossier on 23 April 2007, 26 October 2007, 30 June 2008, 23 September 2009, 04 March 2011 and 01 July 2011 and the clinical dossier on 03 March 2011 and 01 July 2011.

5 The applications were determined and granted on 20 September 2011.

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Alfacalcidol 0.25 microgram Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 0.25 microgram alfacalcidol.
Excipient: Sorbitol (E420) 19.19mg/capsule.
For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsules, soft
Clear colourless, oily liquid filled in oval, white opaque, soft gelatine capsules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Alfacalcidol is indicated in all conditions where there is a disturbance of calcium metabolism due to impaired 1-α hydroxylation such as when there is reduced renal function. The main indications are:

a) Renal osteodystrophy
b) Hyperparathyroidism (with bone disease)
c) Hypoparathyroidism
d) Neonatal hypocalcaemia
e) Nutritional and malabsorptive rickets and osteomalacia
f) Pseudo-deficiency (D-dependent) rickets and osteomalacia
g) Hypophosphataemic vitamin D resistant rickets and osteomalacia

4.2 Posology and method of administration

Route of administration: oral
The capsules should be swallowed whole with a drink of water.
Initial dose for all indications:
Adults: 1 microgram/day
Dosage in the elderly: 0.5 microgram/day
Neonates and premature infants: 0.05 – 0.1 microgram/kg/day
Children under 20kg bodyweight: 0.05 microgram/kg/day
Children over 20kg bodyweight: 1 microgram/day

The dose of Alfacalcidol should be adjusted thereafter to avoid hypercalcaemia according to the biochemical response. Indices of response include plasma levels of calcium (ideally corrected for protein binding), alkaline phosphatase, parathyroid hormone, as well as radiographic and histological investigations.

Plasma levels should initially be measured at weekly intervals. The daily dose of Alfacalcidol may be increased by increments of 0.25 – 0.5 microgram. When the dose is stabilised, measurements may be taken every 2 – 4 weeks.
Most adult patients respond to doses between 1 and 3 micrograms per day. When there is biochemical or radiographic evidence of bone healing, (and in hypoparathyroid patients when normal plasma calcium levels have been attained), the dose generally decreases. Maintenance doses are generally in the range of 0.25 to 1 microgram per day. If hypercalcaemia occurs, Alfacalcidol should be stopped until plasma calcium returns to normal (approximately 1 week) then restarted at half the previous dose.

a) Renal bone disease:
Patients with relatively high initial plasma calcium levels may have autonomous hyperparathyroidism, often unresponsive to Alfacalcidol. Other therapeutic measures may be indicated.
Before and during treatment with Alfacalcidol, phosphate binding agents should be considered to prevent hyperphosphataemia. It is particularly important to make frequent plasma calcium measurements in patients with chronic renal failure because prolonged hypercalcaemia may aggravate the decline of renal function.

b) Hyperparathyroidism:
In patients with primary or tertiary hyperparathyroidism about to undergo parathyroidectomy, preoperative treatment with Alfacalcidol for 2-3 weeks alleviates bone pain and myopathy without aggravating pre-operative hypercalcaemia. In order to decrease post-operative hypocalcaemia,

Alfacalcidol should be continued until plasma alkaline phosphatase levels fall to normal or hypercalcaemia occurs.

c) Hypoparathyroidism:
In contrast to the response to parent vitamin D, low plasma calcium levels are restored to normal relatively quickly with Alfacalcidol. Severe hypocalcaemia is corrected more rapidly with higher doses of Alfacalcidol (e.g. 3-5 micrograms) together with calcium supplements.

d) Neonatal hypocalcaemia:
Although the normal starting dose of Alfacalcidol is 0.05-0.1 microgram/kg/day (followed by careful titration) in severe cases doses of up to 2 microgram/kg/day may be required. Whilst ionised serum calcium levels may provide a guide to response, measurement of plasma alkaline phosphatase activity may be more useful. Levels of alkaline phosphatase approximately 7.5 times above the adult range indicates active disease.
A dose of 0.1 microgram/kg/day of Alfacalcidol has proven effective as prophylaxis against early neonatal hypocalcaemia in premature infants.

e) Nutritional and malabsorptive rickets and osteomalacia:
Nutritional rickets and osteomalacia can be cured rapidly with Alfacalcidol. Malabsorptive osteomalacia (responding to large doses of IM or IV parent vitamin D) will respond to small doses of Alfacalcidol.

f) Pseudo-deficiency (D-dependent) rickets and osteomalacia:
Although large doses of parent vitamin D would be required, effective doses of Alfacalcidol are similar to those required to heal nutritional vitamin D deficiency rickets and osteomalacia.

g) Hypophosphataemic vitamin D-resistant rickets and osteomalacia:
Neither large doses of parent vitamin D nor phosphate supplements are entirely satisfactory. Treatment with Alfacalcidol at normal dosage rapidly relieves myopathy when present and increases calcium and phosphate retention. Phosphate supplements may also be required in some patients.

Special populations:
Use in Elderly
The clinical manifestations of hypo- or hyper calcaemia should be considered especially in elderly patients with pre-existing renal or heart conditions.

Paediatric population
Alfacalcidol should be used with caution in infants, who may have increased sensitivity to its effects. Take care to ensure correct dose in infants.

4.3 Contraindications

Hypercalcaemia, metastatic calcification.
Hypersensitivity to Alfacalcidol or other ingredients in the preparation.

4.4 Special warnings and precautions for use

The product contains sorbitol; therefore patients with rare hereditary problems of fructose intolerance should not take this medicine.
Alfacalcidol should be used with caution for:
- patients being treated with cardioactive glycosides or digitalis as hypercalcaemia may lead to arrhythmia in such patients.
- patients with nephrolithiasis

During treatment with Alfacalcidol serum calcium and serum phosphate should be monitored regularly especially in patients with renal impairment and patients receiving high doses. To maintain serum phosphate at an acceptable level in patients with renal bone disease a phosphate binding agent may be used.
Hypercalcaemia may appear in patients treated with Alfacalcidol, the early symptoms are as follows:
- polyuria
- polydipsia
- weakness, headache, nausea, constipation
- dry mouth
- muscle and bone pain
- metallic taste

Hypercalcaemia can be rapidly corrected by stopping treatment until plasma calcium levels return to normal (in about one week). Alfacalcidol treatment may then be restarted at a reduced dose (half the previous dose).

Paediatric population
During treatment with Alfacalcidol serum calcium and serum phosphate should be monitored regularly in children.

4.5 Interaction with other medicinal products and other forms of interaction

Patients taking barbiturates or anticonvulsants may require larger doses of Alfacalcidol to produce the desired effect to the induction of hepatic detoxification enzymes.
Concomitant administration of colestyramine may interfere with the intestinal absorption of alfacalcidol.
Use with caution in patients being treated with thiazide diuretics as they may have an increased risk of developing hypercalcaemia.

Paediatric population
Drug interactions with Alfacalcidol are known to be similar in the paediatric age group and that in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of alfacalcidol in pregnant women. Animal studies are insufficient with respect to effects on pregnancy. The potential risks for humans are unknown. Caution should be taken when prescribing to pregnant women as hypercalcaemia during pregnancy may produce congenital disorders in the offspring.

Breastfeeding
Although it has not been established, it is likely that increased amounts of 1,25-dihydroxyvitamin D will be found in the milk of lactating mothers treated with alfacalcidol. This may influence calcium metabolism in the infant.

Fertility
No fertility data is available for use of alfacalcidol.

4.7 Effects on ability to drive and use machines

Alfacalcidol has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

The most frequently reported undesirable effects are hypercalcaemia and various skin reactions. If hypercalcaemia occurs during treatment with Alfacalcidol, this can be rapidly corrected by stopping treatment until plasma calcium levels return to normal (about 1 week). Alfacalcidol may then be restarted at half the previous dose.
Based on data from post-market use the total undesirable effect 'reporting rate' is rare (≥1/10,000 to <1/1,000) or very rare (<1/10,000); being approximately 1:10,000 patients treated.

System Organ Class	**Adverse Drug Reactions**
Metabolism and Nutrition Disorders	Hypercalcaemia Hyperphosphataemia
Skin and Subcutaneous Tissue Disorders	Pruritus Rash Urticaria
Renal and Urinary Disorders	Nephrocalcinosis Renal impairment

Paediatric population
Frequency and type of adverse reactions in children are the same as in adults.

4.9 Overdose

Hypercalcaemia is treated by stopping Alfacalcidol.

In severe cases of hypercalcaemia general supportive measures should be undertaken. Keep the patient well hydrated by i.v. infusion of saline (force diuresis), measure electrolytes, calcium and renal function indices; assess electrocardiographic abnormalities, especially in patients on digitalis. More specifically, treatment with glucocorticosteroids, loop diuretics, bisphosphonates, calcitonin and eventually haemodialysis with low calcium content should be considered.

Paediatric population
Infants and children are generally more susceptible to the toxic effects of vitamin D.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vitamin D and analogues
ATC code: A11CC03
Alfacalcidol is converted rapidly in the liver to 1,25-dihydroxyvitamin D. This is the metabolite of vitamin D which acts as a regulator of calcium and phosphate metabolism. Since this conversion is rapid, the clinical effects of Alfacalcidol and 1,25-dihydroxyvitamin D are very similar.
Impaired 1-α hydroxylation by the kidneys reduces endogenous 1,25-dihydroxyvitamin D production. This contributes to the disturbances in mineral metabolism found in several disorders, including renal bone disease and hypoparathyoidism. These disorders, which require high doses of parent vitamin D for their correction, will respond to small doses of Alfacalcidol.
The delay in response and high dosage required in treating these disorders with parent vitamin D makes dosage adjustment difficult. This can result in unpredictable hypercalcaemia which may take weeks or months to reverse. The major advantage of Alfacalcidol is the more rapid onset of response, which allows a more accurate titration of dosage. Should inadvertent hypercalcaemia occur it can be reversed within days of stopping treatment.

Paediatric population
When 1-α hydroxylation by the kidneys is impaired, endogenous 1,25-dihydroxyvitamin D production is reduced. Disorders in which this can occur include neonatal hypocalcaemia and Vitamin D-dependent rickets. Such conditions require high doses of Vitamin D for their correction but will respond to small doses of Alfacalcidol, which does not depend on the renal 1-α hydroxylation process.

5.2 Pharmacokinetic properties

Absorption
In patients with renal failure, 1-5µg/day of 1α- hydroxyvitamin D (1α-OHD3) increased intestinal calcium and phosphorus absorption in a dose-related manner. This effect was observed within 3 days of starting the drug and conversely, it was reversed within 3 days of its discontinuation.
In patients with nutritional osteomalacia, increases in calcium absorption were noted within 6 hours of giving 1µg 1α-OHD3 orally and usually peaked at 24 hours. 1α-OHD3 also produced increases in plasma inorganic phosphorus due to increased intestinal absorption and renal tubular re-absorption. This latter effect is a result of PTH suppression by 1α-OHD3. The effect of the drug on calcium was about double its effect on phosphorus absorption.
Patients with chronic renal failure have shown increased serum calcium levels within 5 days of receiving 1α-OHD3 in a dose of 0.5 - 1.0µg/day. As serum calcium rose, PTH levels and alkaline phosphatase decreased toward normal.

Distribution
Vitamin D and its metabolites circulate in the blood bound to a specific α-globulin. Alfacalcidol has a more rapid action and shorter half-life.

Biotransformation:
Alfacalcidol undergoes rapid hepatic conversion to 1,25-dihydroxyvitamin D, the Vitamin D metabolite which acts as a regulator of calcium and phosphate metabolism.

Elimination
Vitamin D compounds and their metabolites are excreted mainly in the bile and faeces with only small amounts appearing in urine; there is some enterohepatic recycling but it is considered to have a negligible contribution to vitamin D status.

Paediatric population
Limited data is available in children.

5.3 Preclinical safety data
There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Capsule fill
Butylhydroxyanisole
Butylhydroxytoluene
Triglycerides, medium chain

Capsule shell
Gelatin
Glycerol
Sorbitol 70% solution
Titanium dioxide
Purified water

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25ºC
Keep blisters in the outer carton in order to protect from light

6.5 Nature and contents of container
PVC/PVDC/Aluminium blister pack
Pack size: 30 capsules
Each PVC/PVDC/Aluminium pack contains 3 strips, each containing 10 capsules.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER

Goldshield Pharmaceuticals Ltd.
NLA Tower
12-16 Addiscombe Road
Croydon
Surrey CR0 0XT
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 12762/0186

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/09/2011

10 DATE OF REVISION OF THE TEXT

20/09/2011

1 NAME OF THE MEDICINAL PRODUCT

Alfacalcidol 1 microgram Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 1.0 microgram alfacalcidol.
Excipient: Sorbitol (E420) 19.19mg/capsule.
For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsules, soft
Clear colourless, oily liquid filled in oval, brown opaque, soft gelatine capsules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Alfacalcidol is indicated in all conditions where there is a disturbance of calcium metabolism due to impaired 1-α hydroxylation such as when there is reduced renal function. The main indications are:

a) Renal osteodystrophy
b) Hyperparathyroidism (with bone disease)
c) Hypoparathyroidism
d) Neonatal hypocalcaemia
e) Nutritional and malabsorptive rickets and osteomalacia
f) Pseudo-deficiency (D-dependent) rickets and osteomalacia
g) Hypophosphataemic vitamin D resistant rickets and osteomalacia

4.2 Posology and method of administration

Route of administration: oral
The capsules should be swallowed whole with a drink of water.
Initial dose for all indications:
Adults: 1 microgram/day
Dosage in the elderly: 0.5 microgram/day
Neonates and premature infants: 0.05 – 0.1 microgram/kg/day
Children under 20kg bodyweight: 0.05 microgram/kg/day
Children over 20kg bodyweight: 1 microgram/day

The dose of Alfacalcidol should be adjusted thereafter to avoid hypercalcaemia according to the biochemical response. Indices of response include plasma levels of calcium (ideally corrected for protein binding), alkaline phosphatase, parathyroid hormone, as well as radiographic and histological investigations.

Plasma levels should initially be measured at weekly intervals. The daily dose of Alfacalcidol may be increased by increments of 0.25 – 0.5 microgram. When the dose is stabilised, measurements may be taken every 2 – 4 weeks.

Most adult patients respond to doses between 1 and 3 micrograms per day. When there is biochemical or radiographic evidence of bone healing, (and in hypoparathyroid patients when normal plasma calcium levels have been attained), the dose generally decreases. Maintenance doses are generally in the range of 0.25 to 1 microgram per day. If hypercalcaemia occurs, Alfacalcidol should be stopped until plasma calcium returns to normal (approximately 1 week) then restarted at half the previous dose.

a) Renal bone disease:
Patients with relatively high initial plasma calcium levels may have autonomous hyperparathyroidism, often unresponsive to Alfacalcidol. Other therapeutic measures may be indicated.
Before and during treatment with Alfacalcidol, phosphate binding agents should be considered to prevent hyperphosphataemia. It is particularly important to make frequent plasma calcium measurements in patients with chronic renal failure because prolonged hypercalcaemia may aggravate the decline of renal function.

b) Hyperparathyroidism:
In patients with primary or tertiary hyperparathyroidism about to undergo parathyroidectomy, preoperative treatment with Alfacalcidol for 2-3 weeks alleviates bone pain and myopathy without aggravating pre-operative hypercalcaemia. In order to decrease post-operative hypocalcaemia,

Alfacalcidol should be continued until plasma alkaline phosphatase levels fall to normal or hypercalcaemia occurs.

c) Hypoparathyroidism:
In contrast to the response to parent vitamin D, low plasma calcium levels are restored to normal relatively quickly with Alfacalcidol. Severe hypocalcaemia is corrected more rapidly with higher doses of Alfacalcidol (e.g. 3-5 micrograms) together with calcium supplements.

d) Neonatal hypocalcaemia:
Although the normal starting dose of Alfacalcidol is 0.05-0.1 microgram/kg/day (followed by careful titration) in severe cases doses of up to 2 microgram/kg/day may be required. Whilst ionised serum calcium levels may provide a guide to response, measurement of plasma alkaline phosphatase activity may be more useful. Levels of alkaline phosphatase approximately 7.5 times above the adult range indicates active disease.
A dose of 0.1 microgram/kg/day of Alfacalcidol has proven effective as prophylaxis against early neonatal hypocalcaemia in premature infants.

e) Nutritional and malabsorptive rickets and osteomalacia:
Nutritional rickets and osteomalacia can be cured rapidly with Alfacalcidol. Malabsorptive osteomalacia (responding to large doses of IM or IV parent vitamin D) will respond to small doses of Alfacalcidol.

f) Pseudo-deficiency (D-dependent) rickets and osteomalacia:
Although large doses of parent vitamin D would be required, effective doses of Alfacalcidol are similar to those required to heal nutritional vitamin D deficiency rickets and osteomalacia.

g) Hypophosphataemic vitamin D-resistant rickets and osteomalacia:
Neither large doses of parent vitamin D nor phosphate supplements are entirely satisfactory. Treatment with Alfacalcidol at normal dosage rapidly relieves myopathy when present and increases calcium and phosphate retention. Phosphate supplements may also be required in some patients.

Special populations:
Use in Elderly
The clinical manifestations of hypo- or hyper calcaemia should be considered especially in elderly patients with pre-existing renal or heart conditions.

Paediatric population
Alfacalcidol should be used with caution in infants, who may have increased sensitivity to its effects. Take care to ensure correct dose in infants.

4.3 Contraindications

Hypercalcaemia, metastatic calcification.
Hypersensitivity to Alfacalcidol or other ingredients in the preparation.

4.4 Special warnings and precautions for use

The product contains sorbitol; therefore patients with rare hereditary problems of fructose intolerance should not take this medicine.
Alfacalcidol should be used with caution for:

- patients being treated with cardioactive glycosides or digitalis as hypercalcaemia may lead to arrhythmia in such patients.
- patients with nephrolithiasis

During treatment with Alfacalcidol serum calcium and serum phosphate should be monitored regularly especially in patients with renal impairment and patients receiving high doses. To maintain serum phosphate at an acceptable level in patients with renal bone disease a phosphate binding agent may be used.
Hypercalcaemia may appear in patients treated with Alfacalcidol, the early symptoms are as follows:

- polyuria
- polydipsia
- weakness, headache, nausea, constipation
- dry mouth
- muscle and bone pain
- metallic taste

Hypercalcaemia can be rapidly corrected by stopping treatment until plasma calcium levels return to normal (in about one week). Alfacalcidol treatment may then be restarted at a reduced dose (half the previous dose).

Paediatric population
During treatment with Alfacalcidol serum calcium and serum phosphate should be monitored regularly in children.

4.5 Interaction with other medicinal products and other forms of interaction

Patients taking barbiturates or anticonvulsants may require larger doses of Alfacalcidol to produce the desired effect to the induction of hepatic detoxification enzymes.
Concomitant administration of colestyramine may interfere with the intestinal absorption of alfacalcidol.
Use with caution in patients being treated with thiazide diuretics as they may have an increased risk of developing hypercalcaemia.
Paediatric population
Drug interactions with Alfacalcidol are known to be similar in the paediatric age group and that in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of alfacalcidol in pregnant women. Animal studies are insufficient with respect to effects on pregnancy. The potential risks for humans are unknown. Caution should be taken when prescribing to pregnant women as hypercalcaemia during pregnancy may produce congenital disorders in the offspring.

Breastfeeding
Although it has not been established, it is likely that increased amounts of 1,25-dihydroxyvitamin D will be found in the milk of lactating mothers treated with alfacalcidol. This may influence calcium metabolism in the infant.
Fertility
No fertility data is available for use of alfacalcidol.

4.7 Effects on ability to drive and use machines

Alfacalcidol has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

The most frequently reported undesirable effects are hypercalcaemia and various skin reactions. If hypercalcaemia occurs during treatment with Alfacalcidol, this can be rapidly corrected by stopping treatment until plasma calcium levels return to normal (about 1 week). Alfacalcidol may then be restarted at half the previous dose.
Based on data from post-market use the total undesirable effect 'reporting rate' is rare (≥1/10,000 to <1/1,000) or very rare (<1/10,000); being approximately 1:10,000 patients treated.

System Organ Class	**Adverse Drug Reactions**
Metabolism and Nutrition Disorders	Hypercalcaemia Hyperphosphataemia
Skin and Subcutaneous Tissue Disorders	Pruritus Rash Urticaria
Renal and Urinary Disorders	Nephrocalcinosis Renal impairment

Paediatric population
Frequency and type of adverse reactions in children are the same as in adults.

4.9 Overdose

Hypercalcaemia is treated by stopping Alfacalcidol.
In severe cases of hypercalcaemia general supportive measures should be undertaken. Keep the patient well hydrated by i.v. infusion of saline (force diuresis), measure electrolytes, calcium and renal function indices; assess electrocardiographic abnormalities, especially in patients on digitalis. More

specifically, treatment with glucocorticosteroids, loop diuretics, bisphosphonates, calcitonin and eventually haemodialysis with low calcium content should be considered.
Paediatric population
Infants and children are generally more susceptible to the toxic effects of vitamin D.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vitamin D and analogues
ATC code: A11CC03
Alfacalcidol is converted rapidly in the liver to 1,25-dihydroxyvitamin D. This is the metabolite of vitamin D which acts as a regulator of calcium and phosphate metabolism. Since this conversion is rapid, the clinical effects of Alfacalcidol and 1,25-dihydroxyvitamin D are very similar.
Impaired 1-α hydroxylation by the kidneys reduces endogenous 1,25-dihydroxyvitamin D production. This contributes to the disturbances in mineral metabolism found in several disorders, including renal bone disease and hypoparathyoidism. These disorders, which require high doses of parent vitamin D for their correction, will respond to small doses of Alfacalcidol.
The delay in response and high dosage required in treating these disorders with parent vitamin D makes dosage adjustment difficult. This can result in unpredictable hypercalcaemia which may take weeks or months to reverse. The major advantage of Alfacalcidol is the more rapid onset of response, which allows a more accurate titration of dosage. Should inadvertent hypercalcaemia occur it can be reversed within days of stopping treatment.

Paediatric population
When 1-α hydroxylation by the kidneys is impaired, endogenous 1,25-dihydroxyvitamin D production is reduced. Disorders in which this can occur include neonatal hypocalcaemia and Vitamin D-dependent rickets. Such conditions require high doses of Vitamin D for their correction but will respond to small doses of Alfacalcidol, which does not depend on the renal 1-α hydroxylation process.

5.2 Pharmacokinetic properties

Absorption
In patients with renal failure, 1-5µg/day of 1α- hydroxyvitamin D (1α-OHD3) increased intestinal calcium and phosphorus absorption in a dose-related manner. This effect was observed within 3 days of starting the drug and conversely, it was reversed within 3 days of its discontinuation.
In patients with nutritional osteomalacia, increases in calcium absorption were noted within 6 hours of giving 1µg 1α-OHD3 orally and usually peaked at 24 hours. 1α-OHD3 also produced increases in plasma inorganic phosphorus due to increased intestinal absorption and renal tubular re-absorption. This latter effect is a result of PTH suppression by 1α-OHD3. The effect of the drug on calcium was about double its effect on phosphorus absorption.
Patients with chronic renal failure have shown increased serum calcium levels within 5 days of receiving 1α-OHD3 in a dose of 0.5 - 1.0µg/day. As serum calcium rose, PTH levels and alkaline phosphatase decreased toward normal.

Distribution
Vitamin D and its metabolites circulate in the blood bound to a specific α-globulin. Alfacalcidol has a more rapid action and shorter half-life.

Biotransformation:
Alfacalcidol undergoes rapid hepatic conversion to 1,25-dihydroxyvitamin D, the Vitamin D metabolite which acts as a regulator of calcium and phosphate metabolism.

Elimination
Vitamin D compounds and their metabolites are excreted mainly in the bile and faeces with only small amounts appearing in urine; there is some enterohepatic recycling but it is considered to have a negligible contribution to vitamin D status.
Paediatric population
Limited data is available in children.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule fill
Butylhydroxyanisole
Butylhydroxytoluene
Triglycerides, medium chain
Capsule shell
Gelatin
Glycerol
Sorbitol 70% solution
Black iron oxide
Red iron oxide
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25ºC
Keep blisters in the outer carton in order to protect from light

6.5 Nature and contents of container

PVC/PVDC/Aluminium blister pack
Pack size: 30 capsules
Each PVC/PVDC/Aluminium pack contains 3 strips, each containing 10 capsules.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Goldshield Pharmaceuticals Ltd.
NLA Tower
12-16 Addiscombe Road
Croydon
Surrey CR0 0XT
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 12762/0185

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/09/2011

10 DATE OF REVISION OF THE TEXT

20/09/2011

MODULE 3

Goldshield

PATIENT INFORMATION LEAFLET
Alfacalcidol 0.25microgram & 1microgram Capsules

Please read 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, 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.

In this leaflet:

1. WHAT ALFACALCIDOL CAPSULES ARE AND WHAT THEY ARE USED FOR

Alfacalcidol is a biologically active form of vitamin D. Alfacalcidol promotes the uptake of calcium from food and assists in growth of healthy bones.
They are used in conditions where there is a disturbance in the body's calcium levels, for example in kidney disorders. They are mainly used to treat the following conditions:
- changes in bone caused by kidney failure
- disorders of the parathyroid glands
- low blood calcium in newborn babies
- softening and deformity of the bones due to lack of calcium

2. BEFORE YOU TAKE ALFACALCIDOL CAPSULES

Do not take Alfacalcidol Capsules if:
- If you are allergic (hypersensitive) to alfacalcidol or any of the other ingredients of this medicine.
- If you know you have a condition called hypercalcaemia. This means you have high levels of calcium in your blood.
- If you know that you have a condition called calcification. This means you have high levels of calcium in your body tissues.

Take special care with Alfacalcidol capsules:
Before you take tell your doctor:
- If you are taking another type of medicine called a cardiac glycoside, such as digoxin. These medicines are used to treat problems with your heart.
- If you have any problems with your kidneys. This includes if you have kidney stones.

You may get too much calcium or phosphate in your blood when you take this medicine. Please read section 4 of this leaflet so you can spot any signs this may be happening to you. Your doctor may need to change your dose.
While you are taking Alfacalcidol your doctor will take regular blood tests. This is very important in children, patients with kidney problems, or patients on a high dose of medicine. This is to check the level of calcium and phosphate in your blood while you take your medicine.
Your doctor may prescribe another medicine called a phosphate binding agent to take as well as Alfacalcidol. This will help to keep the right amount of phosphate in your blood.

Taking other medicines
Please tell your doctor or pharmacist if you are taking, or have recently taken any other medicines. This includes any medicines which you have bought without a prescription.
You must tell your doctor or pharmacist if you are taking any of the following medicines:
- Anticonvulsants: for epilepsy or fits. You may need a larger dose of Alfacalcidol
- Barbiturates: for sleeping disorders. You may need a larger dose of Alfacalcidol
- Cardiac glycosides, such as digoxin: for heart problems.
  You may get too much calcium in your blood. This may cause an abnormal heart beat.
- Colestyramine: for lowering your cholesterol level, or to help stop some types of diarrhoea or itching. Your Alfacalcidol may not enter your blood as usual.
- Thiazide diuretics, often called "water pills": for increasing the amount of water (urine) that your body makes. You may get too much calcium in your blood.

Pregnancy and breast-feeding
Please ask your doctor or pharmacist for advice before taking Alfacalcidol.
- If you are pregnant, or think you are pregnant.
- If you are breast-feeding.

Tell your doctor if you become pregnant while taking this medicine.

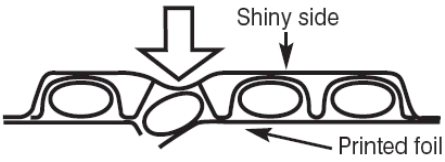
Driving and using machines
Usually your medicine may have very little or no effect on your ability to drive or use machines. Check with your doctor if you feel any side effect that may stop you from driving or using machines.

Important information about some of the ingredients of Alfacalcidol Capsules
This medicinal product contains sorbitol. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE ALFACALCIDOL CAPSULES

Always use Alfacalcidol exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.
You should continue to take these capsules for as long as your doctor tells you to.
The capsules should be swallowed with a drink of water.

To remove the capsules from the blister, press on the shiny side of the blister so that the capsule comes out through the printed foil (see diagram).



The usual dose is:

Adults

- The normal starting dose for adults is 1 microgram per day. This dosage may then be adjusted, depending on your particular needs.
- Most adults respond to a dose between 1 and 3 micrograms per day.Once the dose is stabilised, the maintenance dose is in the range of 0.25 to 1 microgram per day.
- Doses of 3 to 5 micrograms of Alfacalcidol Capsules may be given with calcium supplements where there are very low blood calcium levels which have been caused by underactivity of the parathyroid glands (parathyroid glands regulate calcium levels in the body).

Children

The dose depends on the weight of the child and will be calculated by your child's doctor.

Elderly

The starting dose is 0.5 micrograms per day.

At the beginning of your treatment calcium levels in your blood should be measured regularly. The dosage of alfacalcidol can then be adjusted to achieve the correct response. When the correct dosage has been found, your calcium levels may continue to be measured but less often. Also, if your doctor thinks it is necessary he/she may prescribe extra calcium supplements to be taken during your treatment.

If you take more Alfacalcidol Capsules than you should

Tell your doctor straight away. You may need to stop taking this medicine.
You may get too much calcium or phosphate in your blood. Please read section 4 of this leaflet so you can spot any signs if this may be happening to you.

If you forget to take Alfacalcidol Capsules

If you forget to take a capsule, take one as soon as you remember, unless it is nearly time to take the next one. Do not take a double dose to make up for a forgotten dose. Take the remaining doses at the correct time.

Ask your doctor or pharmacist if you have any further questions on the use of this product.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Alfacalcidol can cause side effects, although not everybody gets them.

Important side effects to look out for:

You must get urgent medical help if you have any of the following symptoms. You may be having an allergic reaction:

- You have difficulty breathing.
- Your face or throat swell.
- Your skin develops a severe rash.

You should tell your doctor straight away if you spot any of the following signs which may be due to too much calcium or phosphate in your blood:

- You need to pass water (urine) more often
- You feel thirsty
- You have a dry mouth, or a metallic taste in your mouth.
- You feel weak or have pain in your muscles or bones.
- You feel sick or have constipation.

Other possible side effects:

Skin problems:

- Itching skin
- Rash
- Hives (urticaria)

Kidney problems:

- Needing to pass water (urine) less often.
- Swelling of any parts of your body.
- Fever with a pain in your side.

These are signs that there may be problems developing with your kidneys. Kidney stones may be forming. Kidney stones may cause a sharp spasm in one side of your lower back.
The possible side effects described in this section of the leaflet probably affect about 1 in 10,000 people.
Skin problems or too much calcium in your blood are the side effects most people get.
If any of the side effects become serious, or you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

5. HOW TO STORE ALFACALCIDOL CAPSULES

Keep out of reach and sight of children.

Do not store above 25°C. Keep blisters in the outer carton in order to protect from light. Do not use Alfacalcidol after the expiry date that is stated on the outer packaging.

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 Alfacalcidol Capsules contain:

The active ingredient is alfacalcidol

- Each Alfacalcidol 0.25 microgram Capsule contains 0.25 micrograms of alfacalcidol
- Each Alfacalcidol 1 microgram Capsule contains 1 microgam of alfacalcidol
- The other ingredients are butylhydroxyanisole, butylhydroxytoluene, triglycerides, gelatin, glycerol, sorbitol 70% solution, purified water.

Alfacalcidol 0.25 microgram Capsules also contain titanium dioxide.

Alfacalcidol 1 microgram Capsules also contain iron oxide black and iron oxide red.

What Alfacalcidol Capsules look like and contents of the pack:

- Alfacalcidol 0.25 microgram Capsules are opaque, white, oval, soft gelatine capsules.
- Alfacalcidol 1 microgram Capsules are opaque, brown, oval, soft gelatine capsules.

Alfacalcidol Capsules are available in pack sizes of 30 Capsules.

Marketing Authorisation Holder & Manufacturer:

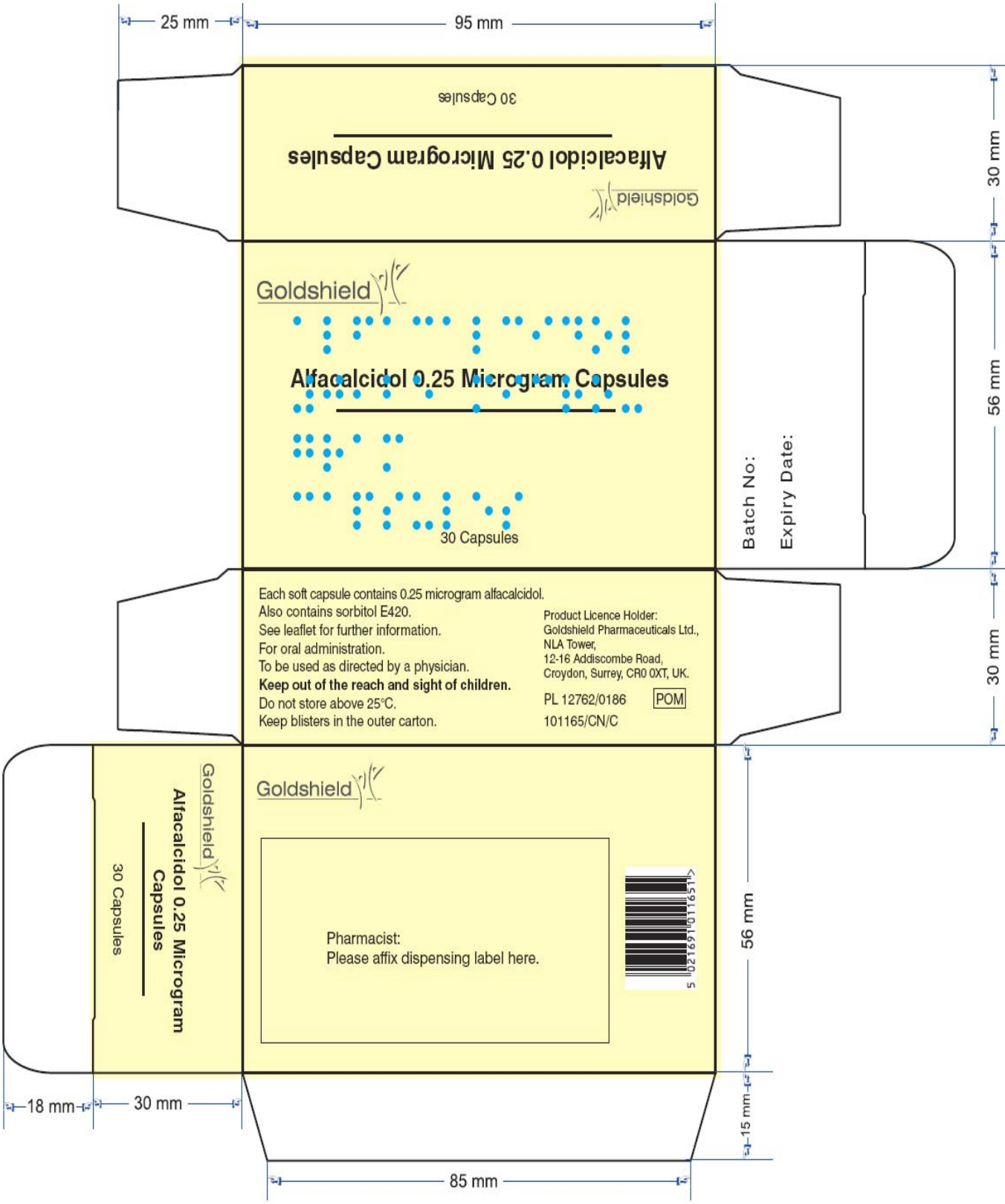
Goldshield Pharmaceuticals Ltd.,
NLA Tower, 12-16 Addiscombe Road,
Croydon, Surrey, CR0 0XT, UK.

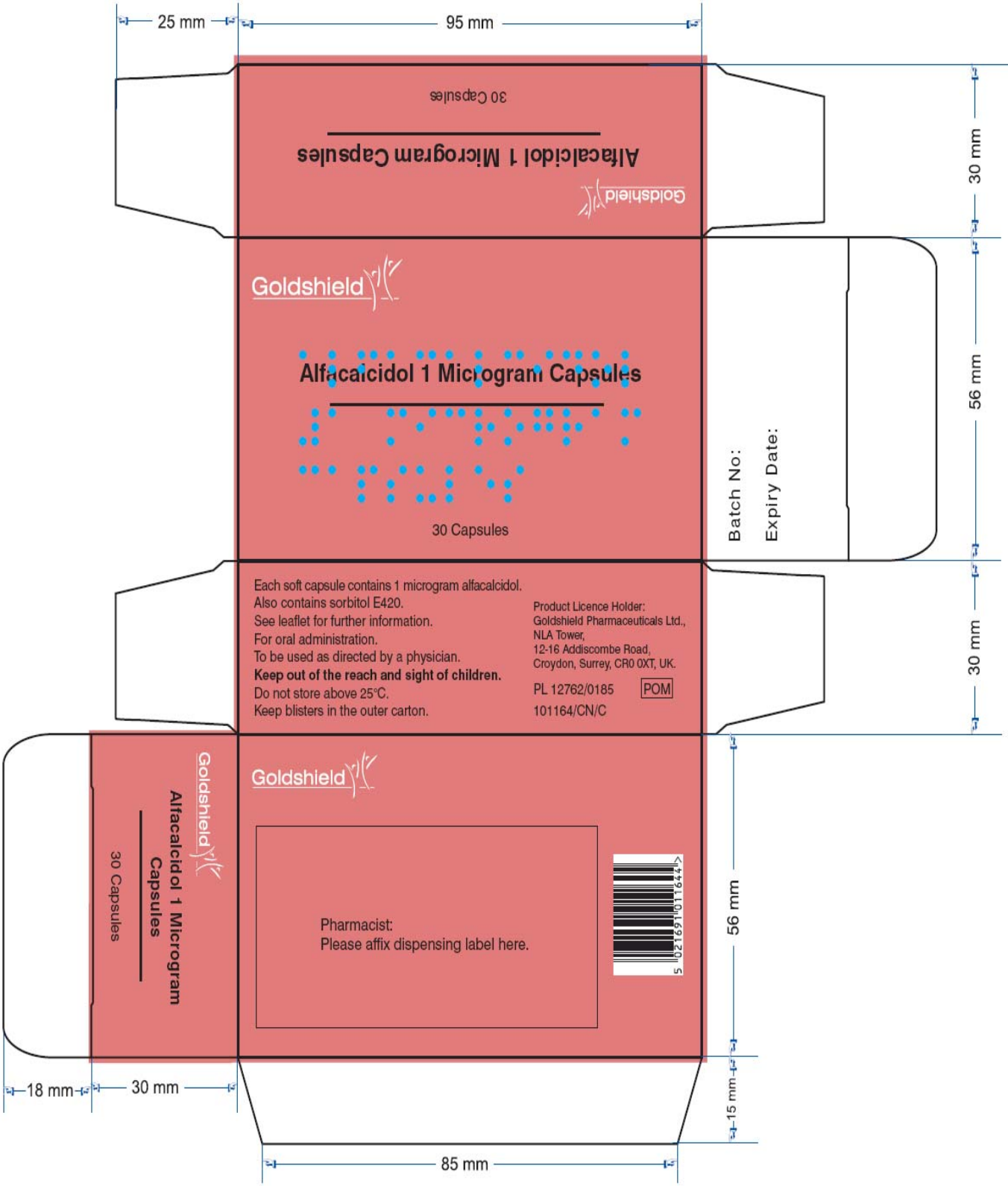
This leaflet was revised in June 2011.

101164-101165/LF/B

MODULE 4

Carton

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Alfacalcidol 1 Microgram Capsules
Goldshield
Goldshield
Alfacalcidol 1 Microgram Capsules
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30 Capsules
Batch No:
Expiry Date:
Each soft capsule contains 1 microgram alfacalcidol.
Also contains sorbitol E420.
See leaflet for further information.
For oral administration.
To be used as directed by a physician.
Keep out of the reach and sight of children.
Do not store above 25°C.
Keep blisters in the outer carton.
Product Licence Holder:
Goldshield Pharmaceuticals Ltd.,
NLA Tower,
12-16 Addiscombe Road,
Croydon, Surrey, CR0 0XT, UK.
PL 12762/0185
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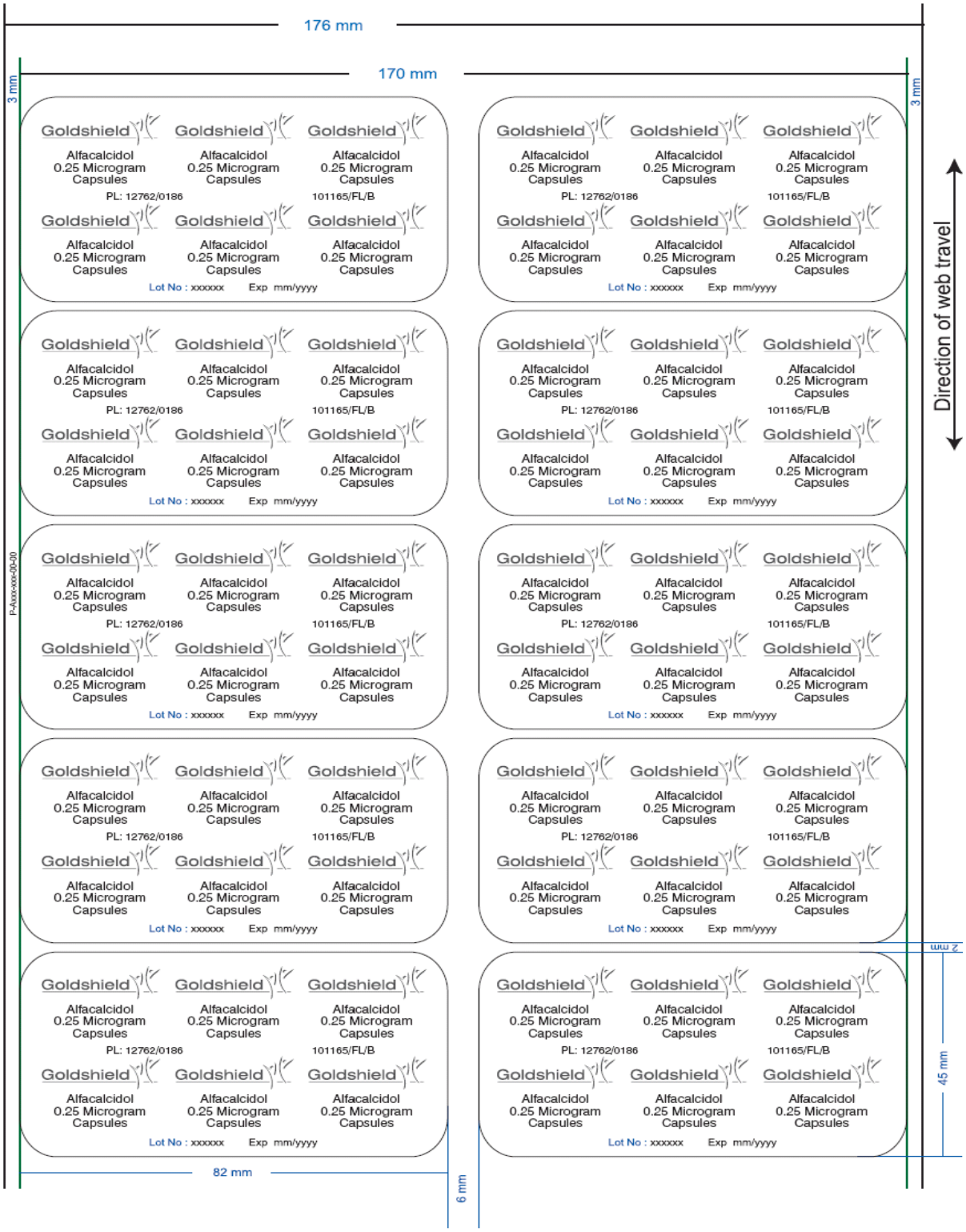
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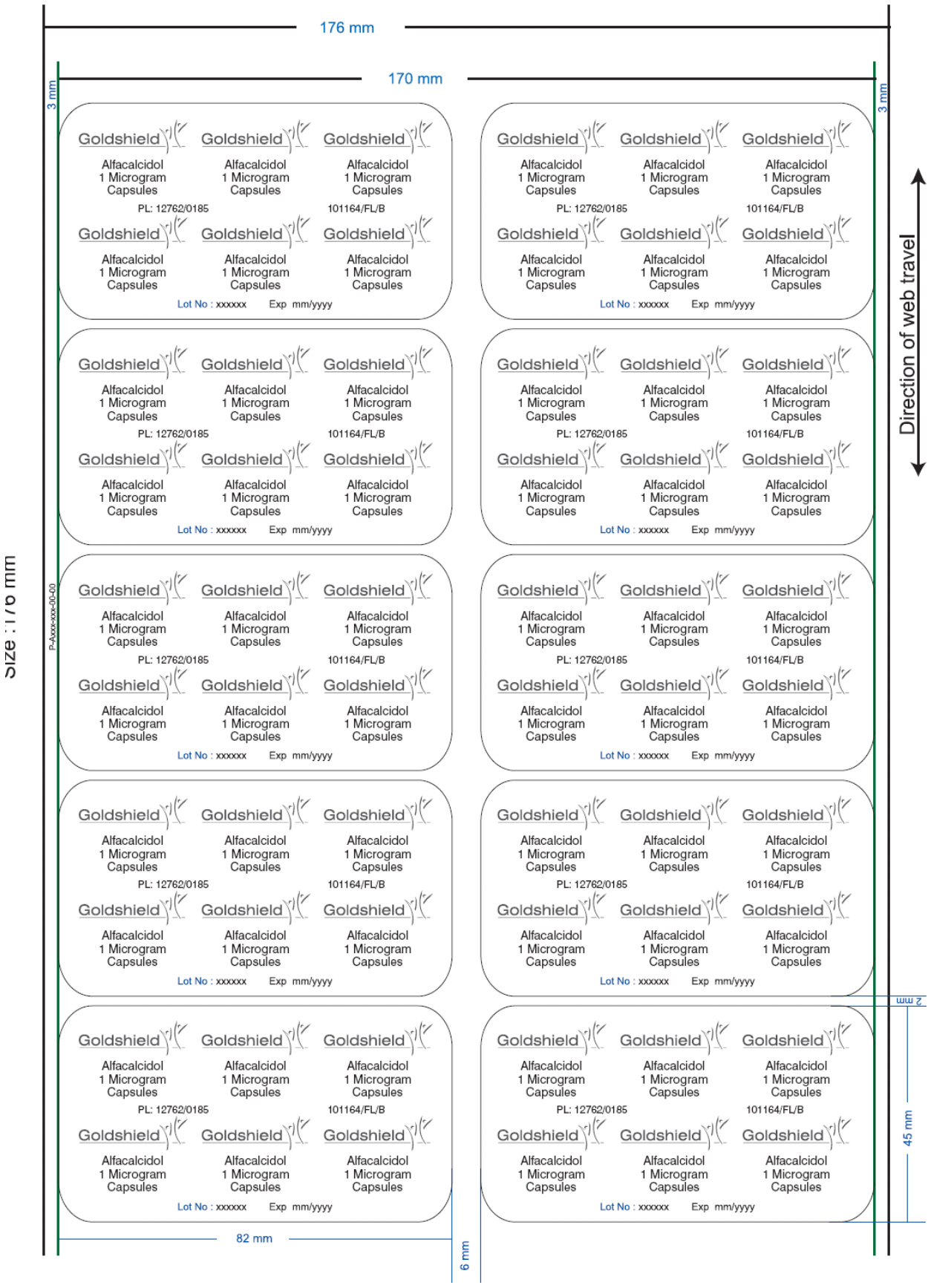
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