# OSTALIS 70 MG TABLETS

**PL 16508/0024**

**UKPAR**

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**OSTALIS 70 MG TABLETS**

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## LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted ProStrakan Limited a Marketing Authorisation (licence) for the medicinal product Ostalis 70 mg Tablets (Product Licence number: 16508/0024). This product is only available with a prescription.

Ostalis 70 mg Tablets contain the active ingredient alendronic acid. Following menopause the cells that break down the bone (osteoclasts) may become more active than those that stimulate the manufacture of new bone (osteoblasts) and, as a result, loss of bone density and osteoporosis can occur. Alendronic acid can restore the osteoclast-to-osteoblast balance by blocking osteoclasts, thus preventing loss of bone mass and helping to rebuild lost bone.

No new or unexpected safety concerns arose from this simple application and it was, therefore, judged that the benefits of taking Ostalis 70 mg Tablets outweigh the risks, hence a Marketing Authorisation has been granted.

**OSTALIS 70 MG TABLETS**

**PL 16508/0024**

## SCIENTIFIC DISCUSSION

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# INTRODUCTION

The UK granted a marketing authorisation for the medicinal product Ostalis 70 mg Tablets (PL 16508/0024) to ProStrakan Limited on 5 December 2006. This product is a Prescription Only Medicine (POM).

The application was submitted as an abridged informed consent application according to Article 10c of EC Directive 2001/83. The cross reference product is Generics UK Alendronic acid 70 mg tablets (PL 04569/0625), held by Generics (UK) Limited and granted 4 October 2005.

No new data were submitted, nor was it necessary for this simple application as the data are identical to those 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.

# PHARMACEUTICAL ASSESSMENT REPORT

## REQUESTS FOR INSPECTION ACTION PRIOR TO AUTHORISATION

No inspection action prior to authorisation is requested.

## INTRODUCTION

### *Legal Basis*

This simple abridged national application is for Ostalis 70 mg tablets. Each Ostalis tablet contains 70 mg of alendronic acid as sodium alendronate for the treatment of postmenopausal osteoporosis. This application was made as an informed consent application under Article 10c of Directive 2001/83/EC, as amended. This application refers to the Marketing Authorisation granted to Generics (UK) Limited for Generics UK Alendronic acid 70 mg tablets (PL 04569/0625) on 4 October 2005.

A letter of access has been provided from Generics (UK) Ltd, dated 25 November 2005, authorising the MHRA to refer to PL 04569/0625 as the reference for the purpose of this informed consent application. A signed declaration by ProStrakan Ltd stating that they have the Quality dossier for PL 04569/0625 in their possession is also provided.

A signed declaration from the product manufacturer stating that they are prepared to manufacture the product on behalf of ProStrakan Ltd has been received.

### *Use*

Treatment of postmenopausal osteoporosis

### *Scientific Advice*

No scientific advice has been given regarding this medicinal product by the Committee for Medicinal Products for Human Use CHMP.

### *Legal Status*

Prescription-only medicine (POM)

## DRUG SUBSTANCE

### *General Information*

The active substance, alendronic acid as sodium alendronate, is supplied by a suitable manufacturer in line with the reference product. The active substance supplied is supported by a Drug Master File (DMF) ) and a letter of access has been provided by the drug substance manufacturer with regards to the EU-CTD version dated November 2005. The DMF has previously been accepted for another UK product and there are no outstanding issues.

### *Manufacture*

Satisfactory details have been provided in the DMF.

### *Characterisation*

Satisfactory details have been provided in the DMF.

### *Control of Drug Substance*

The active substance is the subject of a Ph. Eur. monograph. The proposed active substance specification for Ostalis 70mg Tablets is identical to that of the authorised reference product and

is, therefore, acceptable. Satisfactory details have been provided in the DMF.

***Reference Standards or Materials***
Satisfactory details have been provided in the DMF.

***Container Closure System***
Satisfactory details have been provided in the DMF.

***Stability***
Satisfactory details have been provided in the DMF.

**DRUG PRODUCT**
***Description and Composition of the Drug Product***
The unit formula has been verified to be identical to the authorised reference product.

***Pharmaceutical Development***
No product development was carried out for this product. The applicant simply refers to the pharmaceutical development that was carried out for the reference product and this is satisfactory.

***Manufacture***
Manufacturers
The finished product will be manufactured solely at a site that is satisfactory and consistent with the manufacture of the reference product. Copies of the current Manufacturer's Licence for the batch release sites have been provided.

Description of manufacturing process and process controls
The manufacturing process is the same as that for the original reference product.

The sites of manufacture are identical to those used for the reference product and no GMP issues can be identified.

***Control of Excipients***
Control of excipients is in line with the reference product. A Ph. Eur. Certificate of Suitability for TSE has been provided for the component magnesium stearate in the drug product.

***Control of Drug Product***
The proposed finished product specification is essentially identical to that of the reference product and is satisfactory.

The analytical methods used for analysis are identical to those used for the reference product.

***Reference Standards or Materials***
The reference standards and materials are in line with those of the reference product.

***Container Closure System***
The MAA form and the SPC indicate that the product will be packaged into PVC/aluminium blisters. This packaging is identical to the blister packaging for the reference product though the reference product also made use of another type of packaging. The current application by ProStrakan Ltd made no mention of the use of any other packaging and it will be assumed that the MA will be granted solely on the use of PVC/aluminium blister packs.

***Stability***
The stability studies carried out on this product are in line with those of the reference product. The proposed shelf life of 24 months (2 years) is identical to that of the reference product. The proposed storage conditions are also identical to the reference product.

***Bioequivalence / Bioavailability***
No bioavailability and bioequivalence data are required to support this informed consent application as the proposed product is manufactured to the same formula utilising the same process as the reference product. The manufacturing site is also identical to that used by the reference product.

***Essential Similarity***
Not applicable.

**APPENDICES**
***Facilities and Equipment***
Not applicable.

***Adventitious Agents Safety Evaluation***
Not applicable.

***Novel Excipients***
Not applicable.

**REGIONAL INFORMATION**
***Process validation scheme for the drug product***
Acceptable.

***Medical Device issues***
Not applicable.

***TSE Issues***
A Ph. Eur. Certificate of Suitability for TSE has been provided for the component magnesium stearate in the drug product.

**ASSESSOR'S COMMENTS ON MODULE I**
***Name and Appearance (if applicable)***
Not applicable.

***SPC***
The SPC is in-line with that of the reference product and is satisfactory.

***Patient Information Leaflet***
The PIL for this product is satisfactory.

***Label***
A copy of the full size packaging mock up is provided, including the provision of Braille format. All labelling is satisfactory.

***Application Form***
The application form is satisfactory.

***Expert statements***

Quality overall summary

The applicant, ProStrakan Ltd, has provided a comprehensive quality overall summary to support the application along with an expert declaration statement signed and dated by a relevant expert stating, in effect, that the content of the relevant quality module is identical to the dossier of the reference product.

Non-clinical review

The applicant, ProStrakan Ltd, has provided a copy of the reference product non-clinical review to support the application along with a copy of an expert declaration statement signed and dated by a relevant expert stating, in effect, that the non-clinical review for the application is identical to the reference product.

Clinical review

The applicant, ProStrakan Ltd, has provided a copy of the reference product clinical review, along with a copy of an expert declaration statement signed and dated by a relevant expert stating in effect that the clinical review for the application is identical to the reference product.

**ASSESSOR'S OVERALL CONCLUSIONS**

The marketing authorisation may be granted.

## PRECLINICAL ASSESSMENT

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

## CLINICAL ASSESSMENT

No new clinical data have been supplied with this application and none are 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 were submitted and none are required for an application of this type.

### EFFICACY AND SAFETY

The efficacy of alendronic acid tablets has been well documented in the past. No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory.

### 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. The risk benefit ratio is considered to be positive.

**OSTALIS 70 MG TABLETS**

**PL 16508/0024**

## STEPS TAKEN FOR ASSESSMENT

| | |
|---|---|
| **1** | The MHRA received the marketing authorisation application on 17 February 2006 |
| **2** | Following assessment of the application the MHRA requested further information relating to the quality dossier on 27 March 2006 |
| **3** | The applicant responded to the MHRA's requests, providing further information on 1 June 2006 |
| **4** | Following assessment of the response the MHRA requested further information relating to the quality dossier on 12 June 2006 |
| **5** | The applicant responded to the MHRA's requests, providing further information on 3 July 2006 |
| **6** | Following assessment of the response the MHRA requested further information relating to the quality dossier on 10 July 2006 |
| **7** | The applicant responded to the MHRA's requests, providing further information on 21 November 2006 |
| **8** | The application was determined on 5 December 2006 |

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Ostalis 70 mg Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 70mg alendronic acid as sodium alendronate
For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Tablets
White normal concave tablet 9.5mm in diameter, embossed 'AD70' on one side and 'G' on the reverse.

## 4 CLINICAL PARTICULARS

### *4.1 Therapeutic indications*

Treatment of postmenopausal osteoporosis. Ostalis 70mg Tablets reduce the risk of vertebral and hip fractures.

### *4.2 Posology and method of administration*

For oral administration.
The recommended dosage is one 70 mg tablet once weekly.

*To permit adequate absorption of alendronic acid'.*
Ostalis Tablets must be taken at least 30 minutes before the first food, beverage, or medicinal product of the day with plain water only. Other beverages (including mineral water), food and some medicinal products are likely to reduce the absorption of alendronic acid (see section 4.5).

*To facilitate delivery to the stomach and thus reduce the potential for local and oesophageal irritation/adverse experiences (see section 4.4)*:

- Ostalis Tablets should only be swallowed upon arising for the day with a full glass of water (not less than 200ml or 7fl.oz.).
- Patients should not chew the tablet or allow the tablet to dissolve in their mouths because of a potential for oropharyngeal ulceration.

- Patients should not lie down until after their first food of the day which should be at least 30 minutes after taking the tablet.
- Patients should not lie down for at least 30 minutes after taking Ostalis Tablets
- Ostalis Tablets should not be taken at bedtime or before arising for the day.

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate (see section 4.4).

*Use in the elderly*: In clinical studies there was no age-related difference in the efficacy or safety profiles of alendronic acid. Therefore no dosage adjustment is necessary for the elderly.

*Use in renal impairment*: No dosage adjustment is necessary for patients with GFR greater than 35 ml/min. Alendronic acid is not recommended for patients with renal impairment where GFR is less than 35 ml/min, due to lack of experience.

*Use in children*: There is no relevant indication for the use of Ostalis tablet in children.

Alendronic acid has not been investigated in the treatment of glucocorticoid induced osteoporosis.

### *4.3 Contraindications*

- Abnormalities of the oesophagus and other factors which delay oesophageal emptying such as stricture or achalasia.
- Inability to stand or sit upright for at least 30 minutes.
- Hypersensitivity to alendronic acid or any of the excipients.
- Hypocalcaemia.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
See also section 4.4.

### *4.4 Special warnings and precautions for use*

Alendronic acid can cause local irritation of the upper gastro-intestinal mucosa. Because there is a potential for worsening of the underlying disease, caution should be used when Ostalis Tablets are given to patients with active upper gastro-intestinal problems, such as dysphagia, oesophageal disease, gastritis, duodenitis, ulcers or with a recent history (within the previous year) of major gastro-intestinal disease such as peptic ulcer, or active gastro-intestinal bleeding, or surgery of the upper gastro-intestinal tract other than pyloroplasty.(see section 4.3).

Oesophageal reactions (sometimes severe and requiring hospitalisation), such as oesophagitis, oesophageal ulcers and oesophageal erosions, rarely followed by oesophageal stricture, have been reported in patients receiving alendronic acid. Physicians should therefore be alert to any signs or symptoms signalling a possible oesophageal reaction and patients should be instructed to discontinue Ostalis Tablets and seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing or retrosternal pain, new or worsening heartburn.

The risk of severe oesophageal adverse experiences appears to be greater in patients who fail to take Ostalis Tablets properly and/or who continue to take Ostalis Tablets after developing symptoms suggestive of oesophageal irritation. It is very important that the full dosing instructions are provided to, and understood by the patient (see section 4.2). Patients should be informed that failure to follow these instructions may increase their risk of oesophageal problems.

While no increased risk was observed in extensive clinical trials, there have been rare (post- marketing) reports of gastric and duodenal ulcers, some severe and with complications. However a causal relationship cannot be ruled out.

Patients should be instructed that if they miss a dose of Ostalis 70mg Tablets, they should take one tablet on the morning after they remember. They should not take two tablets on the same day but should return to taking one tablet once a week, as originally scheduled on their chosen day.

Alendronic acid is not recommended for patients with renal impairment where GFR is less than 35 ml/min, (see section 4.2).

Causes of osteoporosis other than oestrogen deficiency and ageing should be considered.

Hypocalcaemia must be corrected before initiating therapy with alendronic acid (see section 4.3). Other disturbances of mineral metabolism (such as vitamin D deficiency) should also be effectively treated. Due to the positive effects of alendronic acid to increase bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur, especially in patients receiving glucocorticoids, in whom calcium absorption may be decreased. Ensuring adequate calcium and vitamin D intake is therefore particularly important in patients receiving glucocorticoids.

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer receiving treatment regimens including primarily intravenously administered bisphosphonates. Many of these patients were also receiving chemotherapy with corticosteriods. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g cancer, chemotherapy, radiotherapy, corticosteriods, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonates therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw.

Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

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

If taken at the same time, it is likely that food and beverages (including mineral water, calcium supplements, antacids, and some oral medications) will interfere with absorption of alendronic acid. Therefore, patients must wait at least 30 minutes after taking Ostalis Tablets before taking any other oral medicinal product (see sections 4.2 and 5.2).

No other interactions with medicinal products of clinical significance are anticipated. A number of patients in the clinical trials received oestrogen (intravaginal, transdermal, or oral) while taking alendronic acid. No adverse experiences attributable to their concomitant use were identified.

Although specific interaction studies were not performed, in clinical studies alendronic acid was used concomitantly with a wide range of commonly prescribed medicinal products without evidence of clinical adverse interactions.

### *4.6 Pregnancy and lactation*

*Use during pregnancy*

There are no adequate data from the use of alendronic acid in pregnant women. Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/fetal development, or postnatal development. Alendronic acid given during pregnancy in rats caused dystocia related to hypocalcemia (see section 5.3). Given the indication, alendronic acid should not be used during pregnancy.

*Use during lactation*

It is not known whether alendronic acid is excreted into human breast milk. Given the indication, alendronic acid should not be used by breast-feeding women.

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

No effects on the ability to drive and use machines have been observed with Ostalis tablets.

### *4.8 Undesirable effects*

In a one-year study in post-menopausal women with osteoporosis the overall safety profiles of Ostalis 70mg Tablets (n=519) and alendronic acid 10mg/day (n=370) were similar.

In two three-year studies of virtually identical design, in post-menopausal women (alendronic acid 10mg: n=196, placebo: n=397) the overall safety profiles of alendronic acid 10 mg/day and placebo were similar.

| | **One-Year Study** | | **Three-Year Studies** | |
|---|---|---|---|---|
| | **Ostalis 70mg Tablets (n = 519) %** | **Alendronic acid 10 mg/day (n = 370) %** | **Alendronic acid 10 mg/day (n = 196) %** | **Placebo (n = 397) %** |
| *Gastro-intestinal* | | | | |
| abdominal pain | 3.7 | 3.0 | 6.6 | 4.8 |
| dyspepsia | 2.7 | 2.2 | 3.6 | 3.5 |
| acid regurgitation | 1.9 | 2.4 | 2.0 | 4.3 |
| nausea | 1.9 | 2.4 | 3.6 | 4.0 |
| abdominal distension | 1.0 | 1.4 | 1.0 | 0.8 |
| constipation | 0.8 | 1.6 | 3.1 | 1.8 |
| diarrhoea | 0.6 | 0.5 | 3.1 | 1.8 |
| dysphagia | 0.4 | 0.5 | 1.0 | 0.0 |
| flatulence | 0.4 | 1.6 | 2.6 | 0.5 |
| gastritis | 0.2 | 1.1 | 0.5 | 1.3 |
| gastric ulcer | 0.0 | 1.1 | 0.0 | 0.0 |
| oesophageal ulcer | 0.0 | 0.0 | 1.5 | 0.0 |
| *Musculoskeletal* | | | | |
| musculoskeletal (bone, muscle or joint) | 2.9 | 3.2 | 4.1 | 2.5 |

| | | | | |
|---|---|---|---|---|
| pain | | | | |
| muscle cramp | 0.2 | 1.1 | 0.0 | 1.0 |
| *Neurological* | | | | |
| headache | 0.4 | 0.3 | 2.6 | 1.5 |

Adverse experiences reported by the investigators as possibly, probably or definitely drug-related are presented below if they occurred in ≥1% in either treatment group in the one-year study, or in ≥ 1% of patients treated with alendronic acid 10mg/day and at a greater incidence than in patients given placebo in the three-year studies:

The following adverse experiences have also been reported during clinical studies and/or post-marketing use:

| | **Common (≥1/100, <1/10)** | **Uncommon (≥1/1,000, <1/100)** | **Rare (≥1/10,000, <1/1,000)** |
|---|---|---|---|
| **Nervous system disorders** | • headache | | |
| **Eye disorders** | | | • uveitis<br>• scleritis |
| **Gastrointestinal disorders** | • abdominal pain<br>• dyspepsia<br>• constipation<br>• diarrhoea<br>• flatulence<br>• oesophageal ulcer*<br>• melaena<br>• dysphagia*<br>• abdominal distension<br>• acid regurgitation | • nausea<br>• vomiting<br>• gastritis<br>• oesophagitis*<br>• oesophageal erosions* | • oesophageal stricture*<br>• oropharyngeal ulceration*<br>• upper gastrointestinal PUBs (perforation, ulcers, bleeding), although a causal relationship cannot be ruled out |
| **Musculoskeletal, connective tissue and bone disorders** | • musculoskeletal (bone, muscle or joint) pain | | |
| **General disorders and administration site conditions** | | • rash<br>• erythema | • hypersensitivity reactions including urticaria and angioedema<br>• rash with photosensitivity |

* See sections 4.4 and 4.2.

*Laboratory test findings*

In clinical studies, asymptomatic, mild and transient decreases in serum calcium and phosphate were observed in approximately 18 and 10%, respectively, of patients taking alendronic acid 10mg/day versus approximately 12 and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dl (2.0 mmol/l) and serum phosphate to ≤ 2.0 mg/dl (0.65 mmol/l) were similar in both treatment groups. Osteonecrosis of the jaw has been reported in patients treated by bisphosphonates. The majority of the reports refer to cancer patients, but such cases have also been reported in

patients treated for osteoporosis. Osteonecrosis of the jaw is generally associated with tooth extraction and/or local infection (including osteomyelitis). Diagnosis of cancer, chemotherapy, radiotherapy, corticosteroids and poor oral hygiene are also deemed as risk factors (see section 4.4)

### *4.9 Overdose*

Hypocalcaemia, hypophosphataemia and upper gastro-intestinal adverse events, such as upset stomach, heartburn, oesophagitis, gastritis, or ulcer, may result from oral overdosage.

No specific information is available on the the treatment of overdosage with alendronic acid. Milk or antacids should be given to bind alendronic acid. Owing to the risk of oesophageal irritation, vomiting should not be induced and the patient should remain fully upright.

## 5. PHARMACOLOGICAL PROPERTIES

### *5.1 Pharmacodynamic properties*

Pharmacotherapeutic group: Bisphonate, for the treatment of bone diseases.
ATC Code: M05B A04

The active ingredient of Ostalis 70mg Tablets, alendronic acid provided as alendronate sodium trihydrate, is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation. Preclinical studies have shown preferential localization of alendronic acid to sites of active resorption. Activity of osteoclasts is inhibited, but recruitment or attachment of osteoclasts is not affected. The bone formed during treatment with alendronic acid is of normal quality.

*Treatment of post-menopausal osteoporosis*

**Osteoporosis is defined as BMD of the spine or hip 2.5 SD below the mean value of a normal young population or as a previous fragility fracture, irrespective of BMD.**
The therapeutic equivalence of Ostalis 70mg Tablets (n=519) and alendronic acid 10mg daily (n=370) was demonstrated in a one-year multicentre study of post-menopausal women with osteoporosis. The mean increases from baseline in lumbar spine BMD at one year were 5.1% (95% CI: 4.8, 5.4%) in the Ostalis 70mg Tablets group and 5.4% (95% CI: 5.0, 5.8%) in the 10 mg daily group. The mean BMD increases were 2.3% and 2.9% at the femoral neck and 2.9% and 3.1% at the total hip in the Ostalis 70mg Tablets and 10mg daily groups, respectively. The two treatment groups were also similar with regard to BMD increases at other skeletal sites.

The effects of alendronic acid on bone mass and fracture incidence in post-menopausal women were examined in two initial efficacy studies of identical design (n=994) as well as in the Fracture Intervention Trial (FIT: n=6,459).

In the initial efficacy studies, the mean bone mineral density (BMD) increases with alendronic acid 10mg/day relative to placebo at three years were 8.8%, 5.9% and 7.8% at the spine, femoral neck and trochanter, respectively. Total body BMD also increased significantly. There was a 48% reduction (alendronic acid 3.2% Vs placebo 6.2%) in the proportion of patients treated with alendronic acid experiencing one or more vertebral fractures relative to those treated with placebo. In the two-year extension of these studies BMD at the spine and trochanter continued to increase and BMD at the femoral neck and total body were maintained.

FIT consisted of two placebo-controlled studies using alendronic acid daily (5 mg daily for two years and 10 mg daily for either one or two additional years):

- FIT 1: A three-year study of 2,027 patients who had at least one baseline vertebral (compression) fracture. In this study alendronic acid daily reduced the incidence of ≥ 1 new vertebral fracture by 47% (alendronic acid 7.9% vs. placebo 15.0%). In addition, a statistically significant reduction was found in the incidence of hip fractures (1.1% vs. 2.2%, a reduction of 51%).

- FIT 2: A four-year study of 4,432 patients with low bone mass but without a baseline vertebral fracture. In this study, a significant difference was observed in the analysis of the subgroup of osteoporotic women (37% of the global population who correspond with the above definition of osteoporosis) in the incidence of hip fractures (alendronic acid 1.0% vs. placebo 2.2%, a reduction of 56%) and in the incidence of ≥ 1 vertebral fracture (2.9% vs. 5.8%, a reduction of 50%).

## *5.2 Pharmacokinetic properties*

*Absorption*

Relative to an intravenous reference dose, the oral mean bioavailability of alendronic acid in women was 0.64% for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardised breakfast. Bioavailability was decreased similarly to an estimated 0.46% and 0.39% when alendronic acid was administered one hour or half an hour before a standardised breakfast. In osteoporosis studies, alendronic acid was effective when administered at least 30 minutes before the first food or beverage of the day.

Bioavailability was negligible whether alendronic acid was administered with, or up to two hours after, a standardised breakfast. Concomitant administration of alendronic acid with coffee or orange juice reduced bioavailability by approximately 60%.

In healthy subjects, oral prednisone (20mg three times daily for five days) did not produce a clinically meaningful change in oral bioavailability of alendronic acid (a mean increase ranging from 20% to 44%).

*Distribution*

Studies in rats show that alendronic acid transiently distributes to soft tissues following 1 mg/kg intravenous administration but is then rapidly redistributed to bone or excreted in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 litres in humans. Concentrations of drug in plasma following therapeutic oral doses are too low for analytical detection (<5 ng/ml). Protein binding in human plasma is approximately 78%.

*Biotransformation*

There is no evidence that alendronic acid is metabolised in animals or humans.

*Elimination*

Following a single intravenous dose of [$^{14}$C]alendronic acid, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the faeces. Following a single 10 mg intravenous dose, the renal clearance of alendronic acid was 71 ml/min, and systemic clearance did not exceed 200 ml/min.

Plasma concentrations fell by more than 95% within six hours following intravenous administration. The terminal half-life in humans is estimated to exceed ten years, reflecting release of alendronic acid from the skeleton. Alendronic acid is not excreted through the acidic or basic transport systems of the kidney in rats, and thus it is not anticipated to interfere with the excretion of other medicinal products by those systems in humans.

*Characteristics in patients*
Preclinical studies show that the drug that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after chronic dosing with cumulative intravenous doses up to 35 mg/kg in animals. Although no clinical information is available, it is likely that, as in animals, elimination of alendronic acid via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronic acid in bone might be expected in patients with impaired renal function (see 4.2).

### *5.3 Preclinical safety data*
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Studies in rats have shown that treatment with alendronate during pregnancy was associated with dystocia in dams during parturition that was related to hypocalcaemia. Fetuses from rats given high doses showed an increased incidence of incomplete ossification. The relevance to humans in unknown.

## 6. PHARMACEUTICAL PARTICULARS

### *6.1 List of excipients*
Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Magnesium stearate
Povidone (K29 – 32)

### *6.2 Incompatibilities*
Not applicable.

### *6.3 Shelf life*
2 years.

### *6.4 Special precautions for storage*
There are no special storage instructions.

### *6.5 Nature and contents of container*
Pack Types: PVC / Aluminium Blisters.
Pack Sizes: 4.

### *6.6 Special precautions for disposal*
No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

Prostrakan Limited,
Galabank Business Park,
Galashiels,
TD1 1QH,
United Kingdom.

## 8. MARKETING AUTHORISATION NUMBER(S)

PL 16508/0024

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/12/2006

## 10 DATE OF REVISION OF THE TEXT

05/12/2006

# PATIENT INFORMATION LEAFLET

# Ostalis® 70 mg Tablets

ProStrakan

Alendronic Acid

**Read all of this leaflet carefully before you start taking this medicine.**
- Keep this leaflet. You may want 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 gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist

**In this leaflet:**



## 1. WHAT OSTALIS 70 mg TABLETS ARE AND WHAT THEY ARE USED FOR

Your medicine is in the form of a tablet. Alendronic acid belongs to a group of medicines called bisphosphonates. Bisphosphonates can be used to help bone disease such as osteoporosis. Alendronic acid can treat and prevent osteoporosis in post-menopausal women, by stopping bones becoming thin and weak.

## 2. BEFORE YOU TAKE OSTALIS 70 mg TABLETS

**Do not take Ostalis 70 mg Tablets if:**
- you are allergic to alendronic acid or any of the tablet ingredients
- you have problems with your food pipe (oesophagus) causing difficulty swallowing
- you know you have very low calcium levels in your blood (hypocalcaemia)
- you are unable to stand or sit upright for at least 30 minutes.

**Take special care with Ostalis 70 mg Tablets**
Tell your doctor or pharmacist if:
- you have difficulty swallowing or have digestive or gut problems
- you have had stomach or gut ulcers in the past year
- you have had stomach or gut surgery in the past year
- your dietary intake of Vitamin D and calcium is low (foods rich in these include dairy products)
- you have severe kidney problems.

If you are having dental treatment or need dental surgery, tell your dentist you are taking this medicine.

**Taking other medicines:**
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines including medicines obtained without a prescription. This includes in particular, calcium supplements or antacids for indigestion. Wait at least 30 minutes after taking Ostalis 70 mg Tablets before taking any other medicines.

**Taking Ostalis 70 mg Tablets with food and drink:**
If taken at the same time it is likely that food and drink (including mineral water) will interfere with the absorption of Ostalis. Therefore you should take Ostalis 70 mg Tablets with plain water at least 30 minutes before any food or drink.

**Pregnancy and breast-feeding:**
Do not take Ostalis 70 mg Tablets if you are pregnant, planning to become pregnant or you are breast-feeding.

**Driving and using machines:**
Ostalis 70 mg Tablets has no effects on the ability to drive and use machines.

**Important information about some of the ingredients of Ostalis 70 mg Tablets:**
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 OSTALIS 70 mg TABLETS

Always take Ostalis 70 mg Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose is one tablet once weekly. Your doctor will tell you which day of the week to take your tablet.

- Swallow the tablet whole while standing upright. Take with a full glass (not less than

200 mls or 7 fl. oz.) of plain water (not mineral water). Do not chew or let the tablet dissolve in your mouth.
- Take on an empty stomach, as soon as you get out of bed in the morning, before you eat or drink anything. Do not lie down for at least 30 minutes after taking Ostalis 70 mg Tablets.
- Wait at least 30 minutes after swallowing the tablet before you eat, drink or take any other medicines.

**Stop taking this medicine and tell your doctor if you notice:**
- soreness, pain and difficulty swallowing
- pain in the centre of the chest
- heartburn, either new or worse than usual
- ulcers in your mouth and throat.

Ostalis 70 mg Tablets must not be given to children.

**If you take more Ostalis 70 mg Tablets than you should:**
Drink a full glass of milk and contact your doctor or nearest hospital casualty department immediately. Take any remaining tablets and the container with you. Do not make yourself vomit, and do not lie down.

**If you forget to take Ostalis 70 mg Tablets:**
Take the tablet on the morning after you remember. Do not take two tablets on the same day but return to taking one tablet once a week, on the day instructed by your doctor.

**If you stop taking Ostalis 70 mg Tablets:**
Always talk to your doctor or pharmacist before stopping taking Ostalis 70 mg Tablets.

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

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, Ostalis 70 mg Tablets can cause side effects although not everybody gets them.

Tell your doctor if you have pain, swelling or numbness of your jaw or a tooth becomes loose (more likely in patients on chemotherapy or radiation treatment, corticosteroid treatment or those with poor oral hygiene).

Common side effects, occurring in less than one in 10 patients but more than one in 100, include stomach pain or swelling, wind or feeling bloated, constipation or diarrhoea, indigestion, heartburn, blood in the stools, headache and bone, muscle or joint pain, difficulty swallowing, oesophageal ulcer and acid regurgitation.

Uncommon side effects, occurring in less than one in a 100 patients but more than one in 1,000, include feeling or being sick, a sore inflamed stomach, skin rash and red skin.

Rare side effects, occurring in less than one in 1,000 patients but more than one in 10,000, include allergic reactions such as itchy red skin, sensitive skin to light, swelling of the face or lips, feeling wheezy or breathless, red painful eyes, oesophageal stenosis and ulcers in mouth, throat and oesophagus.

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

## 5. HOW TO STORE OSTALIS 70 mg TABLETS

Keep Ostalis 70 mg Tablets out of the reach and sight of children.

**Do not take Ostalis 70 mg Tablets after the expiry date which is stated on the label and blister after "Exp".** The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

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 Ostalis 70 mg Tablets contains:**
Each tablet contains 70 mg of the active ingredient alendronic acid as sodium alendronate. It also contains lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone and magnesium stearate.

**What Ostalis 70 mg Tablets looks like and contents of the pack:**
Ostalis 70 mg Tablets are concave, white and marked 'AD70' on one side and 'G' on the other. Ostalis 70 mg Tablets are available in cartons of 4 tablets. The pharmacist will dispense the number of tablets prescribed by your doctor.

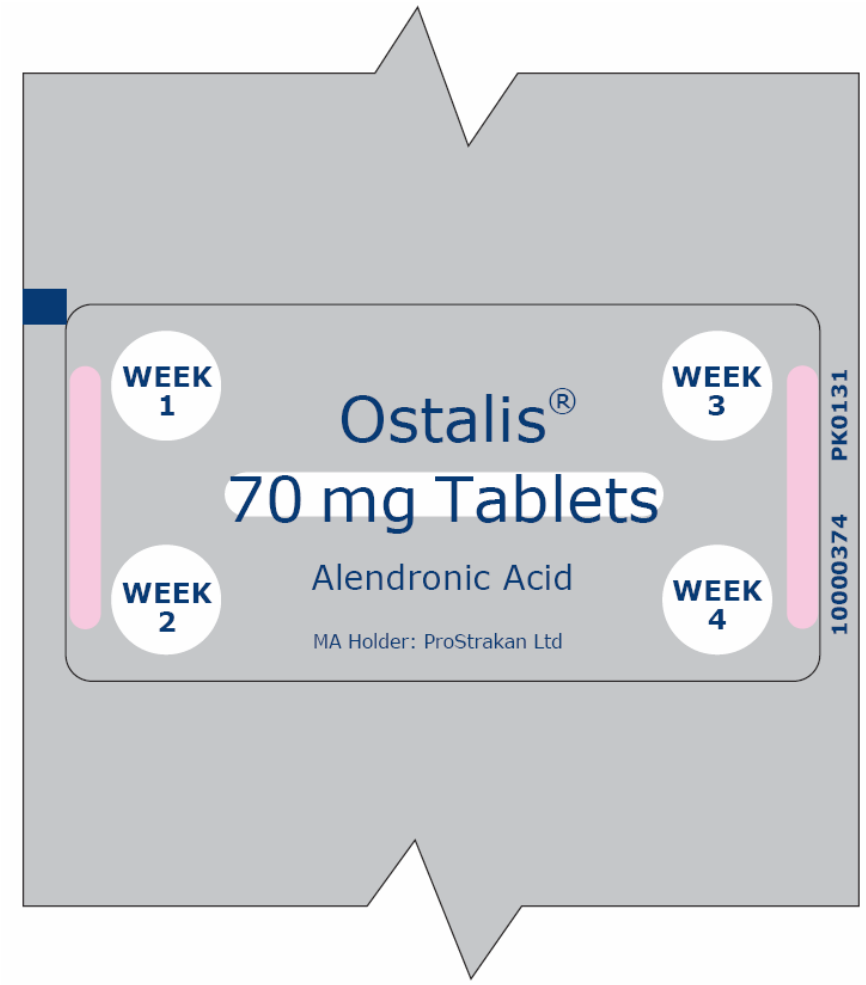
**Marketing Authorisation holder:**
ProStrakan Ltd, Galabank Business Park, Galashiels, TD1 1QH.

**Manufacturer:**
Generics [UK] Limited, Station Close, Potters Bar, Hertfordshire, EN6 1TL.
McDermott Laboratories Ltd t/a Gerard Laboratories, 35/36 Baldoyle Industrial Estate, Grange Road, Dublin 13, Ireland.

Date of leaflet preparation: October 2006 PG0130 10000410

# LABELLING

**Blister:**



**Carton:**


Ostalis® 70 mg Tablets
Alendronic Acid
4 Tablets in a single blister
ProStrakan
Ostalis® 70 mg Tablets
Alendronic Acid
4 Tablets in a single blister
ProStrakan
PF0129
Dosage: For oral use as directed by the doctor.
Read the package leaflet before use.
Keep out of the reach and sight of children.
PL 16508/0024
10000372 POM
MA Holder:
ProStrakan Ltd, Galabank Business Park, Galashiels, TD1 1QH
4 tablets in a single blister
Each tablet contains: 70 mg of the active ingredient alendronic acid as sodium alendronate. Also contains: lactose.
5 038903 000297 >
Affix Dispensing Label Here
Ostalis® 70 mg Tablets
Alendronic Acid
4 Tablets in a single blister