

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1 NAME OF THE MEDICINAL PRODUCT**

Alendronic Acid 70 mg Film-coated Tablets

### **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film-coated tablet contains 70 mg of alendronic acid (as sodium trihydrate).

For the full list of excipients, see section 6.1.

### **3 PHARMACEUTICAL FORM**

Film-coated tablet.

White, round, biconvex film coated tablet, debossed with "ALN 70" on one side, with a diameter of approximately 10 mm.

### **4 CLINICAL PARTICULARS**

#### **4.1 Therapeutic indications**

Alendronate is indicated in adults for the treatment of post-menopausal osteoporosis.

Alendronate reduces the risk of vertebral and hip fractures.

#### **4.2 Posology and method of administration**

For oral use.

The recommended dose is one 70 mg tablet per week.

*To obtain satisfactory absorption of alendronate*

Alendronic Acid must be taken on an empty stomach immediately on rising in the morning, with plain water only, at least 30 minutes before the first food, drink or other medication of the day. Other drinks (including mineral water),

food and some medicines are likely to reduce the absorption of alendronate (see section 4.5).

*To assist delivery to the stomach and thus reduce the risk of irritation/side effects locally and in the oesophagus (see section 4.4).*

- Alendronic Acid should only be swallowed on arising for the day with a whole glass of water (not less than 200 ml or 7 fl. oz).
- Alendronic Acid should be swallowed whole. The tablets should not be chewed, sucked or allowed to dissolve in the mouth on account of the risk of oropharyngeal ulceration.
- Patients should not lie down until after the first meal of the day, which must be at least 30 minutes after taking the tablet.
- Patients should not lie down within 30 minutes of taking Alendronic Acid.
- Alendronic Acid should not be taken at bedtime or before arising for the day.

The optimal duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of alendronate on an individual patient basis, particularly after 5 or more years of use.

Patients should be given a calcium and vitamin D supplement if the diet is inadequate (see section 4.4).

#### *Elderly*

In clinical trials there was no age-related difference with regard to efficacy or safety profiles of alendronate. Therefore no adjustment of the dose is necessary for elderly patients.

*Renal function:* No dose adjustment is necessary in patients with a glomerular filtration rate (GFR) greater than 35 ml/min. Alendronate is not recommended for patients with impaired renal function if the GFR is less than 35 ml/min, as there is no experience of this.

#### *Hepatic function*

No dose adjustment is necessary.

*Use in children (Under 18 years):* Alendronate has been studied in a small number of patients with osteogenesis imperfecta under 18 years of age. Results are insufficient to support its use in children. Alendronic acid has not been investigated in the treatment of glucocorticoid –induced osteoporosis.

### 4.3 Contraindications

- Oesophageal abnormalities and other factors that delay oesophageal emptying, such as stricture or achalasia.
- Inability to stand or sit upright for at least 30 minutes.
- Hypersensitivity to the active substance or to any of the excipients.
- Hypocalcaemia.

### 4.4 Special warnings and precautions for use

#### Upper gastrointestinal adverse reactions

Alendronate can cause local irritation to the upper gastrointestinal mucosa. As there is a risk of worsening of the underlying disease, caution should be observed if alendronate is given to patients with active upper gastrointestinal tract problems, such as dysphagia, oesophageal disease, gastritis, duodenitis or ulcers, or in cases of recent (during the last year) severe gastrointestinal disease such as gastric ulcer, active gastrointestinal bleeding or surgery in the upper gastrointestinal tract other than pyloroplasty (see section 4.3). In patients with known Barrett's oesophagus, prescribers should consider the benefits and potential risks of alendronate on an individual patient basis.

Oesophageal side effects (in some cases severe and requiring hospitalisation) such as oesophagitis, oesophageal ulcers or oesophageal erosions, in rare cases followed by oesophageal stricture, have been reported in patients receiving treatment with alendronate. The physician should therefore be alert to any signs or symptoms of possible oesophageal reaction. The patients should be instructed to discontinue alendronate and seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain or new/worsened heartburn.

The risk of severe oesophageal side effects is thought to be greater in patients who do not take alendronate correctly and/or continue to take alendronate after developing symptoms indicative of oesophageal irritation. It is very important that complete administration instructions are given to, and understood, by the patient (see section 4.2). Patients should be informed that the risk of oesophageal problems may increase if they do not follow these instructions.

Despite no increased risk having been observed in extensive clinical trials, there have been post-marketing reports of rare cases of gastric and duodenal ulcers, some of them severe and with complications.

#### Osteonecrosis of the jaw

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 and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates.

The following risk factors should be considered when evaluating an individual's risk of developing osteonecrosis of the jaw:

- potency of the bisphosphonate (highest for zoledronic acid), route of administration (see above) and cumulative dose
- cancer, chemotherapy, radiotherapy, corticosteroids, angiogenesis inhibitors, smoking
- a history of dental disease, poor oral hygiene, periodontal disease, invasive dental procedures and poorly fitting dentures.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with oral bisphosphonates in patients with poor dental status.

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While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate 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.

During bisphosphonate treatment, all patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain or swelling.

#### Osteonecrosis of the external auditory canal

Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections.

#### Musculoskeletal pain

Bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. In post-marketing experience, these symptoms have rarely been severe and/or incapacitating (see section 4.8). The time to onset of

symptoms varied from one day to several months after starting treatment. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when re-challenged with the same drug or another bisphosphonate.

#### Atypical fractures of the femur

Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment.

During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.

#### Skin reactions

In post-marketing experience, there have been rare reports of severe skin reactions including Stevens Johnson syndrome and toxic epidermal necrolysis.

#### Missed dose

If patients forget to take a dose of Alendronic Acid, they should be instructed to take the tablet the morning after they remember. They must not take two tablets on the same day, but should revert to taking one tablet per week, as originally scheduled on their chosen day.

#### Renal impairment

Alendronate is not recommended for patients with impaired renal function if the creatinine clearance is less than 35 ml/min (see section 4.2).

#### Bone and mineral metabolism

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

Hypocalcaemia must be corrected before treatment with alendronate is initiated (see section 4.3). Other disorders of mineral metabolism (such as vitamin D deficiency and hypoparathyroidism) should also be effectively treated before starting alendronate. In patients with these conditions serum calcium and symptoms of hypocalcaemia should be monitored during treatment with alendronate.

On account of the positive effects of alendronate on the increase in bone mineralisation, reductions in serum calcium and serum phosphate may occur especially in patients taking glucocorticoids in whom calcium absorption may be decreased. These are usually slight and asymptomatic. However, in rare cases symptomatic hypocalcaemia has been reported which occasionally has been severe and often occurred in patients with predisposing conditions (e.g. hypoparathyroidism, vitamin D deficiency and in cases of calcium malabsorption).

It is therefore particularly important to ensure that patients taking glucocorticoids have an adequate calcium and vitamin D intake.

Alendronic Acid contains sodium.

This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

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

If taken at the same time, it is likely that foods and drinks (including mineral water), calcium supplements, antacids and some oral medicines will affect the absorption of alendronate. Patients must therefore wait for at least 30 minutes after taking alendronate before taking any other oral medicine (see section 4.2).

No other clinically significant drug interactions are expected. A number of patients in the clinical trials received oestrogen (intravaginally, transdermally or orally) concomitantly with alendronate. No undesirable effects could be related to the combination treatment.

No specific interaction studies have been carried out, but alendronate was used in clinical trials concomitantly with a number of other commonly prescribed medicines without any evidence of clinically unfavourable interactions.

#### **4.6 Fertility, pregnancy and lactation**

There are no or limited amount of data from the use of alendronate in pregnant women. Studies in animals have shown reproductive toxicity.

. Alendronate given to pregnant rats caused hypocalcaemia-related dystocia (see section 5.3). Alendronate should not be used during pregnancy.

### *Use during lactation*

It is not known whether alendronate/metabolites is excreted into breast milk in humans. A risk to the newborns/infants cannot be excluded. Alendronate should not be used by breast-feeding women.

### Fertility

Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use (see section 5.2). There are no data on foetal risk in humans. However, there is a theoretical risk of foetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied.

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

Alendronate has no or negligible direct influence on the ability to drive and use machines.

## **4.8 Undesirable effects**

### Summary of the safety profile

In a one-year study in post-menopausal women with osteoporosis the overall safety profiles for alendronate once-weekly tablets (n=519) and alendronate 10 mg daily (n=370) were similar.

In two three-year studies of almost identical design, with post-menopausal women (alendronate 10 mg: n=196; placebo: n= 397) the overall safety profiles for alendronate 10 mg daily and placebo were similar.

Undesirable effects reported by the investigators as possibly, probably or definitely related to the drug are presented below if they occurred in  $\geq 1$  % of any in the treatment groups in the one-year study or in  $\geq 1$  % of the patients who were treated with alendronate 10 mg per day and with an incidence higher than in patients who were treated with placebo in three-year

The following undesirable effects have also been reported in clinical trials and/or post marketing:

*The one-year study*

*Three-year studies*

	Alendronate once-weekly tablet (n=519) %	Alendronate 10 mg daily (n=370) %	Alendronate 10 mg daily (n=196) %	Placebo (n=397) %
<i>Gastrointestinal</i>				
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
<i>Musculoskeletal</i>				
Musculoskeletal pain (bone, muscle or joints)	2.9	3.2	4.1	2.5
Muscle cramps	0.2	1.1	0.0	1.0
<i>Neurological</i>				
Headache	0.4	0.3	2.6	1.5

The following undesirable effects have also been reported in clinical trials and/or post marketing:

Frequencies are defined as:

Very common: ( $\geq 1/10$ )

Common: ( $\geq 1/100$  to  $< 1/10$ )

Uncommon: ( $\geq 1/1,000$  to  $< 1/100$ )

Rare: ( $\geq 1/10,000$  to  $< 1/1,000$ )

Very rare: ( $< 1/10,000$ ),

Nervous system disorders:

*Common:* Headache

Eye disorders:

*Rare:* Uveitis, scleritis, episcleritis

Gastrointestinal disorders:

*Common:* Abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcers\*, dysphagia\*, abdominal distension, acid regurgitation.

*Uncommon:* Nausea, vomiting, gastritis, oesophagitis\* oesophageal erosions\*, melaena.

*Rare:* Oesophageal stricture\*, oropharyngeal ulceration\*, upper gastrointestinal PUB (perforations, ulcers, bleeding)<sup>§</sup> (see section 4.4).

\*See sections 4.2 and 4.4.

Skin and subcutaneous tissue disorders:

*Uncommon:* rash, pruritus, erythema.

*Rare:* rash with photosensitivity.

*Very rare:* Isolated cases of severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Musculoskeletal and connective tissue disorders:

*Common:* Musculoskeletal (bone, muscle or joint) pain

*Rare:* Osteonecrosis of the jaw<sup>§</sup> 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; severe musculoskeletal (bone, muscle or joint) pain (see section 4.4).

*During post-marketing experience the following reactions have been reported (frequency rare):*

Atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction)

Metabolism and nutrition disorders:

*Rare:* Symptomatic hypocalcaemia, generally in connection with predisposing conditions (see section 4.4).

*Very rare:* osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)

General disorders and administration site conditions:

*Rare:* Transient symptoms as in an acute phase reaction (myalgia, malaise and in rare cases fever) usually in connection with the start of treatment.

Immune system disorders:

*Rare:* hypersensitivity reactions including urticaria and angioedema.

During post-marketing experience the following reactions have been reported (frequency unknown):

Nervous system disorders:

Dizziness

Ear and labyrinth disorders:

Vertigo

Musculoskeletal and connective tissue disorders:

Joint swelling

General disorders and administration site conditions

Asthenia, peripheral oedema

During post-marketing experience the following reactions have been reported (frequency rare):

Atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction)

*Laboratory values:* In clinical trials, asymptomatic, slight and transient decreases in serum calcium and serum phosphate were observed in approx. 18 and 10 % respectively of the patients taking alendronate 10 mg/day versus 12 and 3 % respectively of those taking placebo. However, the incidence of reductions in serum calcium to < 8.0 mg/dl (2.0 mmol/l) and serum phosphate to ≤ 2.0 mg/dl (0.65 mmol/l) was comparable in the two groups.

## **4.9 Overdose**

### Symptoms

Hypocalcaemia, hypophosphataemia and upper gastrointestinal side effects such as upset stomach, heartburn, oesophagitis, gastritis or ulcer can occur on oral overdosage.

## Management

There is no specific information available on the treatment of overdosage with alendronate. Milk or antacids should be given in order to bind alendronate. On account of the risk of oesophageal irritation, vomiting should not be induced and the patient should be kept in an upright position.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for treatment of bone diseases, bisphosphonates.

ATC code: M05BA04

The active substance in Alendronic Acid, sodium alendronate trihydrate, is a bisphosphonate that inhibits osteoclastic bone resorption without any direct effect on bone formation. Preclinical studies have demonstrated a preference for localisation of alendronate to sites where active resorption takes place. Osteoclastic activity is inhibited but formation and binding of the osteoclasts is not affected. Bone formed during treatment with alendronate is of normal quality.

#### *Treatment of post-menopausal osteoporosis*

**Osteoporosis is defined as bone mineral density (BMD) of the spine or hip 2.5 standard deviations below the mean value of a normal young population or as a previous fragility fracture, irrespective of BMD.**

The therapeutic equivalence of alendronate once-weekly tablets (n=519) and alendronate 10 mg daily (n=370) was demonstrated in a one-year multicentre study in post-menopausal women with osteoporosis. The mean increase from baseline of BMD in the lumbar spine after one year was 5.1 % (95 % confidence interval: 4.8, 5.4 %) in the group receiving 70 mg once per week and 5.4 % (95 % confidence interval: 5.0, 5.8 %) in the group receiving 10 mg daily. The average increases in BMD in the group receiving 70 mg once per week and in the group receiving 10 mg daily were 2.3 % and 2.9 % in the femoral neck and 2.9 % and 3.1 % at the total hip. The two treatment groups were also similar with regard to increased bone density in other parts of the skeleton.

The effects of alendronate on BMD and fracture incidence in post-menopausal women were studied in two initial efficacy studies of identical design (n=994), and in the *Fracture Intervention Trial* (FIT: n=6459).

In the initial efficacy studies, the increases in BMD with alendronate 10 mg daily relative to placebo after three years were 8.8 %, 5.9 % and 7.8 % at the spine, femoral neck and trochanter respectively. Total body BMD also increased significantly. In the patients treated with alendronate, the proportion of patients who suffered one or more vertebral fractures was reduced by 48 % (alendronate 3.2 % versus placebo 6.2 %). In the two-year extensions of these studies the BMD in the spine and trochanter continued to increase. In addition, BMD at the femoral neck and total body was maintained.

The FIT study included two placebo-controlled trials in which alendronate was given daily (5 mg daily for two years and 10 mg daily for a further one or two years).

- FIT 1: A three-year study with 2027 patients who had had at least one baseline vertebral (compression) fracture. In this study alendronate daily reduced the incidence of  $\geq 1$  new vertebral fracture by 47 % (alendronate 7.9 % versus placebo 15.0 %). In addition, a statistically significant reduction in the incidence of hip fractures was confirmed (1.1 % versus 2.2 %, a reduction of 51 %).
- FIT 2: A four-year study with 4432 patients who had a low bone mass but had not had any vertebral fracture at the start of the study. In this study, in a subgroup analysis of osteoporotic women (37 % of the total population who fulfilled the definition of osteoporosis given above) a significant difference was seen in the incidence of hip fractures (alendronate 1.0 % versus placebo 2.2 %, a reduction of 56 %) and in the incidence of  $\geq 1$  vertebral fracture (2.9 % versus 5.8 %, a reduction of 50 %).

### 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 alendronate 10 mg/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  $\leq 2.0$  mg/dl (0.65 mmol/l) were similar in both treatment groups.

## **5.2 Pharmacokinetic properties**

### *Absorption*

Compared with an intravenous reference dose, the mean oral bioavailability of alendronate in women was 0.64 % for doses ranging from 5 to 70 mg given after an overnight fast and two hours before a standardised breakfast. Bioavailability decreased to an estimated 0.46 % and 0.39 % when alendronate was given an hour or half an hour before a standardised breakfast. In osteoporosis studies alendronate was effective when it was given at least 30

minutes before the first meal or drink of the day. Bioavailability was negligible irrespective of whether alendronate was given together with or up to two hours after a standardised breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approx. 60 %. In healthy persons, oral prednisolone (20 mg three times daily for five days) did not result in any clinically meaningful change in the oral bioavailability of alendronate (a mean increase ranging from 20 % to 44 %).

#### *Distribution*

Studies in rats show that alendronate is initially distributed to soft tissues after intravenous administration of 1 mg/kg, but is then rapidly redistributed to the skeleton 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 alendronate is metabolised in animals or humans.

#### *Elimination*

Following a single intravenous dose of (<sup>14</sup>C) alendronate, 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 intravenous dose of 10 mg, the renal clearance of alendronate was 71 ml/min, and systemic clearance did not exceed 200 ml/min. Plasma concentrations fell by more than 95% within 6 hours following intravenous administration. The terminal half-life in humans is estimated to exceed ten years, reflecting release of alendronate from the skeleton. Alendronate is not excreted through the acidic or basic transport systems of the kidney in rats, and thus it is not thought to interfere with the excretion of other drugs by those systems in humans.

#### Renal impairment

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 alendronate via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function (see section 4.2).

### **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Studies in female rats showed that treatment with alendronate during

pregnancy was associated with dystocia during parturition, which was related to hypocalcaemia. Studies in which rats were given high doses showed an increased incidence of incomplete foetal bone formation. The relevance for humans is unknown.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Microcrystalline cellulose

Colloidal anhydrous silica

Croscarmellose sodium

Magnesium stearate

Carrageenan

Macrogol

### **6.2 Incompatibilities**

Not applicable

### **6.3 Shelf life**

3 years

### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions

### **6.5 Nature and contents of container**

The film-coated tablets are packed in OPA-Aluminium-PVC/Aluminium blister and inserted in a carton

Pack sizes:

Blister: 2, 4, 6, 8, 12, 14 film-coated tablets

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**7 MARKETING AUTHORISATION HOLDER**

Sandoz Limited  
Maxis 1  
Western Road  
Bracknell  
United Kingdom  
RG12 1RF

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 04416/0801

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

11/07/2008

**10 DATE OF REVISION OF THE TEXT**

03/07/2025