1. NAME OF THE MEDICINAL PRODUCT

Alendronic Acid 10 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg alendronic acid (as sodium monohydrate).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
White to off-white, round biconvex tablet, debossed with "T" on one side and "10" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

– Treatment of osteoporosis in post-menopausal women.
  Alendronate reduces the risk of vertebral and hip fractures.
– Treatment of osteoporosis in men.
  Alendronate reduces the risk of vertebral fractures.

4.2. Posology and method of administration

For oral use

The recommended dosage is 10 mg once a 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 alendronic acid on an individual patient basis, particularly after 5 or more years of use.

To permit adequate absorption of alendronate

Alendronate 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 alendronate (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):

– Alendronate should only be swallowed upon rising for the day in the morning with a full glass of plain water (not less than 200 ml or 7 fl.oz.).
– Patients should only swallow alendronate whole. Patients should not crush or chew the tablet or allow the tablet to dissolve in their mouths because of a potential for oropharyngeal ulceration.
– Patients should not lie down [should stay upright (sitting or standing up)] 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 alendronate.
– Alendronate should not be taken at bedtime or before rising for the day.

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

Elderly

In clinical studies there was no age-related difference in the efficacy or safety profiles of alendronate. There is therefore no need to reduce dosage for the elderly.

Renal impairment

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

Paediatric population

Alendronate sodium is not recommended for use in children under the age of 18 years due to insufficient data on safety and efficacy in conditions associated with paediatric osteoporosis (also see section 5.1).

4.3. Contraindications

Hypersensitivity to the active substance, other bisphosphonates, or to any of the excipients listed in section 6.1
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.
Hypocalcaemia.
See also section 4.4.

4.4. Special warnings and precautions for use

Alendronate can cause local irritation of the upper gastro-intestinal mucosa. Because there is a potential for worsening of the underlying disease, caution should be exercised when alendronate is 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). In patients with known Barrett's oesophagus, prescribers should consider the benefits and potential risks of alendronate on an individual patient basis.

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

The risk of severe oesophageal adverse events appears to be greater in patients who fail to take alendronate properly and/or who continue to take alendronate 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. A causal relationship cannot be ruled out.

Alendronate 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 alendronate (see section 4.3). Other disorders affecting mineral metabolism (such as vitamin D deficiency and hypoparathyroidism) should also

be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcaemia should be monitored during therapy with alendronate.

Due to the positive effects of alendronate in increasing bone mineral, decreases in serum calcium and phosphate may occur especially in patients taking glucocorticoids in whom calcium absorption may be decreased. These are usually small and asymptomatic. However, there have been rare reports of symptomatic hypocalcaemia, which have occasionally been severe and often occurred in patients with predisposing conditions (eg hypoparathyroidism, vitamin D deficiency and calcium malabsorption).

Ensuring adequate calcium and vitamin D intake is particularly important in patients receiving glucocorticoids.

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 rechallenged with the same drug or another bisphosphonate.
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.

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 osteroporosis 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, 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.
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 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.

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

Patients should be instructed that if they miss a dose of alendronate, 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 day, as originally scheduled.

Excipient

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per 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 food and beverages (including mineral water), calcium supplements, antacids, and some oral medicinal products will interfere with absorption of alendronate. Therefore, patients must wait at least 30 minutes after taking alendronate 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 alendronate. No adverse experiences attributable to their concomitant use were identified.

Since NSAID use is associated with gastrointestinal irritation, caution should be used during concomitant use with alendronate.
Although specific interaction studies were not performed, in clinical studies alendronate was used concomitantly with a wide range of commonly prescribed medicinal products without evidence of clinical adverse interactions.

4.6. Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

It is not known whether alendronate is excreted into human breast milk. Alendronate should not be used by breast-feeding women.

4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, certain adverse reactions that have been reported with alendronate may affect some patients' ability to drive or operate machinery. Individual responses to alendronate may vary (see section 4.8).

4.8. Undesirable effects

Alendronate has been studied in nine major clinical studies (n=5,886). In the longest running trials in post-menopausal women, up to five years' experience has been accumulated. Two years' safety data is available in men with osteoporosis.

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

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

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 alendronate 10 mg/day and at a greater incidence than in patients given placebo in the three-year studies:

	One-Year Study		**Three-Year Studies**	
	Alendronate once weekly 70 mg (n=519) %	Alendronate 10 mg/day (n=370) %	Alendronate 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 distention	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) pain	2.9	3.2	4.1	2.5
- muscle cramp	0.2	1.1	0.0	1.0
Neurological				
- Headache	0.4	0.3	2.6	1.5

Tabulated list of adverse reactions

The following adverse events have been reported in clinical studies and/or after the marketing of alendronate:

The frequencies of adverse events are ranked according to the following: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Immune system disorders	
Rare	Hypersensitivity reactions including urticaria and angioedema
Nervous system disorders	
Common	Headache, dizziness†
Uncommon	Dysgeusia†
Metabolism and nutrition disorders	
Rare	Symptomatic hypocalcaemia, occasionally severe, often in association with predisposing conditions§
Eye disorders	
Uncommon	Eye inflammation (uveitis, scleritis, episcleritis)
Ear and labyrinth disorders	
Common	Vertigo†
Gastrointestinal disorders	
Common	Abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer*, dysphagia*, abdominal distension, acid regurgitation
Uncommon	Nausea, vomiting, gastritis, oesophagitis*, oesophageal erosions*, melaena†
Rare	Oesophageal stricture*, oropharyngeal ulceration*, upper gastrointestinal PUBs (perforation, ulcers, bleeding)§, although the causal relationship has not been established
Skin and subcutaneous tissue disorders	
Common	Alopecia†, pruritus†
Uncommon	Rash, erythema
Rare	Rash with photosensitivity, severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis‡
Musculoskeletal and connective tissue disorders	
Very common	Musculoskeletal (bone, muscle or joint) pain which is sometimes severe† §
Common	Joint swelling†
Rare	Osteonecrosis of the jaw‡ §, atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction)⊥
Very rare	Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)
General disorders and administration site conditions	
Common	Asthenia†, peripheral oedema†
Uncommon	Transient symptoms as in an acute-phase response (myalgia, malaise and rarely fever), typically in association with initiation of treatment. †

§see section 4.4
† frequency in clinical trials was similar in the drug and placebo group.
*see sections 4.2 and 4.4
‡this adverse reaction was identified through post-marketing surveillance. The frequency of rare was estimated based on relevant clinical trials
⊥identified in postmarketing experience.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9. Overdose

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

No specific information is available on the treatment of overdosage with alendronate. Milk or antacids should be consumed in order to bind alendronate. 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: Drugs for treatment of bone diseases, bisphosphonates
ATC code: M05B A04

Alendronate is an amino-bisphosphonate, which in animal studies was deposited among the osteoclasts in areas with bone resorption. It inhibits bone resorption with no direct effect on bone formation. Since bone resorption and bone formation are coupled, bone formation is also reduced, but to a lesser extent than resorption, resulting in a progressive increase in bone mass, with normal bone structure. Alendronate is stored in the bone matrix, where it is pharmacologically inactive.

In rats the lowest dose of alendronate which influenced bone mineralisation (leading to osteomalacia) was 6000 times greater than the antiresorptive dose. This data indicates that alendronate administered in therapeutic doses is most unlikely to induce osteomalacia.

Osteoporosis in post-menopausal women

Alendronate treatment of post-menopausal women produces biochemical changes which indicate dose-dependent inhibition of bone resorption.

In investigations lasting up to 5 years, 10 mg/day alendronate for 3-6 months, reduced the biochemical markers for bone resorption by approx. 50-70% to a level corresponding to that seen in healthy pre-menopausal women. The markers of bone formation were similarly reduced by 25-50% after 6-12 months. The new plateau for bone resorption and bone formation was maintained for the rest of the period of alendronate treatment.

Effect on bone mineral density

In clinical studies, 10 mg alendronate once a day for 3 years produced an increase in bone mineral density (BMD) in post-menopausal women with osteoporosis. After three years treatment with 10 mg alendronate once a day there was an increase (compared with placebo) in BMD of approx. 8.8% in the lumbar spine, 5.9% in the femoral neck, 7.8% in the trochanter, 2.2% in the forearm and 2.5% in the whole body. In the 2-year extension of these studies, treatment with 10 mg alendronate once a day lead to continued increase in BMD in the spinal column and trochanter (further absolute increase between years 3 and 5: spinal column, 0.94%, trochanter 0.88%,). BMD in the femoral neck, forearm and whole body was maintained.

The effect of alendronate was the same regardless of age, race, initial rate of bone turnover, kidney function and use together with a wide-ranging assortment of other medicinal products.

After withdrawal of alendronate after 1-2 years' therapy, neither further increase in bone mass, nor accelerated bone loss was observed. This data indicates that daily treatment with alendronate has to be continued in order to produce progressive increase in bone mass.

Effect on incidence of fracture

Alendronate produced the same reduction of incidence in both vertebral and non-vertebral fractures in patients who have had no previous fractures and those with previous vertebral fractures.

Analysis of 3 years' pooled data from the two largest treatment studies in which various doses of alendronate were administered to post-menopausal women, yielded the following results: 48% reduction in the proportion of patients who experienced one or several vertebral fractures (alendronate 3.2% v. placebo 6.2%). In patients who did have vertebral fracture, the loss in height was less in those who were treated with alendronate (5.9mm v. 23.3mm). Pooled data from 5 studies of 2-3 years' duration showed 29% reduction in the number of non-vertebral fractures (alendronate 9.0% v. placebo 12.6%).
Three years' treatment with alendronate (5 mg/day for the first 2 years, 10 mg/day for the 3rd year) in post-menopausal women with osteoporosis (who had had at least one crush fracture of the spinal vertebrae) led to reduction of incidence of fracture as follows:
Ratio of patients who experienced at least one new vertebral fracture (alendronate 8.0% v. placebo 15.0%, a reduction of 47%); at least two new vertebral fractures (0.5% v. 4.9%, a reduction of 90%); any clinical (i.e. painful) fracture (13.7% v. 18.3%, a reduction of 28%); hip fracture (1.1% v. 2.2%, a reduction of 51%); and wrist (forearm) fracture (2.2% v. 4.1%, a reduction of 48%).

Bone histology

Bone histology in 270 post-menopausal women with osteoporosis treated with alendronate at doses from 1-20 mg/day for 1-3 years showed normal mineralisation and structure as well as the expected decrease in bone turnover relative to placebo.

Prevention of post-menopausal osteoporosis

The effects of alendronate to prevent bone loss were examined in two studies of post-menopausal women aged ≤60 years. In the larger study of 1,609 women (≥6 months post-menopausal) those receiving alendronate 5 mg daily for two years had BMD increases of 3.5%, 1.3%, 3.0% and 0.7% at the spine femoral neck, trochanter and total body, respectively. In the smaller study (n=447), similar results were observed in women (6 to 36 months post-menopausal) treated with alendronate 5 mg daily for three years. In contrast, in both studies, women receiving placebo lost bone mass at a rate of approximately 1% per year. The longer term effects of alendronate in an osteoporosis prevention population are not known but clinical trial extensions of up to 10 years of continuous treatment are currently in progress.

Concomitant use with oestrogen/hormone replacement therapy (HRT)

The effects on BMD of treatment with alendronate 10 mg once-daily and conjugated oestrogen (0.625 mg/day) either alone or in combination were assessed in a two-year study of hysterectomised, post-menopausal, osteoporotic women. At two years, the increases in lumbar spine BMD from baseline were significantly greater with the combination (8.3%) than with either oestrogen or alendronate alone (both 6.0%).

The effects on BMD when alendronate was added to stable doses (for at least one year) of HRT (oestrogen ± progestin) were assessed in a one-year study in post-menopausal, osteoporotic women. The addition of alendronate 10 mg once-daily to HRT produced, at one year, significantly greater increases in lumbar spine BMD (3.7%) vs. HRT alone (1.1%).

In these studies, significant increases or favourable trends in BMD for combined therapy compared with HRT alone were seen at the total hip, femoral neck and trochanter. No significant effect was seen for total body BMD.

Osteoporosis in men

The efficacy of alendronate 10 mg once daily in men (ages 31 to 87; mean, 63) with osteoporosis was demonstrated in a two-year study. At two years, the mean increases relative to placebo in BMD in men receiving alendronate 10 mg/day were: lumbar spine, 5.3%; femoral neck, 2.6%; trochanter, 3.1%; and total body, 1.6%. Alendronate was effective regardless of age, race, gonadal function, baseline rate of bone turnover, or baseline BMD. Consistent with much larger studies in post-menopausal women, in these 127 men, alendronate 10 mg/day reduced the incidence of new vertebral fracture (assessed by quantitative radiography) relative to placebo (0.8% vs. 7.1%) and, correspondingly, also reduced height loss (-0.6 vs. -2.4 mm). The effect on hip fractures has not been established.

Glucocorticoid-induced osteoporosis

The efficacy of alendronate 5 and 10 mg once daily in men and women receiving at least 7.5 mg/day of prednisone (or equivalent) was demonstrated in two studies. At two years of treatment, spine BMD increased by 3.7% and 5.0% (relative to placebo) with alendronate 5 and 10 mg/day respectively. Significant increases in BMD were also observed at the femoral neck, trochanter, and total body. In post-menopausal women not receiving HRT, greater increases in lumbar spine and trochanter BMD were seen in those receiving 10 mg alendronate than those receiving 5 mg. Alendronate was effective regardless of dose or duration of glucocorticoid use. Data pooled from three groups (5 or 10 mg for two years or 2.5 mg for one year followed by 10 mg for one year) showed a significant reduction in the incidence of patients with a new vertebral fracture at two years (alendronate 0.7% vs. placebo 6.8).

Risk factors often associated with the development of osteoporosis include thin body build, family history of osteoporosis, early menopause, moderately low bone mass and long-term glucocorticoid therapy, especially with high doses (≥15 mg/day).

Paediatric population:

Alendronate sodium has been studied in a small number of patients with osteogenesis imperfecta under the age of 18 years. Results are insufficient to support the use of alendronate sodium in paediatric patients with osteogenesis imperfecta.

5.2. Pharmacokinetic properties

Absorption

Oral bioavailability of alendronate in women is 0,7% for doses ranging from 5 to 40 mg, when administered after an overnight fast and two hours before a standardised breakfast. Oral bioavailability in men (0.6%) was approx. the same as in women. Bioavailability is reduced by approx. 40%, when alendronate was administered ½ hour to 1 hour before a standardised breakfast. In osteoporosis studies, alendronate was effective when administered at least 30 minutes before the first food or beverage of the day. Bioavailability was negligible if alendronate was taken with or up to two hours after a standard breakfast. Coffee and orange juice reduced bioavailability by approx. 60% (see section 4.2).

In healthy test subjects, oral prednisone (20 mg 3 times daily for 5 days) did not significantly affect the oral bioavailability of alendronate (average increase 20-44%).

Distribution

Protein binding is approx. 78%. Preclinical investigation shows that alendronate is distributed to the soft tissues and then is rapidly redistributed to the bones, where is binds or is eliminated in the urine. The steady-state distribution volume in the soft areas of the body are at least 28 litres (22-35 litres). Plasma concentrations of the active substance after administration of an oral therapeutic dose are below the level of detection (<5 ng/ml).

Biotransformation

Alendronate has no known metabolites.

Elimination

Approx. 50% of ^{14}C-tagged alendronate is excreted in the urine within 72 hours. Very little or no radioactivity was recovered in the faeces. The remainder is deposited in bone tissue, where it is inactive. Renal clearance was 71 ml/minute, systemic clearance did not exceed 200 ml/minute, after a single I.V. dose of 10 mg. Within 6 hours the plasma concentration fell by more than 95% after I.V. administration. This is followed by a slow release of alendronate from the skeleton. The estimated half-life is thus > 10 years.

Alendronate 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 active substances by those systems in humans.

Characteristics in patients

Preclinical investigations show that the active substance, which is not deposited in the bones, is rapidly excreted in the urine. After chronic dosage with cumulative doses I.V., up to 35 mg/kg in animals, no saturation of bone uptake was observed. In animals, elimination of alendronate via the kidneys was reduced in impaired renal function. There is no corresponding information in man, but greater accumulation of alendronate in bone should be anticipated in people with impaired renal function (see section 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 which was related to hypocalcaemia. In studies, rats given high doses showed an increased incidence of incomplete foetal ossification. The relevance to humans is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Low-substituted hyprolose
Hyprolose
Colloidal hydrated silica
Sodium stearyl fumarate

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

PVC/PVdC/Aluminium blister pack containing 14, 28, 30, 50, 56, 84, 90, 98, 112, 140 tablets, 28 tablets in calendar pack, 50 x 1 (individual blisters)

Not all pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

TEVA UK Limited,
Brampton Road
Hampden Park
Eastbourne
East Sussex
BN22 9AG

8. MARKETING AUTHORISATION NUMBER

PL 00289/0703

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07.04.05

10. DATE OF REVISION OF THE TEXT

14/08/2020