SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Alendra 70 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:
Sodium alendronate BP, equivalent to Alendronic acid 70 mg.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM: Tablets.

General physico-chemical properties: White or almost white oval shaped biconvex uncoated tablets plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Alendra is indicated for the treatment of osteoporosis in post-menopausal women to prevent fractures.
Alendra is indicated for the treatment of osteoporosis in men to prevent fractures.
Alendra is indicated for the treatment of glucocorticoid-induced osteoporosis and prevention of bone loss in post-menopausal women considered at risk of developing the disease.
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).

4.2 Posology and method of administration

Posology

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 Alendra on an individual patient basis, particularly after 5 or more years of use.

Treatment of osteoporosis in post-menopausal women: The recommended dosage is 10 mg once a day.

Treatment of osteoporosis in men: The recommended dosage is 10 mg once a day.

Treatment and prevention of glucocorticoid-induced osteoporosis: For post-menopausal women not receiving hormone replacement therapy (HRT) with an oestrogen, the recommended dosage is 10 mg once a day.

Older people

In clinical studies there was no age-related difference in the efficacy or safety profiles of alendronate. Therefore no dosage adjustment is necessary for older people.

Patients with renal impairment

No dosage adjustment is necessary for patients with creatinine clearance greater than 35 ml/min. Alendronate is not recommended for patients with renal impairment where creatinine clearance 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).

Method of administration Oral use.

To permit adequate absorption of alendronate:

Alendra 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):

- Alendra should only be swallowed upon arising for the day with a full glass of water (not less than 200 ml).
- Patients should only swallow Alendra 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 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 Alendra.
- Alendra 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).

4.3 Contraindications

- Hypersensitivity to the active substance 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.

4.4 Special warnings and precautions for use

Upper gastrointestinal adverse reactions

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 used 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 hospitalization), such as oesophagitis, oesophageal ulcers and oesophageal erosions, rarely followed by oesophageal stricture, have been reported in patients receiving alendronate. Physicians should therefore be alert to any signs or symptoms signalling 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, new or worsening heartburn.

The risk of severe oesophageal adverse experiences 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.

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.

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 such as pain or discharge, or 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 rechallenged 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.

Renal impairment

Alendronate is not recommended for patients with renal impairment where 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 and glucocorticoid use 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 Alendra.

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 (e.g. hypoparathyroidism, vitamin D deficiency and calcium malabsorption).

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

Excipients

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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 drug 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.
Concomitant use of HRT (oestrogen ± progestin) and alendronate was assessed in two clinical studies of one or two years duration in post-menopausal osteoporotic women (see section 5.1). Combined use of alendronate and HRT resulted in greater increases in bone mass, together with greater decreases in bone turnover, than seen with either treatment alone. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments.

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

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 during pregnancy in rats caused dystocia related to hypocalcemia (see section 5.3).

Alendra should not be used during pregnancy.

Breast-feeding

It is unknown whether alendronate/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Alendronate should not be used during breast-feeding.

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

Alendra has no or negligible direct influence on the ability to drive and use machines. However, certain adverse reactions that have been reported with alendronate may affect some patients' ability to drive or operate machinery. Individual responses to Alendra may vary (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

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 collected. Two years safety data are available in both men with osteoporosis and men and women on glucocorticoids.
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 Weekly 70 (n = 519) %	Alendronat 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	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 experiences have also been reported during clinical studies and/or post-marketing use:

Frequencies are defined as: Very common *(≥1/10), Common (≥1/100, < 1/10), Uncommon (≥1/1,000, < 1/100), Rare (≥1/10,000, < 1/1,000), Very rare (< 1/10,000 including isolated cases*)

System Organ Class	Frequency	Adverse Experience Term
Immune system disorders	Rare	hypersensitivity reactions including urticaria and angioedema
Metabolism and nutrition disorders:	Rare	symptomatic hypocalcaemia, often in association with predisposing conditions§
Nervous system disorders	Common	headache, dizziness†
	Uncommon	dysgeusia†
Eye disorders	Uncommon	eye inflammation (uveitis, scleritis, episcleritis)
Ear and labyrinth disorders	Common	vertigo†
	Very Rare	osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)
Gastrointestinal disorders	Common	abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer*, dysphagia*, abdominal distension, acid regurgitation
	Uncommon	nausea, vomiting, gastritis, oesophagitis*, oesophageal erosions*, melena†
	Rare	oesophageal stricture*, oropharyngeal ulceration*, upper gastrointestinal PUBs (perforation, ulcers, bleeding) §
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)⊥
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 post marketing 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 EFDA yellow Card Scheme, online at https://primaryreporting.who-umc.org/ET or toll free call 8482 to Ethiopian food and drug authority (EFDA).

4.9 Overdose

Symptoms

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

Management

No specific information is available on the treatment of overdosage with alendronate. Milk or antacids should be given 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: Bisphosphonate, for the treatment of bone diseases

ATC Code: M05B A04

Mechanism of action

Alendronate is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation. The bone formed during treatment with alendronate is of normal quality.

Clinical efficacy and safety

Treatment of post-menopausal osteoporosis

The effects of alendronate 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 alendronate10 mg/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 in the proportion of patients treated with alendronate 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: a three-year study of 2,027 patients who had at least one baseline vertebral (compression) fracture and a four-year study of 4,432 patients with low bone mass but without a baseline vertebral fracture, 37% of whom had osteoporosis as defined by a baseline femoral neck BMD at least 2.5 standard deviations below the mean for young, adult women. In all FIT patients with osteoporosis from both studies, alendronate reduced the incidence of: ≥1 vertebral fracture by 48%, multiple vertebral fractures by 87%, ≥1 painful vertebral fracture by 45%, any painful fracture by 31% and hip fracture by 54%.

Overall these results demonstrate the consistent effect of alendronate to reduce the incidence of fractures, including those of the spine and hip, which are the sites of osteoporotic fracture associated

with the greatest morbidity.

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 alendronate5 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 alendronate10 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 alendronate10 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.

Treatment of osteoporosis in men

The efficacy of alendronate10 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 alendronate10 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).

Glucocorticoid-induced osteoporosis

The efficacy of alendronate5 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 oestrogen, 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 dosage 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 (Alendronate0.7% vs. placebo 6.8%).

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 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.

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 imperfect.

5.2 Pharmacokinetic properties

Absorption

Relative to an intravenous (IV) reference dose, the oral bioavailability of alendronate in women was 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 similar to that in women. Bioavailability was decreased similarly to an estimated 0.46% and 0.39% when alendronate was administered one hour or half an 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 whether alendronate was administered with, or up to two hours after, a standardised breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60%.

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

Distribution

Studies in rats show that alendronate transiently distributes to soft tissues following 1 mg/kg IV 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 alendronate is metabolised in animals or humans.

Elimination

Following a single IV dose of [^{14}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 10 mg IV dose, 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 six hours following IV 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 anticipated to interfere with the excretion of other medicinal products 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 IV 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

In test animal species the main target organs for toxicity were kidneys and gastro-intestinal tract. Renal toxicity was seen only at doses >2 mg/kg/day orally (ten times the recommended dose) and was evident only on histological examination as small widely scattered foci of nephritis, with no evidence of effect on renal function. The gastro-intestinal toxicity, seen in rodents only, occurred at doses >2.5 mg/kg/day and appears to be due to a direct effect on the mucosa. There is no additional relevant information.

Significant lethality after single oral doses was seen in female rats and mice at 552 mg/kg (3,256 mg/m^2) and 966 mg/kg (2,898 mg/m^2) (equivalent to human oral doses* of 27,600 and 48,300 mg), respectively. In males, these values were slightly higher, 626 and 1,280 mg/kg, respectively. There was no lethality in dogs at oral doses up to 200 mg/kg (4,000 mg/m^2) (equivalent to a human oral

dose* of 10,000 mg).

* Based on a patient weight of 50 kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, colloidal anhydrous silica.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C.
Keep all medicines out of reach of children.

6.5 Nature and contents of container <and special equipment for use, administration or implantation

4 tablets are packed in a blister, each blister is packed in a carton envelope along with packaging insert.

6.6 Special precautions for disposal <and other handling>

Not applicable

7. MARKETING AUTHORISATION HOLDER

Kusum Healthcare Pvt. Ltd.

SP-289(A), RIICO Industrial Area, Chopanki, Bhiwadi, Dist. Alwar (Rajasthan) India

8. MARKETING AUTHORISATION NUMBER(S)

04632/07016/NMR/2018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 September 2019

10. DATE OF REVISION OF THE TEXT

08/2023

11. REFERENCES

SmPC published on electronic medicines compendium
https://www.medicines.org.uk/emc#gref

The MHRA published product information
https://products.mhra.gov.uk/

Human medicine European public assessment report

https://www.ema.europa.eu/en/medicines