

1. NAME OF THE MEDICINAL PRODUCT

Lendrate 70 mg, tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 70 mg alendronic acid (as sodium alendronate trihydrate).
This medicinal product contains lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Round, white, biconvex tablets with the inscription “70” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of postmenopausal osteoporosis. Alendronic acid reduces the risk of vertebral and hip fractures.

4.2 Posology and method of administration

The recommended dosage is one 70 mg tablet once weekly.

To permit adequate absorption of alendronate:

Lendrate 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):

- Lendrate should only be swallowed upon arising for the day with a full glass of water (not less than 200 ml or 7 fl.oz.).
- Patients should not chew the tablet or allow the tablet to dissolve in their mouths because of a potential of 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 Lendrate tablets.
- Lendrate 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 alendronate. 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. Alendronate is not recommended for patients with renal impairment where GFR is less than 35 ml/min, due to lack of experience.

Use in children and adolescents: 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 and adolescents.

Lendrate 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 alendronate or to any of the excipients.
- 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 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).

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 signaling 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, generally associated with tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer receiving treatment regimes 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.

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, corticosteroids, 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 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 patients based on individual benefit/risk assessment.

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.

Patients should be instructed that if they miss a dose of Lendrate, 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.

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 Lendrate.

Due to the positive effects of alendronate in increasing bone mineral, decreases in serum calcium and phosphate may occur. 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, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medical 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 section 4.2 and section 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.

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 Pregnancy and lactation

Use during pregnancy

There are no adequate data from the use of alendronate in pregnant women. Animal studies revealed effects on foetal bone formation at high doses.

Alendronate given during pregnancy in rats caused dystocia related to hypocalcaemia (see section 5.3). Given the indication, alendronate should not be used during pregnancy.

Use during lactation

It is not known whether alendronate is excreted into human breast milk. Given the indication, 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.

4.8 Undesirable effects

In a one-year study in post-menopausal women with osteoporosis the overall safety profiles of alendronic acid 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 $\geq 1\%$ in either treatment group in the one-year study, or in $\geq 1\%$ 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	
	Alenronic acid 70 mg (n=519)	Alendronate 10 mg/day (n=370)	Alendronate 10 mg/day (n=196)	Placebo (n=397)
	%	%	%	%
<i>Gastro-intestinal</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 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
<i>Musculoskeletal</i>				
musculoskeletal (bone-, muscle- or joint) pain	2,9	3,2	4,1	2,5
muscle cramp	0,2	1,1	0,0	1,0
<i>Neurological</i>				
headache	0,4	0,3	2,6	1,5

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

[Common ($\geq 1/100$, $< 1/10$), Uncommon ($\geq 1/1000$, $< 1/100$), Rare ($\geq 1/10,000$, $< 1/1000$), Very rare ($< 1/10,000$), not known (cannot be estimated from the available data)]

Immune system disorders:

Rare: hypersensitivity reactions including urticaria and angioedema

Metabolism and nutrition disorders:

Rare: symptomatic hypocalcaemia, often in association with predisposing conditions. (see section 4.4)

Nervous system disorders:

Common: headache

Eye disorders:

Rare: uveitis, scleritis, episcleritis

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)(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 and isolated cases: isolated cases of severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis

Musculoskeletal, connective tissue and bone disorders:

Common: musculoskeletal (bone, muscle or joint) pain

Rare: 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; severe musculoskeletal (bone, muscle or joint) pain (see section 4.4)

General disorders and administration site conditions:

Rare: transient symptoms as in an acute-phase response (myalgia, malaise and rarely, fever) typically in association with initiation of treatment.

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

Nervous system disorders: dizziness

Ear and labyrinth disorders: vertigo

Musculoskeletal, connective tissue and bone disorders:
joint swelling

General disorders and administration site conditions:
asthenia, peripheral oedema

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 ≤ 2.0 mg/dl (0.65 mmol/l) were similar in both treatment groups.

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 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

The active ingredient of Lendrate, 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 alendronate 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 alendronate 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 alendronic acid 70 mg (n=519) and alendronate 10 mg 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 70 mg once-weekly 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 70 mg once weekly and 10 mg daily groups, respectively. The two treatment groups were also similar with regard to BMD increases at other skeletal sites.

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 alendronate 10 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 (alendronate 3.2% vs placebo 6.2%) 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 maintained.

FIT consisted of two placebo-controlled studies using alendronate 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 alendronate daily reduced the incidence of ≥ 1 new vertebral fracture by 47% (alendronate 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 (alendronate 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 alendronate in women was 0.64% for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardized breakfast. Bioavailability was decreased similarly to an estimated 0.46% and 0.39% when alendronate was administered one hour or half an hour before a standardized 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 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 alendronate is metabolized in animals or humans.

Elimination

Following a single intravenous dose of [¹⁴C]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 intravenous 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 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 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 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 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

Cellactose 80 (lactose monohydrate and cellulose, powdered)
Croscarmellose sodium (E468)
Colloidal anhydrous silica (E551)
Magnesium stearate (E470b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 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/Aluminium blisters in packs containing 2, 4 or 12 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavíkurvegur 76-78,
220 Hafnarfjörður,
Iceland

8. MARKETING AUTHORISATION NUMBER

MA628/03801

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/11/2008

10. DATE OF REVISION OF THE TEXT

N/A