Forend tab. 70mg

(alendronate sodium)

■ **COMPOSITION**

Each tablet contains the equivalent of 70mg of alendronic acid as 91.37mg alendronate sodium trihydrate.

■ **APPEARENCE**

This drug are available as oval, white tablets.

■ **INDICATION**

1) Treatment of osteoporosis in postmenopausal women
2) Treatment of osteoporosis in men

■ **DOSAGE & ADMINISTRATION**

The recommended dosage is one 70 mg tablet once weekly. This drug 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. To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation patients should be instructed to swallow each tablet of this drug with a full glass of water (170~230mL). Patients should not lie down and take first food of the day at least 30 minutes after taking the tablet.
Patients should be specifically instructed not to take this drug at bedtime or before arising of the day. Patients should be informed that failure to follow these instructions may increase their risk of esophageal problems. Patients should be instructed that if they miss a dose of this drug once Weekly, they should take one tablet on the next 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.

■ **PRECAUTION**

1. WARNINGS

This drug, like other bisphosphonates, may cause local irritation of the upper gastrointestinal mucosa. Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with this drug. In some cases these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue this drug and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn. The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking this drug and/or who fail to swallow it with the recommended amount of water, and/or who continue to take this drug after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient. In patients who cannot comply with dosing instructions due to mental disability, therapy with this drug should be used under appropriate supervision.Because of possible irritant effects of this drug on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease, caution should be used when this drug is given to patients with active upper gastrointestinal problems (such as dysphagia, esophageal diseases, gastritis, duodenitis, or ulcers). There have been post-marketing reports of gastric and duodenal ulcers, some severe and with complications, although no increased risk was observed in controlled clinical trials.

2. CONTRAINDICATIONS

1) Abnormalities of the esophagus and other factors which delay esophageal emptying such as stricture or achalasia.
2) Inability to stand or sit upright for at least 30 minutes.
3) Hypersensitivity to alendronate
4) Hypocalcaemia. (see PRECAUTIONS, General)

3. ADVERSE REACTIONS

1) In clinical studies of up to five years in duration adverse experiences associated with this drug usually were mild, and generally did not require discontinuation of therapy. This drug has been evaluated for safety in approximately 8000 postmenopausal women in clinical studies.
2) Treatment of osteoporosis in postmenopausal women
(1) In two identically designed, three-year, placebo-controlled, double-blind, multicenter studies (United States and Multinational; n=994), discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with this drug 10 mg/day and 6.0% of 397 patients treated with placebo. In the Fracture Intervention Trial (n=6459), discontinuation of therapy due to any clinical adverse experience occurred in 9.1% of 3236 patients treated with alendronate 5 mg/day for 2 years and 10 mg/day for either one or two additional years and 10.1% of 3223 patients treated with placebo. Discontinuations due to upper gastrointestinal adverse experiences were: this drug, 3.2%; placebo, 2.7%. In these study populations, 49-54% had a history of gastrointestinal disorders at baseline and 54-89% used nonsteroidal anti-inflammatory drugs or aspirin at some time during the studies. Adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either this drug or placebo are presented in the following table.

Osteoporosis Treatment Studies in Postmenopausal Women Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients

Clinical Trial / Adverse reactions	United States/Multinational Studies		Fracture Intervention Trial	
	This drug* % (n=196)	placebo % (n=397)	This drug **% (n=3236)	placebo % (n=3223)
Gastro-intestinal				
abdominal pain	6.6	4.8	1.5	1.5
nausea	3.6	4.0	1.1	1.5
dyspepsia	3.6	3.5	1.1	1.2
constipation	3.1	1.8	0.0	0.2
diarrhea	3.1	1.8	0.6	0.3
flatulence	2.6	0.5	0.2	0.3
acid regurgitation	2.0	4.3	1.1	0.9
esophageal ulcer	1.5	0.0	0.1	0.1
vomiting	1.0	1.5	0.2	0.3
dysphagia	1.0	0.0	0.1	0.1
abdominal distention	1.0	0.8	0.0	0.0
gastritis	0.5	1.3	0.6	0.7
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	4.1	2.5	0.4	0.3
muscle cramp	0.0	1.0	0.2	0.1
Neurogical				
headache	2.6	1.5	0.2	0.2
dizziness	0.0	1.0	0.0	0.1
Special sense				
dysgeusia	0.5	1.0	0.1	0.0

* 10 mg/day for three years
** 5 mg/day for 2 years and 10 mg/day for either 1 or 2 additional years

Rarely, rash and erythema have occurred. One patient treated with alendronate (10 mg/day), who had a history of peptic ulcer disease and gastrectomy and who was taking concomitant aspirin developed an anastomotic ulcer with mild hemorrhage, which was considered drug related. Aspirin and this drug were discontinued and the patient recovered. The adverse experience profile was similar for the 401 patients treated with either 5 or 20 mg doses of this drug in the United States and Multinational studies. The adverse experience profile for the 296 patients who received continued treatment with either 5 or 10 mg doses of alendronate in the two-year extension of these studies (treatment years 4 and 5) was similar to that observed during the three-year placebo-controlled period. During the extension period, of the 151 patients treated with alendronate 10 mg/day, the proportion of patients who discontinued therapy due to any clinical adverse experience was similar to that during the first three years of the study.

(2) In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly alendronate 70 mg and alendronate 10 mg daily were similar. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients in either treatment group are presented in the following table.

Osteoporosis Treatment Studies in Postmenopausal Women Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients

Clinical Trial / Adverse reactions	alendronate 70mg/once weekly%	alendronate 10mg/day %
Gastro-intestinal		
abdominal pain	3.7	3.0
dyspepsia	2.7	2.2
acid regurgitation	1.9	2.4
nausea	1.9	2.4
abdominal distention	1.0	1.4
constipation	0.8	1.6
flatulence	0.4	1.6
gastritis	0.2	1.1
gastric ulcer	0.0	1.1
Musculoskeletal		
musculoskeletal pain (bone, muscle or joint)	2.9	3.2
muscle cramp	0.2	1.1

3) Treatment of osteoporosis in Men

(1) In two placebo-controlled, double-blind, multicenter studies in men (a two-year study of alendronate 10 mg/day and a one-year study of once weekly alendronate 70 mg) the rates of discontinuation of therapy due to any clinical adverse experience were 2.7% for alendronate 10 mg/day vs. 10.5% for placebo, and 6.4% for once weekly alendronate 70 mg vs. 8.6% for placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥2% of patients treated with either alendronate or placebo are presented in the following table.

Osteoporosis Studies in Men Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥2% of Patients

Clinical Trial / Adverse reactions	Two-Year study		One-Year study	
	alendronate 10mg/day% (n=146)	placebo % (n=95)	alendronate 70mg/once weekly % (n=109)	placebo % (n=58)
Gastro-intestinal				
acid regurgitation	4.1	3.2	0.0	0.0
flatulence	4.1	1.1	0.0	0.0
gastroesophageal reflux disease	0.7	3.2	2.8	0.0
dyspepsia	3.4	0.0	2.8	1.7
diarrhea	1.4	1.1	2.8	0.0
abdominal pain	2.1	1.1	0.9	3.4
nausea	2.1	0.0	0.0	0.0

4) The following adverse reactions have been reported in post-marketing use:
(1) Body as a Whole : hypersensitivity reactions including urticaria and rarely angioedema. Transient symptoms of myalgia, malaise and rarely, fever have been reported with this drug, typically in association with initiation of treatment. Rarely, symptomatic hypocalcemia has occurred, generally in association with predisposing conditions.
(2) Gastrointestinal : esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration. Gastric or duodenal ulcers, some severe and with complications have also been reported. Localized osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported rarely.
(3) Musculoskeletal : bone, joint, and/or muscle pain, occasionally severe, and rarely incapacitating.
(4) Skin: rash (occasionally with photosensitivity), pruritus, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.
(5) Special Senses : rarely uveitis, scleritis or episcleritis.

4. PRECAUTIONS

1) General
(1) 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 can not be ruled out.
(2) This drug is not recommended for patients with renal impairment where GFR is less than 35 ml/min.
(3) Causes of osteoporosis other than estrogen deficiency and ageing should be considered.
(4) Hypocalcaemia must be corrected before initiating therapy with this drug. 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 this drug.
(5) Due to 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 reports of symptomatic hypocalcaemia, which occasionally have 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 therefore particularly important in patients receiving glucocorticoids.
(6) In post marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis. However, such reports have been infrequent. This category of drugs includes this drug (alendronate). Most of the patients were postmenopausal women. The time to onset of symptoms varied from one day to several months after starting the drug. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate. Taking this drug, like other bisphosphonates, may cause atypical thigh bone (femur) fractures.
Limitation of Use
Bisphosphonates inhibit the loss of bone mass in people with osteoporosis. Bisphosphonates have been shown to reduce the rate of osteoporotic fractures in people with osteoporosis. While it is not clear whether bisphosphonates are the cause, atypical femur factures, a rare but serious type of thigh bone fracture, have been predominantly reported in patients taking bisphosphonates. The optimal duration of bisphosphonate use for the treatment and/prevent of osteoporosis is unknown, and the FDA is highlighting this uncertainty because these fractures may be related to use of bis phosphonates for longer than five years.

2) Information for Patients
(1) This drug 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.
(2) To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation patients should be instructed to swallow each tablet of this drug with a full glass of water (170~230mL). Patients should not lie down until after their first food of the day which should be at least 30 minutes after taking the tablet.
(3) Patients should not chew or suck on the tablet because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take this drug at bedtime or before arising for the day. Patients should be informed that failure to follow these instructions may increase their risk of esophageal problems. Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn) they should stop taking this drug and consult their physician.
(4) Patients should be instructed to take supplemental calcium and vitamin D, if daily dietary intake is inadequate. Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as cigarette smoking and/or excessive alcohol consumption, if these factors exist.
(5) Physicians should instruct their patients to read the patient package insert before starting therapy with this drug and to reread it each time the prescription is renewed.

5. DRUG INTERACTION

1) Estrogen/hormone replacement therapy (HRT)
Concomitant use of HRT (estrogen ± progestin) and this drug was assessed in two clinical studies of one or two years' duration in postmenopausal osteoporotic women. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments; however, the degree of suppression of bone turnover (as assessed by mineralizing surface) was significantly greater with the combination than with either component alone. The long-term effects of combined this drug and HRT on fracture occurrence have not been studied

2) Calcium Supplements/Antacids
It is likely that calcium supplements, antacids, and some oral medications will interfere with absorption of this drug. Therefore, patients must wait at least one-half hour after taking this drug before taking any other oral medications.

3) Aspirin
In clinical studies, the incidence of upper gastrointestinal adverse events was increased in patients receiving concomitant therapy with daily doses of this drug greater than 10mg and aspirin-containing products.

4) Nonsteroidal Anti-inflammatory Drugs (NSAIDs)
This drug may be administered to patients taking NSAIDs. In a 3-year, controlled, clinical study(n=2027) during which a majority of patients received concomitant NSAIDs, the incidence of upper gastrointestinal adverse events was similar in patients taking alendronate 5 or 10mg/day compared to those taking placebo. However, since NSAID use is associated with gastrointestinal irritation, caution should be used during concomitant use with this drug.

6. USE IN PREGNANCY, LACTATION, CHILDREN, ELDERLY AND RENAL IMPAIRMENTS

1) Use in pregnancy
(1) Reproduction studies in rats showed decreased postimplantation survival at 2 mg/kg/day and decreased body weight gain in normal pups at 1 mg/kg/day. Sites of incomplete fetal ossification were statistically significantly increased in rats beginning at 10 mg/kg/day in vertebral (cervical, thoracic, and lumbar), skull, and sternebral bones. The above doses ranged from 0.26 times (1mg/kg) to 2.6 times (10 mg/kg) a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2. No similar fetal effects were seen when pregnant rabbits were treated at doses up to 35 mg/kg/day (10.3 times a 40 mg human daily dose based on surface area, mg/m^2).
(2) Both total and ionized calcium decreased in pregnant rats at 15 mg/kg/day (3.9 times a 40 mg human daily dose based on surface area, mg/m^2) resulting in delays and failures of delivery. Protracted parturition due to maternal hypocalcemia occurred in rats at doses as low as 0.5 mg/kg/day (0.13 times a 40 mg human daily dose based on surface area, mg/m^2) when rats were treated from before mating through gestation. Maternotoxicity (late pregnancy deaths) occurred in the female rats treated with 15 mg/kg/day for varying periods of time ranging from treatment only during pre-mating to treatment only during early, middle, or late gestation; these deaths were lessened but not eliminated by cessation of treatment. Calcium supplementation either in the drinking water or by minipump could not ameliorate the hypocalcemia or prevent maternal and neonatal deaths due to delays in delivery; calcium supplementation IV prevented maternal, but not fetal deaths.
(3) There are no studies in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

2) Use in lactation
It is not known whether alendronate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when this drug is administered to nursing women.

3) Use in children
Safety and effectiveness in pediatric patients have not been established.

4) Use in the elderly
Of the patients receiving alendronate in the Fracture Intervention Trial (FIT), 71% (n=2302) were≥65 years of age and 17% (n=550) were ≥75 years of age. Of the patients receiving alendronate in the United States and Multinational osteoporosis treatment studies in women, osteoporosis studies in men, glucocorticoid -induced osteoporosis studies, and Paget's disease studies, 45%, 54%, 37%, and 70%, respectively, were 65 years of age or over. No overall differences in efficacy or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

5) Use in renal impairment
No dosage adjustment is necessary for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). This drug is not recommended for patients with more severe renal insufficiency (creatinine clearance <35 mL/min) due to lack of experience with alendronate in renal failure.

7. 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.

8. OVERDOSAGES

1) 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), 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).
2) No specific information is available on the treatment of overdosage with alendronate. Hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as upset stomach, heartburn, esophagitis, gastritis, or ulcer, may result from oral overdosage. Milk or antacids should be given to bind alendronate. Due to the risk of esophageal irritation, vomiting should not be induced and the patient should remain fully upright.
3) Dialysis would not be beneficial.

9. OTHERS

1) Carcinogenesis, Mutagenesis, Impairment of Fertility
(1) Harderian gland (a retro-orbital gland not present in humans) adenomas were increased in high-dose female mice (p=0.003) in a 92-week oral carcinogenicity study at doses of alendronate of 1, 3, and 10 mg/kg/day (males) or 1, 2, and 5 mg/kg/day (females). These doses are equivalent to 0.12 to 1.2 times a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2. The relevance of this finding to humans is unknown. Parafollicular cell (thyroid) adenomas were increased in high-dose male rats (p=0.003) in a 2-year oral carcinogenicity study at doses of 1 and 3.75 mg/kg body weight. These doses are equivalent to 0.26 and 1 times a 40 mg human daily dose based on surface area, mg/m^2. The relevance of this finding to humans is unknown.
(2) Alendronate was not genotoxic in the in vitro microbial mutagenesis assay with and without metabolic activation, in an in vitro mammalian cell mutagenesis assay, in an in vitro alkaline elution assay in rat hepatocytes, and in an in vivo chromosomal aberration assay in mice. In an in vitro chromosomal aberration assay in Chinese hamster ovary cells, however, alendronate gave equivocal results.
(3) Alendronate had no effect on fertility (male or female) in rats at oral doses up to 5 mg/kg/day (1.3 times a 40 mg human daily dose based on surface area, mg/m^2).

10. PRECAUTIONS IN APPLICATIONS

1) Keep out of reach of children
2) Do not change with other containers.

■ **STORAGE** : Air-tight container.
Store at 15~30℃. Protecty from humidity.

■ **USE TERM** : 2 years.

■ **PACKAGE** : 4Tabs./Box

※ This drug is manufactured in accordance with Korea Good Manufacturing Practice (KGMP) as recommended by WHO.