Alendronic Acid

Alendra®

70 mg Tablet
Bisphosphonate/Anti-Osteoporosis

FORMULATION
Each tablet contains:
Alendronic acid .....70 mg
(equivalent to 91.37 mg alendronate sodium)

PRODUCT DESCRIPTION
Alendronic Acid (Alendra) is a white, oval, biconvex tablet with DWP embossed on the side and Λ70 on the other side.

PHARMACODYNAMICS
Alendronate is a bisphosphonate whose main action is to inhibit osteoclast-mediated bone resorption.

Alendronate binds preferentially to active sites of bone resorption where it inhibits the resorptive activity of osteoclasts without inhibiting osteoblast function. Alendronate decreases bone turnover by inhibiting osteoclast action which results in a progressive increase in bone mass and subsequent decrease in osteoporosis-related fractures.

By inhibiting bone resorption, alendronate decreases the concentration of substances released from the bone and leads to significant reductions in plasma calcium and phosphate. This effect may be valuable in severe hypercalcemia, such as that associated with malignancy.

PHARMACOKINETICS
Alendronate's oral bioavailability is very low and estimated to be about 0.76% in women and 0.59% in men for 5 to 80 mg doses.

Food decreases alendronate's bioavailability by about 85-90% while coffee or orange juice reduces absorption by 60%. Taking other medications, especially any calcium-containing compounds and multivalent cations, will bind the bisphosphonate and thus also reduce alendronate's absorption. On the other hand, elevation of gastric pH to above 6 will result in a two-fold increase in alendronate absorption. About 60-70% of alendronate absorption occurs within one hour after oral administration.

Alendronate is transiently distributed to soft tissues after absorption. About 60% of the systemic dose is then rapidly redistributed to the bone and 40% is excreted by the kidney.

Alendronate is about 78% plasma protein-bound at pH 7.4, 2.5 mmol/L calcium, and 1 mg/L alendronate concentration. Plasma protein binding is increased with decreasing alendronate concentration and increasing pH and calcium.

Alendronate does not undergo metabolism. After oral administration, about 40% of the absorbed dose is excreted in the urine unchanged within 8 hours then the next 5% of the dose is excreted over the next 64 hours. Renal clearance is comparable to the glomerular filtration rate. Alendronate's biliary elimination is negligible with less than 2% of the administered dose appearing in the feces.

Alendronate's rate of clearance to bone is comparable to that of plasma flow through this tissue and its mean terminal half-life is estimated to be 10.9 years. The amount of alendronate released from the skeleton daily is estimated to be 25% of the amount absorbed from the gastrointestinal tract after 10 years of oral treatment with alendronate 10 mg daily.

INDICATIONS
- Treatment of osteoporosis in postmenopausal women and in men
- Prevention of osteoporosis in postmenopausal women

DOSAGE AND ADMINISTRATION
Treatment of Osteoporosis in Postmenopausal Women and in Men
Recommended Dosage: Orally, 70 mg (1 tablet) once weekly
Or, as prescribed by a physician.

Prevention of Postmenopausal Osteoporosis
Recommended Dosage: Orally, 35 mg (½ tablet) once weekly
Or, as prescribed by a physician.

Administration Procedures:
- Take alendronate with plain water only at least 30 minutes before the first food, beverage or medication of the day. Alendronate's absorption will likely be reduced when taken with other beverages (including mineral water), food and some medications. Taking alendronate less than 30 minutes after other medications, food and beverages other than plain water will decrease its absorption and lessen its effect.

- Alendronate should only be taken upon arising for the day. It should not be taken at bedtime or before getting up for the day.

  Always swallow alendronate with a full glass of water (6-8 oz; 180-240 mL) to facilitate delivery to the stomach and thus avoid the risk of esophageal irritation.

  Do not chew or suck the tablet to avoid oropharyngeal ulceration. Do not lie down within the next 30 minutes and until after the first food of the day.

  The patient should follow these instructions to decrease the risk of esophageal adverse events.

- Supplemental calcium and vitamin D may be necessary if dietary intake is inadequate. However, patients must wait at least 30 minutes after taking alendronate before taking any other oral medications.

Information on Missed Dose:
When a dose is missed, alendronate 70 mg once-weekly tablet should be taken on the morning after the patient remembers. Do not take two doses on the same day. Return to once-weekly dosing as originally scheduled on the patient's chosen day.

CONTRAINDICATIONS
- Hypersensitivity to bisphosphonates or to any component of this product
- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 30 minutes (e.g., bedridden and hospitalized patients)
- Renal impairment with creatinine clearance < 35 mL/min
- Hypocalcemia (*see Warnings and Precautions, General Precautions*)

WARNINGS AND PRECAUTIONS

Warning on Esophageal and Gastrointestinal Adverse Events:
Esophageal adverse events, such as esophagitis, erosions and ulcerations, occasionally with bleeding and rarely followed by esophageal stricture or perforation have been seen in patients receiving alendronate. Some cases were severe and required hospitalization. Patients should be instructed to discontinue alendronate and seek immediate medical attention if symptoms such as dysphagia, odynophagia (pain on swallowing), worsening heartburn, or retrosternal pain develop.

Strictly follow proper administration of the drug to minimize the risk of severe esophageal adverse experience. (See Dosage and Administration)

Alendronate has possible irritant effects on the upper gastrointestinal mucosa and has a potential for worsening underlying disease. It should therefore be given with caution in patients with active gastrointestinal problems such as dysphagia, esophageal diseases (including Barrett's esophagus), gastritis, duodenitis, or ulcers.

There have been post-marketing reports of gastric and duodenal ulcers, some severe and with complications.

General Precautions
- Consider causes of osteoporosis other than estrogen deficiency, aging and glucocorticoid use.
- Correct hypocalcemia and other disturbances of mineral metabolism such as vitamin D deficiency before initiating alendronate therapy.
- Small, asymptomatic decreases in serum calcium and phosphate may occur, particularly in patients with Paget's disease or patients receiving glucocorticoids.

Osteonecrosis of the Jaw (ONJ)
ONJ, generally associated with tooth extraction and/or local infection (including osteomyelitis) have been reported. Although most reports have been in cancer patients treated with intravenous bisphosphonates, some cases have been seen in patients with osteoporosis receiving oral bisphosphonates.

The known risk factors for ONJ include:
- Diagnosis of cancer
- Concomitant therapies such as chemotherapy, radiotherapy, corticosteroids, immunosuppressive drugs
- Poor oral hygiene
- Co-morbid disorders such as periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection, diabetes mellitus
- Smoking
- Heavy alcohol use

Patients who develop bisphosphonate-associated ONJ should receive appropriate antibiotic therapy and be seen by an oral surgeon. Dental surgery may exacerbate the condition; it is not known whether discontinuation of bisphosphonate therapy may reduce the risk for ONJ in patients requiring dental procedures. The management plan for each patient should be based on the clinical judgment of the physician and on individual risk/benefit assessment.

Patients with concomitant risk factors for ONJ should consider a dental examination with appropriate preventive dentistry prior to treatment with bisphosphonates.

Musculoskeletal Pain
Severe and occasionally incapacitating bone, joint and/or muscle pain have been reported infrequently in patients taking bisphosphonates.

In a small number of bisphosphonate-treated patients, low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported. Some were stress fractures (insufficiency fractures) occurring after minimal or no trauma. Patients with suspected stress fractures should be evaluated and receive appropriate orthopedic care. Some patients experienced thigh pain (often associated with imaging features of stress fractures) weeks to months before presenting with a completed femoral fracture. Bisphosphonate-treated patients who have sustained a femoral shaft fracture should examine their contralateral femur since fractures were often bilateral. Poor healing of these fractures are also reported. Discontinuation of bisphosphonate therapy in patients with stress fracture is advisable based on the patient's benefit risk assessment.

Endocrine and Metabolism
Mild and transient decreases in serum calcium and phosphate have been observed in patients receiving alendronate, especially in patients with Paget's disease.

Atrial Fibrillation
A possible increased risk of atrial fibrillation has been observed with the use of bisphosphonates.

INTERACTION WITH OTHER MEDICAMENTS
- Aluminum-, calcium-, iron-, or magnesium-containing compounds such as antacids, mineral supplements, and some osmotic laxatives may interfere with the absorption of alendronate and should therefore be given at least 30 minutes after taking alendronate.
- Concomitant administration of intravenous ranitidine doubled the bioavailability of oral alendronate. However, it is not known whether the increased bioavailability has any clinical significance and if this increase in bioavailability will occur in patients who are receiving oral H2-antagonists.
- The degree of suppression of bone turnover as assessed by mineralizing surface is significantly greater when Hormone Replacement Therapy (HRT) such as estrogen ± progestin is combined with alendronate therapy than with either agent alone in studies of 1 to 2 years duration in postmenopausal women with osteoporosis.
- Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) should be given with caution in patients receiving alendronate since these drugs may increase the incidence of gastrointestinal or renal adverse events.
- Aminoglycosides may have additive hypocalcemic effects in patients taking alendronate.
- Herbal products may delay the absorption of alendronate when used concomitantly. Take alendronate at least 30 minutes before taking any herbal product.

STATEMENT ON USAGE FOR HIGH RISK GROUPS
Pregnancy
Pregnancy Category C
Alendronate has not been studied in pregnant women. Although no data exist on fetal risk in humans, bisphosphonates are incorporated into the bone matrix and is gradually released over a period of years. This may theoretically cause serious skeletal malformation when a fetus is exposed to alendronate. Alendronate should not be used during pregnancy.
Lactation
It is not known whether alendronate is excreted in human milk. Alendronate should not be used by breastfeeding women.
Infants and Children
Alendronate is not indicated for use in pediatric patients.
Osteogenesis Imperfecta
The overall safety profile of alendronate for 2 years in patients with osteogenesis imperfecta was generally similar to adults. An increased incidence of vomiting, however, was observed in patients with osteogenesis imperfecta compared to those receiving placebo.
Elderly
Dosage adjustment is not necessary in elderly patients. There are no age-related differences in alendronate's efficacy and safety profile. However, some older individuals have greater sensitivity to alendronate.
Renal Impairment
No dosage adjustment is recommended in patients with mild to moderate kidney impairment (creatinine clearance 35 to 60 mL/minute). Alendronate is contraindicated in patients with severe kidney impairment (creatinine clearance <35 mL/minute).

ADVERSE EFFECTS / UNDESIRABLE EFFECTS
Alendronate is generally well tolerated and adverse effects are usually mild and do not require discontinuance of the drug.

Gastrointestinal Effects: The most common adverse effects seen in clinical trials include abdominal pain, nausea, dyspepsia, constipation, diarrhea, flatulence, acid regurgitation, vomiting, dysphagia, abdominal distention, gastritis, gastric ulcer, gastroesophageal reflux disease (GERD), melena, esophagitis, esophageal erosions, esophageal ulcers, and taste perversion. Rarely, esophageal stricture or perforation, oropharyngeal ulceration, and gastric or duodenal ulcers (some severe and with complications).

Anastomotic ulcer with mild hemorrhage has been reported with concomitant aspirin use.

Esophageal cancer has been reported during postmarketing experience in patients receiving alendronate or other bisphosphonates. The most common site of cancer was the distal esophagus, with gastric involvement in some patients.

CNS Effects: Vertigo, headache, dysgeusia and dizziness.

Musculoskeletal / Connective Tissue and Bone Effects: Musculoskeletal (bone, muscle or joint) pain which is occasionally severe but rarely incapacitating, muscle cramp, joint swelling, low-energy femoral shaft fracture, transient symptoms of myalgia, asthenia and malaise.

There have been rare reports of ONJ generally associated with tooth extraction and/or local infection, often with delayed healing.

Skin Reactions: Hypersensitivity reactions including urticaria and rarely, angioedema. Rash (occasionally with photosensitivity), alopecia and erythema have been rarely reported. Pruritus and rarely, severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrosis have also been reported.

Others: Fever typically associated with initiation of treatment, and asymptomatic, mild, and transient decreases in serum calcium and phosphate. Rarely, reports of severe symptomatic hypocalcemia have occurred in patients with predisposing factors such as hypoparathyroidism, Vitamin D deficiency and calcium malabsorption.

Uveitis (rarely), scleritis or episcleritis.

Asthenia and peripheral edema.

OVERDOSAGE AND MANAGEMENT
Specific information on acute alendronate overdosage is not available. However, hypocalcemia, hypophosphatemia and upper gastrointestinal adverse events (e.g., upset stomach, heartburn, esophagitis, gastritis, or ulcer) may result from oral overdosage.

Give milk or antacids to bind alendronate. Do not induce vomiting and keep the patient in an upright position to avoid esophageal irritation.

Dialysis is not beneficial and is therefore not recommended.

STORAGE
Store at temperatures not exceeding 30°C.

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

AVAILABILITY
Blister pack x 4's (Box of 4's)

DATE OF REVISION OF PACKAGE INSERT
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Reg. IPOPHIL

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