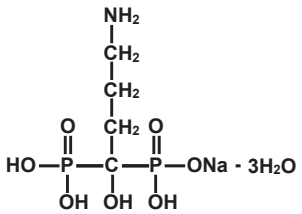
Reventa™

(ALENDRONATE SODIUM TABLETS USP)

Tablets 10mg, 70mg

DESCRIPTION
REVENTA (Alendronate sodium) is an aminobisphosphonate that acts as a potent inhibitor of bone resorption.
Alendronate sodium is chemically described as (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate. The molecular formula is $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$ and the structural formula is



Alendronate Sodium

QUALITATIVE AND QUANTITATIVE COMPOSITION
REVENTA (Alendronate sodium) is available for oral administration as:

REVENTA Tablets 10mg
Each tablet contains:
Alendronate sodium USP
equivalent to Alendronic acid...10mg

REVENTA Tablets 70mg
Each tablet contains:
Alendronate sodium USP
equivalent to Alendronic acid... 70mg

CLINICAL PHARMACOLOGY
Mechanism of Action
At the cellular level, alendronate shows preferential localization to sites of bone resorption, specifically under osteoclasts. The osteoclasts adhere normally to the bone surface but lack the ruffled border that is indicative of active resorption. Alendronate does not interfere with osteoclast recruitment or attachment, but it does inhibit osteoclast activity. While incorporated in bone matrix, alendronate is not pharmacologically active. Thus, alendronate must be continuously administered to suppress osteoclasts on newly formed resorption surfaces.

Pharmacokinetics
Absorption
Like other bisphosphonates, alendronate is poorly absorbed following oral administration. Absorption is decreased by food, especially by products containing calcium or other polyvalent cations. Bioavailability is about 0.4% when administered half an hour before food, reduced from 0.7% in the fasting state absorption is negligible when taken up to 2 hours after a meal.

Distribution
The mean steady-state volume of distribution, exclusive of bone, is at least 28L in humans. Concentrations of drug in plasma following therapeutic oral doses are too low (less than 5ng/mL) for analytical detection. Protein binding in human plasma is approximately 78%.

Metabolism
There is no evidence that alendronate is metabolized in animals or humans.

Elimination
About half of the absorbed portion is excreted in the urine; the remainder is sequestered to bone for a prolonged period. The terminal half-life in humans is estimated to exceed 10 years, probably reflecting release of alendronate from the skeleton.

Special Populations:
Pediatric
Alendronate pharmacokinetics have not been studied in patients <18 years of age.

Geriatric
Bioavailability and urinary excretion are similar in elderly (>60 years of age) and younger subjects. No dosage adjustment is necessary.

Renal Insufficiency
No dosage adjustment is necessary for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60mL/min). Alendronate is not recommended in patients with severe renal impairment.

Hepatic Insufficiency:
As there is evidence that alendronate is not metabolized or excreted in the bile, no studies were conducted in patients with hepatic insufficiency. No dosage adjustment is necessary.

Drug-Drug Relationship
Ranitidine: Intravenous ranitidine was shown to double the bioavailability of oral alendronate. The clinical significance of this increased bioavailability and whether similar increase will occur in patients given oral H_2-antagonists is unknown.

Prednisone: Prednisone (20mg three times daily for five days) did not produce a clinically meaningful change in the oral bioavailability of alendronate (mean increase ranging from 20 to 44%)

THERAPEUTIC INDICATIONS
REVENTA (Alendronate sodium) is indicated:
- In postmenopausal women for the treatment of osteoporosis to prevent fractures, including those of the hip and spine (vertebral compression fractures).
- In postmenopausal women who are at risk of developing osteoporosis.
- For the treatment of osteoporosis in men to prevent fractures.
- For the treatment and prevention of glucocorticoid-induced osteoporosis in men and women.
- For the treatment of Paget's disease of bone in men and women.

DOSAGE AND ADMINISTRATION
Reventa (Alendronate sodium) must be taken *at least* 30 minutes before the first food beverage, or medication of the day with plain water only. Food and drinks affect the absorption of REVENTA (Alendronate sodium). Therefore, it is very important that REVENTA must not be used with food or drinks (other than water). The tablets must be swallowed whole, with a full glass of water and not chewed. Patients should not lie down for 30 minutes after taking the tablet. REVENTA should not be taken at bedtime.

Treatment of Osteoporosis in Postmenopausal Women and Men
The recommended dosage is:
– One REVENTA 70mg tablet once weekly **OR**
– One REVENTA 10mg tablet once daily.

Prevention of Osteoporosis in Postmenopausal Women
The recommended dosage is $^1/_2$ REVENTA 10mg (5mg) tablet once daily.

Treatment and Prevention of Glucocorticoid-Induced Osteoporosis in Men and Women

The recommended dosage is 1/2 REVENTA 10mg (5mg) tablet once a day except for postmenopausal women not receiving estrogen, for whom the recommended dosage is REVENTA tablet 10mg once daily.

Paget's Disease of Bone in Men and Women
The recommended treatment regimen is 40mg once daily for six months.

ADVERSE REACTIONS
The adverse reactions experienced were usually mild and generally did not require discontinuation of therapy. The following adverse reactions have been reported:

Body as a Whole:
Common: Hypersensitivity reactions including urticaria, transient symptoms of myalgia and malaise.
Rare: Angioedema, fever, symptomatic hypocalcemia.
Gastrointestinal:
Common: Esophagitis, esophageal erosions, esophageal ulcers.
Rare: Esophageal stricture or perforation and oropharyngeal ulceration.
Gastric or duodenal ulcers, some severe and with complications, have also been reported.
Skin:
Common: Rash (occasionally with photosensitivity), pruritis.
Rare: Severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.
Special Senses:
Rare: Uveitis, scleritis.

CONTRAINDICATIONS
- Hypersensitivity 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.
- Hypocalcemia.

PRECAUTIONS:
General:
- Causes of osteoporosis other than estrogen deficiency, aging and glucocorticoid use should be considered.
- Hypocalcemia must be corrected before initiating therapy with alendronate.
- Other disorders affecting mineral metabolism (such as vitamin D deficiency) should also be treated. Patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy.
- Ensuring adequate calcium absorption and vitamin D intake is especially important in patients with Paget's disease of bone and in patients receiving glucocorticoids as small asymptomatic decreases in serum calcium and phosphate may occur with the treatment of alendronate.

Gastrointestinal
- Physicians should be alert to symptoms signaling a possible esophageal reaction including dysphasia, odynophagia, retrosternal pain or new/worsening heartburn. Patients should be instructed to discontinue alendronate.
- Because of possible irritant effects of alendronate on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease, caution should be used when alendronate is given to patients with active upper gastrointestinal problems.

Renal insufficiency
Alendronate is not recommended for patients with severe renal insufficiency (creatinine clearance <35mL/min) due to lack of experience in renal failure.

Glucocorticoid-induced osteoporosis
The risk versus benefit of alendronate for treatment at daily dosages of glucocorticoids less than 7.5mg of prednisone or equivalent has not been established. Before initiating treatment, the hormonal status of both men and women should be ascertained and appropriate replacement considered. A bone mineral density measurement should be made at the initiation of therapy and repeated after 6 to 12 months of combined alendronate and glucocorticoid treatment.

Pediatric Patients
Safety and effectiveness in pediatric patients have not been established.

Drug Interactions
Estrogen/Hormone Replacement Therapy (HRT)
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. The safety and tolerability profile of the combination was consistent with those of the individual treatments.

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

Aspirin
The incidence of upper gastrointestinal adverse events increased in patients receiving concomitant therapy with daily doses of alendronate greater than 10mg and aspirin-containing products.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)
Since NSAID use is associated with gastrointestinal irritation, caution should be used during concomitant use with alendronate.

Pregnancy
There are no studies in pregnant women. Alendronate should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Nursing Mothers
It is not known whether alendronate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when alendronate is administered to nursing women.

OVERDOSAGE
No specific information is available on the treatment of overdosage with alendronate. Hypocalcemia, hypophosphataemia 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.

STORAGE
Store below 30°C.
Protect from sunlight & moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
REVENTA (Alendronate sodium) 10mg tablets is available in blister packs of 10's.

REVENTA (Alendronate sodium) 70mg tablets is available in blister packs of 4's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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EXP-200008486

Manufactured by: Getz Pharma (Pvt.) Limited, 29-30/27, K.I.A., Karachi - 74900, Pakistan.