Alendronate

CAS Number : 66376-36-1
Molecular Weight : 249.09 g/mol
Molecular Formula : C₄H₁₃NO₇P₂
Systematic (IUPAC) : (4-amino-1-hydroxy-1-phosphonobutyl) phosphonic acid

Type : small molecule

Description : Alendronate is a nitrogen-containing, second generation bisphosphonate. Bisphosphonates were first used to treat Paget’s disease in 1971. This class of medications is comprised of inorganic pyrophosphate analogues that contain non-hydrolyzable P-C-P bonds. Similar to other bisphosphonates, alendronate has a
high affinity for bone mineral and is taken up during osteoclast resorption. Alendronate inhibits farnesyl pyrophosphate synthetase, one of the enzymes in the mevalonic acid pathway involved in producing isoprenoid compounds that are essential for post-translational modification of small guanosine triphosphate (GTP)-binding proteins, such as Rho, Ras and Rab. Inhibition of this process interferes with osteoclast function and survival. Alendronate is used for the treatment of osteoporosis and Paget’s disease.

Categories
Antihypocalcemic Agents
Bisphosphonates
Antiresorptives
Bone Density Conservation Agents

Taxonomy

Kingdom : Organic

Classes : Bisphosphonates

Substructures
Hydroxy Compounds
Carboxylic Acids and Derivatives
Phosphonic Acids and Derivatives
Aliphatic and Aryl Amines
Phosphinic Acids and Derivatives
Bisphosphonates
**Pharmacology**

**Indication**: For the treatment and prevention of osteoporosis in women and Paget's disease of bone in both men and women.

**Pharmacodynamics**: Alendronate, a second-generation bisphosphonate is the first member of a group of drugs which strengthens bone. Alendronate is used to reduce hypercalcemia in tumor-induced bone disease, to treat corticosteroid-induced osteoporosis and Paget's disease, and to prevent osteoporosis in postmenopausal women.

**Mechanism of action**: The action of Alendronate on bone tissue is based partly on its affinity for hydroxyapatite, which is part of the mineral matrix of bone. Alendronate also targets farnesyl pyrophosphate (FPP) synthase. Nitrogen-containing bisphosphonates (such as pamidronate, alendronate, risedronate, ibandronate and zoledronate) appear to act as analogues of isoprenoid diphosphate lipids, thereby inhibiting FPP synthase, an enzyme in the mevalonate pathway. Inhibition of this enzyme in osteoclasts prevents the biosynthesis of isoprenoid lipids (FPP and GGPP) that are essential for the post-translational farnesylation and geranylgeranylation of small GTPase signalling proteins. This activity inhibits osteoclast activity and reduces bone resorption and turnover. In postmenopausal women, it reduces the elevated rate of bone turnover, leading to, on average, a net gain in bone mass.
**Absorption**: Relative to an intravenous (IV) reference dose, the mean 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 standardized breakfast. Oral bioavailability of the 10 mg tablet in men (0.59%) was similar to that in women (0.78%) when administered after an overnight fast and 2 hours before breakfast.

**Volume of distribution**: 28 L

**Protein binding**: 78%

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

**Route of 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 feces.

**Half life**: >10 years

**Clearance**: <200 mL/min [A single 10 mg IV dose]

**Toxicity**: Alendronate can damage the esophagus both by toxicity from the medication itself and by nonspecific irritation secondary to contact between the pill and the esophageal mucosa, similar to other cases of "pill esophagitis."
Affected organisms: Humans and other mammals

Drug Class And Mechanisms
Alendronate is in a class of medications called bisphosphonates. The bisphosphonate class includes etidronate (Didronel), ibandronate (Boniva), pamidronate (Aredia), risedronate (Actonel), and tiludronate (Skelid). Bisphosphonates are used for treating osteoporosis (reduced density of bone that leads to fractures) and bone pain from diseases such as metastatic breast cancer, multiple myeloma, and Paget's disease. Bone is in a constant state of remodeling. New bone is laid down by cells called osteoblasts while old bone is removed by cells called osteoclasts. Bisphosphonates strengthen bone by inhibiting bone removal (resorption) by osteoclasts. After menopause, there is an increased rate of bone loss leading to osteoporosis, and alendronate has been shown to increase bone density and decrease fractures of bones. The FDA approved alendronate in September 1995.

Dosing
The recommended dose for treatment of osteoporosis is 5-10 mg daily or 35-70 mg weekly. Paget's disease is treated with 40 mg once daily for six months. Since food, other medications, and vitamins can interfere with the absorption of alendronate, they should be taken at least 30 minutes before alendronate. In order to avoid chemical irritation of the esophagus (the swallowing tube that connects the mouth with the stomach), alendronate should be taken with a full glass of plain water immediately upon arising in the morning and never chewed or sucked. It should be avoided by
patients with abnormalities of the esophagus which delay esophageal emptying, such as scarring (stricture) or poor motility (achalasia). Patients should also not lie down for 30 minutes after swallowing the tablets. Those patients who are unable to remain upright for at least 30 minutes after taking alendronate should not take it.

**Drug interactions**
Calcium supplements and antacids reduce the absorption of alendronate. Therefore, alendronate should be taken at least 30 minutes before calcium and antacids.

Intravenous ranitidine (Zantac) increases blood levels of alendronate. The importance of this reaction is unknown.

The risk of stomach and intestinal side effects may increase when alendronate is combined with aspirin or other nonsteroidal antiinflammatory drugs (NSAIDs).

**Why is this medication prescribed?**
Alendronate is used to treat and prevent osteoporosis (a condition in which the bones become thin and weak and break easily) in women who have undergone menopause ("change of life," end of menstrual periods) and to treat osteoporosis in men. Alendronate is also used to treat osteoporosis in men and women who are taking corticosteroids (a type of medication that may cause osteoporosis in some patients). Alendronate is also used to treat Paget's disease of bone (a condition in which the bones are soft and weak and may be deformed, painful, or easily broken). Alendronate is in a class of medications called bisphosphonates. It works by
preventing bone breakdown and increasing bone density (thickness).

**How should this medicine be used?**

Alendronate comes as a tablet and a solution (liquid) to take by mouth. The solution is usually taken on an empty stomach once a week in the morning. The 5-mg and 10-mg tablets are usually taken on an empty stomach once a day in the morning, and the 35-mg and 70-mg tablets are usually taken on an empty stomach once a week in the morning. The 40-mg tablets are usually taken once a day in the morning for six months to treat Paget's disease of bone. Follow the directions on your prescription label carefully, and ask your doctor or pharmacist to explain any part you do not understand.

Take alendronate exactly as directed. Do not take more or less of it or take it more often than prescribed by your doctor.

Alendronate may not work properly and may damage the esophagus (tube between the mouth and stomach) or cause sores in the mouth if it is not taken according to the following instructions. Tell your doctor if you do not understand, you do not think you will remember, or you are unable to follow these instructions:

You must take alendronate just after you get out of bed in the morning, before you eat or drink anything. Never take alendronate at bedtime or before you wake up and get out of bed for the day.

Swallow alendronate tablets with a full glass (6-8 ounces [180-240 mL]) of plain water. Drink at least a quarter of a cup (2 ounces [60 mL]) of plain water after you take alendronate solution. Never take alendronate tablets or
solution with tea, coffee, juice, milk, mineral water, sparkling water, or any liquid other than plain water. Swallow the tablets whole; do not split, chew or crush them. Do not suck on the tablets. After you take alendronate, do not eat, drink, or take any other medications (including vitamins or antacids) for at least 30 minutes. Do not lie down for at least 30 minutes after you take alendronate. Sit upright or stand upright until at least 30 minutes have passed and you have eaten your first food of the day. Alendronate controls osteoporosis and Paget's disease of bone but does not cure these conditions. It may take 3 months or longer before your bone density begins to increase. Alendronate helps to treat and prevent osteoporosis only as long as it is taken regularly. Continue to take alendronate even if you feel well. Do not stop taking alendronate without talking to your doctor, but talk to your doctor from time to time about whether you still need to take alendronate. Ask your pharmacist or doctor for a copy of the manufacturer's information for the patient.

**Other uses for this medicine**
This medication may be prescribed for other uses; ask your doctor or pharmacist for more information.

**What special precautions should I follow?**
Before taking alendronate,
tell your doctor and pharmacist if you are allergic to alendronate or any other medications.
tell your doctor and pharmacist what prescription and nonprescription medications, vitamins, nutritional supplements, and herbal products you are taking or plan
to take. Be sure to mention any of the following: aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Advil, Motrin) and naproxen (Aleve, Naprosyn); cancer chemotherapy; or oral steroids such as dexamethasone (Decadron, Dexone), methylprednisolone (Medrol), and prednisone (Deltasone). Your doctor may need to change the doses of your medications or monitor you carefully for side effects.

if you are taking any other medications including supplements, vitamins, or antacids by mouth, take them at least 30 minutes after you take alendronate. tell your doctor if you are unable to sit upright or stand upright for at least 30 minutes and if you have or have ever had a low level of calcium in your blood or any problems with your esophagus. Your doctor may tell you that you should not take alendronate.

tell your doctor if you are undergoing radiation therapy and if you have or have ever had anemia (condition in which the red blood cells do not bring enough oxygen to all the parts of the body); a low level of vitamin D in your body; difficulty swallowing; heartburn; ulcers or other stomach problems; cancer; any type of infection, especially in your mouth; problems with your mouth, teeth, or gums; any condition that stops your blood from clotting normally; or dental or kidney disease.
tell your doctor if you are pregnant or are breast-feeding. Also tell your doctor if you plan to become pregnant at any time in the future, because alendronate may remain in your body for years after you stop taking it. Call your doctor if you become pregnant during or after your treatment.
you should know that alendronate may cause serious problems with your jaw, especially if you have dental
surgery or treatment while you are taking the medication. A dentist should examine your teeth and perform any needed treatments before you start to take alendronate. Be sure to brush your teeth and clean your mouth properly while you are taking alendronate. Talk to your doctor before having any dental treatments while you are taking this medication.

you should know that alendronate may cause severe bone, muscle, or joint pain. You may begin to feel this pain within days, months, or years after you first take alendronate. Although this type of pain may begin after you have taken alendronate for some time, it is important for you and your doctor to realize that it may be caused by alendronate. Call your doctor right away if you experience severe pain at any time during your treatment with alendronate. Your doctor may tell you to stop taking alendronate and your pain may go away after you stop taking the medication.

talk to your doctor about other things you can do to prevent osteoporosis from developing or worsening. Your doctor will probably tell you to avoid smoking and drinking large amounts of alcohol and to follow a regular program of weight-bearing exercise.

What special dietary instructions should I follow?
You should eat and drink plenty of foods and drinks that are rich in calcium and vitamin D while you are taking alendronate. Your doctor will tell you which foods and drinks are good sources of these nutrients and how many servings you need each day. If you find it difficult to eat enough of these foods, tell your doctor. In that
case, your doctor can prescribe or recommend a supplement.

**What should I do if I forget a dose?**

If you miss a dose of once-daily alendronate, do not take it later in the day. Skip the missed dose and take one dose the next morning as usual. If you miss a dose of once-weekly alendronate, take one dose the morning after you remember. Then return to taking one dose once each week on your regularly scheduled day. Never take a double dose to make up for a missed one, and never take more than one dose in one day.

**What side effects can this medication cause?**

Alendronate may cause side effects. Tell your doctor if any of these symptoms are severe or do not go away:

- nausea
- stomach pain
- constipation
- diarrhea
- gas
- bloating or fullness in the stomach
- change in ability to taste food
- headache
- dizziness
- swelling of the joints, hands, or legs

Some side effects can be serious. If you experience any of the following symptoms, call your doctor immediately before you take any more alendronate:

- new or worsening heartburn
- difficulty swallowing
- pain on swallowing
- chest pain
bloody vomit or vomit that looks like coffee grounds
black, tarry, or bloody stools
fever
blisters or peeling skin
rash (may be made worse by sunlight)
itching
hives
swelling of eyes, face, lips, tongue, or throat
difficulty breathing
hoarseness
painful or swollen gums
loosening of the teeth
numbness or heavy feeling in the jaw
poor healing of the jaw
eye pain
dull, aching pain in the hips, groin, or thighs

Taking a bisphosphonate medication such as alendronate for osteoporosis may increase the risk that you will break your thigh bone(s). You may feel pain in your hips, groin, or thighs for several weeks or months before the bone(s) break, and you may find that one or both of your thigh bones have broken even though you have not fallen or experienced other trauma. It is unusual for the thigh bone to break in healthy people, but people who have osteoporosis may break this bone even if they do not take alendronate. Talk to your doctor about the risks of taking alendronate.

Alendronate may cause other side effects. Call your doctor if you have any unusual problems while taking this medication.
What storage conditions are needed for this medicine?
Keep this medication in the container it came in, tightly closed, and out of reach of children. Store it at room temperature and away from excess heat and moisture (not in the bathroom). Do not freeze alendronate solution. Throw away any medication that is outdated or no longer needed. Talk to your pharmacist about the proper disposal of your medication.

Symptoms of overdose may include the following:
- heartburn
- nausea
- stomach pain
- bloody vomit or vomit that looks like coffee grounds
- difficulty swallowing or pain when swallowing
- bloody or black and tarry stools

What other information should I know?
Keep all appointments with your doctor and the laboratory. Your doctor may order certain lab tests to check your body's response to alendronate.
Do not let anyone else take your medication. Ask your pharmacist any questions you have about refilling your prescription.
It is important for you to keep a written list of all of the prescription and nonprescription (over-the-counter) medicines you are taking, as well as any products such as vitamins, minerals, or other dietary supplements. You should bring this list with you each time you visit a doctor or if you are admitted to a hospital. It is also
important information to carry with you in case of emergencies.

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