PRODUCT MONOGRAPH

PrAPO-ETIDRONATE

etidronate disodium tablets USP

200 mg and 400 mg

Bone Metabolism Regulator, Anti-Pagetic Agent
Anti-Hypercalcemic Agent

APOTEX INC.
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Control No. 210905

DATE OF REVISION:
December 07, 2017

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[Pr]APO- ETIDRONATE

etidronate disodium tablets USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-medicinal Ingredients
Oral	Tablets 200 mg, 400 mg	The Non-medicinal ingredients include crospovidone and magnesium stearate.

INDICATIONS AND CLINICAL USE

APO-ETIDRONATE (etidronate disodium) is indicated for:

- the treatment of symptomatic Paget's disease of the bone (osteitis deformans).
- the short-term (30 to90 days) maintenance of clinically acceptable serum calcium levels following treatment with etidronate disodium I.V. Infusion (for patients with hypercalcemia of malignancy). The relapse rate without oral etidronate disodium follow-up after about one month is high (90%); with such follow-up it is lower (50%). A second course of etidronate disodium I.V. infusion may be effective if hypercalcemia recurs.

Pediatrics
The safety and effectiveness of etidronate disodium in children has not been established.

CONTRAINDICATIONS

APO-ETIDRONATE (etidronate disodium) is contraindicated for:

- Patients with known hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING.**
- Patients with clinically overt osteomalacia; appropriate treatment to resolve their osteomalacia should be initiated before prescribing APO-ETIDRONATE.

WARNINGS AND PRECAUTIONS

General
The physician should adhere to the recommended dose regimen in order to avoid unnecessary overtreatment with etidronate disodium. (see **DOSAGE AND ADMINISTRATION**).

In post-marketing reporting, osteonecrosis of the jaw has been reported in patients treated with bisphosphonates. The majority of reports occurred following dental procedures such as tooth extractions; and have involved cancer patients treated with intravenous bisphosphonates, but some occurred in patients receiving oral treatment for postmenopausal osteoporosis and other diagnoses. Many had signs of local infection, including osteomyelitis. A dental examination with appropriate preventative dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, immune suppression, head and neck radiotherapy or poor oral hygiene). While on treatment, these patients should avoid invasive dental procedures if possible. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment prior to the procedure reduces the risk of osteonecrosis of the jaw. Clinical judgment, based on individual risk assessment, should guide the management of patients undergoing dental procedures. The following should be considered when evaluating a patient's risk of developing ONJ:

- Potency of the medicinal product that inhibits bone resorption (higher risk for highly potent compounds),
- Route of administration (higher risk for parenteral administration)
- Cumulative dose of bone resorption therapy.
- Co-morbid conditions (e.g. anaemia, coagulopathies) and smoking
- Periodontal disease, poorly fitting dentures, history of dental disease.

Carcinogenesis

The incidence of osteogenic sarcoma is known to be increased in Paget's disease. Pagetic lesions, with or without therapy, may appear by x-ray to progress markedly, possibly with some loss of definition of periosteal margins. Such lesions should be evaluated carefully to differentiate these from osteogenic sarcoma.

Gastrointestinal

Etidronate disodium therapy should be approached with caution in patients with gastrointestinal disease, because APO-ETIDRONATE may cause diarrhea in some patients at doses above 5 mg/kg/day.

Musculoskeletal

Although there is no evidence of impaired fracture healing with etidronate disodium, in case of spontaneous or pathological fractures occurring during APO-ETIDRONATE therapy of Paget's disease, the drug should be discontinued until complete healing of the fracture takes place. (See **ADVERSE REACTIONS**).

Osteoid Mineralization:

In Paget's disease, etidronate disodium may retard mineralization of osteoid laid down during the bone accretion process. This effect is dose and time-dependent. There may be an overlap of beneficial and mineralization inhibition effects in some patients at higher doses. Extended periods of continuous medication should be approached cautiously.

When administered at doses of 20 mg/kg/day, etidronate disodium suppresses bone turnover and essentially stops mineralization of new bone in Pagetic lesions and, to a lesser extent, in the uninvolved skeleton. Mineralization of Pagetic lesions has been demonstrated to occur normally after discontinuation of the drug. (see **CONTRAINDICATIONS**).

Bone Pain:
Bone pain at the Pagetic site may increase or recur during APO-ETIDRONATE therapy even in patients who are experiencing relief of their original symptoms. Continuance of therapy will usually result in resolution of pain. However, on occasion, therapy may have to be discontinued (see **ADVERSE REACTIONS**).

Nutrition
Patients with Paget's disease of bone should maintain an adequate nutritional status, and particularly, an adequate intake of calcium and vitamin D. Patients with restricted vitamin D and calcium intake may be particularly sensitive to drugs that affect calcium homeostasis and should be closely followed while under treatment with etidronate disodium.

Renal
Since absorbed etidronate disodium is excreted through the kidneys, periodic renal function assessment should be carried out in patients whose renal function may be deteriorating. While there is no experience to specifically guide treatment in patients with impaired renal function, in such cases renal function should be monitored carefully.

Ophthalmologic
Ocular disturbances including conjunctivitis, uveitis, episcleritis, iritis and scleritis have been reported with bisphosphonate use. There have been published reports of conjunctivitis with etidronate. Patients with ocular events other than uncomplicated conjunctivitis should be referred to an ophthalmologist for evaluation. Treatment may need to be discontinued.

Atypical Subtrochanteric and Diaphyseal Femoral Fractures
Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. Poor healing of these fractures was also reported. Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb.

Interruption of bisphosphonate therapy should be considered pending a risk/benefit assessment.

Special Populations

Pregnant Women:
Studies performed in rats and rabbits using orally administered etidronate disodium at doses up to five times the maximum human dose have revealed no evidence of impaired fertility or harm to the fetus. At doses of twenty-two times the maximum human dose, a decrease in live fetuses was observed in rats. Malformations occurred only in rats at exaggerated doses following parenteral administration and were skeletal in nature. These malformations were deemed to be the result of the pharmacologic action of the drug. The relationship of oral and intravenous routes of administration in reproduction/teratology studies is unknown. There are no adequate, well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Women:
Etidronate disodium is not intended for administration during lactation. It is not known whether etidronate is excreted in human milk; it is excreted in the milk of rats. Because many drugs are excreted in human milk and because of the potential for adverse effects on the skeletons of infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Geriatrics:
Special precautions related to the use of etidronate disodium in geriatric patients have not been identified. However, serum creatinine levels should be closely monitored in patients with renal impairment.

Monitoring and Laboratory Tests
During therapy of **Paget's disease**, periodic monitoring of urinary hydroxyproline excretion and/or serum alkaline phosphatase levels to assess disease activity is desirable. Additionally, monitoring of serum phosphate levels may provide indications of patient compliance. A failure of serum phosphate levels to increase at APO-ETIDRONATE dose levels of 10 mg/kg/day or above may be suggestive of non-compliance.

Hyperphosphatemia:
Etidronate disodium therapy for Paget's disease at daily doses of 10 mg/kg/day and above, and occasionally at doses of 5 mg/kg/day, is associated with serum phosphate elevations, probably due to increased renal tubular reabsorption of phosphate. Serum values of up to 2.26 mmol/L (7 mg %) are seen at the highest doses. The usual increments are approximately 0.32 mmol/L **(**1 mg %) over the pretreatment levels. Serum phosphate returns to normal within two to four weeks after the drug is discontinued.

Therapy with etidronate disodium alone is not accompanied by clinically significant changes in serum parathyroid hormone or serum calcium levels.

Hypercalcemia of malignancy: Serum calcium levels should be monitored in patients receiving etidronate disodium I.V. Infusion therapy and/or oral etidronate disodium maintenance therapy for hypercalcemia of malignancy. The physiologically important component of serum calcium is the ionized portion. In most institutions, this cannot be measured directly. It is important to recognize that factors influencing the ratio of free and bound calcium such as serum proteins, particularly albumin, may complicate the interpretation of total serum calcium measurements. If indicated, a corrected (adjusted) serum calcium value should be calculated using an established algorithm, such as:

$$Ca_{adj} = Ca_T - 0.71\ (A - A_m),$$

where,

Ca_{adj} = adjusted calcium concentration (mg/100 mL)

Ca_T = total calcium concentration (mg/100 mL)

A = albumin concentration (g/100 mL)

A_m = mean normal albumin concentration for given laboratory. (g/100 mL)

Serum creatinine and blood urea nitrogen should be monitored in patients with known or suspected renal insufficiency.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and approximate rates of occurrence.

General
Diarrhea and loose bowel movement may occur in some patients when etidronate disodiumis administered at doses greater than 5 mg/kg/day. The incidence is approximately 20% in patients treated with 20 mg/kg/day of etidronate disodium.

Paget's Disease
Increased or recurrent bone pain at existing Pagetic sites and/or the appearance of pain at sites previously asymptomatic may occur even when the patient's overall clinical status is improved. The incidence was about 7% in placebo-treated patients and not substantially higher at the 5 mg/kg/day dose level. At higher doses the figure rose to approximately 20%. In etidronate disodium treated patients, the pain resolved while

therapy was continued in some patients, but persisted for several months in others.

Fractures are recognized as a common feature in patients with Paget's disease. The risk of fracture may be increased when etidronate disodium is taken at a dose level of 20 mg/kg/day in excess of 3 months. This risk may be greater in patients with extensive and severe disease, a history of multiple fractures, and/or rapidly advancing osteolytic lesions. It is recommended that the drug be discontinued when fractures occur and that therapy not be reinstated until fracture healing is complete.

Hypercalcemia of Malignancy
Continuous oral medication at doses of 20 mg/kg/day for longer than 3 months, or 10 mg/kg/day for longer than 6 months, may result in the accumulation of unmineralized osteoid. Adverse reactions associated with such changes have not been reported in patients treated for hypercalcemia of malignancy.

Post Market Adverse Drug Reactions
Other adverse events that have been reported in postmarketing studies of a number of indications, and were thought to be possibly related to etidronate disodium include the following: nausea, alopecia; arthropathies, including arthralgia and arthritis; bone fracture; esophagitis; glossitis; hypersensitivity reactions, including angioedema, skin rashes (such as follicular eruption, macular rash, maculopapular rash), pruritus, Stevens Johnson syndrome, and urticaria; osteomalacia; neuropsychiatric events, including amnesia, confusion, depression, and hallucination; paresthesias; burning tongue; erythema multiforme; and exacerbation of asthma.

In patients receiving etidronate disodium, there have been rare reports of leukopenia, agranulocytosis, and pancytopenia. Also, there have been very rare cases of leukemia reported with etidronate use (1/100,000) in ongoing safety surveillance since 1978 encompassing approximately 1.5 million patient-years of treatment. Any causal relationship to either the treatment or to the patients' underlying disease has not been established.

A number of cases of osteonecrosis (primarily of the jaw) have been reported in patients receiving treatment with bisphosphonates. Osteonecrosis has other well documented multiple risk factors. It is not possible to determine if these events are related to bisphosphonates, to concomitant drugs or other therapies (e.g. chemotherapy, radiotherapy, corticosteroids), to the patient's underlying disease or to other co-morbid risk factors (e.g. anemia, infection, preexisting oral disease). See **WARNINGS AND PRECAUTIONS, General**.

Exacerbation of existing peptic ulcer disease with resulting complications has been reported in a few patients.

DRUG INTERACTIONS

Drug-Drug Interactions

The concurrent use of etidronate disodium with corticosteroid, phosphate, calcitonin, furosemide or mithramycin therapies may result in additive effects.

The concurrent use of etidronate disodium with warfarin has been associated with isolated reports of patients experiencing increases in their prothrombin time. The majority of these reports concerned variable elevations in prothrombin times without clinically significant sequelae. Although the relevance of these reports and any mechanism of coagulation alterations is unclear, patients on warfarin should have their prothrombin time more closely monitored.

Drug-Food Interactions

Food in the stomach or upper portions of the small intestine, particularly materials with a high calcium content such as milk, may reduce absorption of the etidronate disodium. (See **DOSAGE AND ADMINISTRATION**.)

Drug-Herb Interactions

Interactions with herbs have not been established.

Drug-Laboratory Interactions

Depending on the time elapsed since the last dose of etidronate, the Etidronate therapy may prevent bone-imaging diagnostic agents (e.g., technetium-^{99m}-methylene diphosphonate) used in bone scans, from adhering to bone and thus affect the interpretation of imaging results.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- For the treatment of Paget's disease, the physician should adhere to the recommended dose regimen in order to avoid unnecessary overtreatment with APO-ETIDRONATE (See **ADVERSE REACTIONS**).

- The response to therapy may be slow onset and may continue even for months after treatment when the drug has been discontinued. Dosage should not be increased prematurely nor should treatment be resumed before there is clear evidence of reactivation of the disease process.

- Retreatment should not be initiated until the patient has had at least a three-month drug-free interval to determine whether remission has occurred and to promote mineralization of any unmineralized osteoid which may have developed.

- APO-ETIDRONATE should be taken on an empty stomach as a single oral daily dose, at least two hours before or after meals with a full glass of water. However,

should gastrointestinal discomfort occur, the dose may be divided. To maximize absorption, patients should avoid taking the following items within two hours of dosing:

- Food, especially those high in calcium, such as milk or milk products.
- Vitamins with mineral supplements or antacids which are high in metals such as calcium, iron, magnesium or aluminum.

Recommended Dose and Dosage Adjustment

Paget's Disease

Initial Treatment Guidelines: The recommended initial dose of APO-ETIDRONATE for most patients is 5 mg/kg body weight/day, not to exceed a period of six months. Doses above 10 mg/kg/day should be reserved for use when there is an overriding requirement for suppression of increased bone turnover associated with Paget's disease or when the patient requires more prompt reduction of elevated cardiac output. Treatment with doses above 10 mg/kg/day should be approached cautiously and should not exceed three months duration. Doses in excess of 20 mg/kg/day are not recommended.

Urine hydroxyproline excretion and/or serum alkaline phosphatase levels should be monitored periodically during the course of APO-ETIDRONATE therapy.

Retreatment Guidelines: Retreatment should be initiated only after:
1) An etidronate disodium-free period of at least 90 days and,
2) There is biochemical, symptomatic or other evidence of active disease process.

It is advisable to monitor patients every 3 to6 months, although some patients may go drug-free for extended periods. Retreatment regimens are the same as for initial treatment. For most patients the original dose will be adequate for retreatment. If not, consideration should be given to increasing the dose within the recommended guidelines.

Hypercalcemia of Malignancy

APO-ETIDRONATE tablets may be started on the day following the last dose of etidronate disodium I.V. Infusion. The recommended oral dose of APO-ETIDRONATE for patients who have hypercalcemia is 20 mg/kg body weight/day for 30 days. If serum calcium levels remain normal or at clinically acceptable levels, treatment may be extended. Treatment for more than 90 days has not been adequately studied and is not recommended.

Missed Dose
Patients should be instructed that if they miss a dose of APO-ETIDRONATE, they should take 1 tablet as they normally would for their next dose. Patients should not double their next dose or take 2 tablets on the same day.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

Clinical experience with etidronate disodium overdosage is extremely limited. Decreases in serum calcium following substantial overdosage may be expected in some patients. Signs and symptoms of hypocalcemia also may occur in some of these patients. In one event, an 18-year-old female who ingested an estimated single dose of 4,000 to6,000 mg (67 to100 mg/kg) of etidronate disodium was reported to be mildly hypocalcemic (1.88 mmol/L or 7.52 mg/dL) and experienced paresthesia of the fingers. Hypocalcemia resolved 6 hours after lavage and treatment with intravenous calcium gluconate. A 92-year-old female who accidentally received 1,600 mg of etidronate disodium per day for 3.5 days experienced marked diarrhea and required treatment for electrolyte imbalance. Some patients may develop vomiting and expel the drug. Gastric lavage may remove unabsorbed drug. Standard procedures for treating hypocalcemia, including the intravenous administration of ionizable calcium salts, would be expected to restore physiologic amounts of ionized calcium and relieve signs and symptoms of hypocalcemia. Such treatment has been effective.

ACTION AND CLINICAL PHARMACOLOGY

Etidronate disodium acts primarily on bone. It can inhibit the formation, growth and dissolution of hydroxyapatite crystals and their amorphous precursors by chemisorption to calcium phosphate surfaces. Inhibition of crystal resorption occurs at lower doses than are required to inhibit crystal growth. Both effects increase as the dose increases.

General
The gastrointestinal absorption of etidronate disodium is approximately 3.5%. The plasma half life ($t_{½}$) is between 1 to 6 hours. The drug is not metabolized. It is either rapidly excreted unchanged in the urine or is taken up by bone. About half the dose is deposited in the skeleton, with the subsequent elimination controlled by bone turnover rate, which in turn is influenced by the metabolic conditions and specific bone type.

Paget's Disease
Etidronate disodium acts on bones by slowing the rate of turnover (resorption and accretion) both in Pagetic lesions and to a lesser extent in the normal bone remodeling process. During treatment with etidronate disodium histologic examination of bone from Pagetic lesions shows a decrease in the excessive cellular activity accompanied by a suppression of bone turnover, an improved histologic pattern including lamellar bone

formation, a decrease in fibrotic marrow pattern, a decrease in vascularity, and an increase in normal hematopoietic marrow elements.

Etidronate disodium therapy, in patients with Paget's disease, results in lowering of urinary hydroxyproline as well as serum alkaline phosphatase, and radionuclide uptake by Pagetic bone is reduced in many patients. The associated pathophysiological manifestations of increased bone vascularity, increased skin temperature, and increased cardiac output are also improved. These actions are generally accompanied by symptomatic improvement, including reduction of bone pain.

At a dose of 20 mg/kg/day in excess of three months and after six or more months of therapy at doses of 10 mg/kg/day, unmineralized osteoid can accumulate. (See **WARNINGS AND PRECAUTIONS**).

Hypercalcemia of Malignancy
Hypercalcemia of malignancy is usually related to increased bone resorption associated with the presence of neoplastic tissue. It occurs in 8 to 20% of patients with malignant disease. Whereas hypercalcemia is more often seen in patients with demonstrable osteolytic, osteoblastic, or mixed metastatic tumors in bone, discrete skeletal lesions cannot be demonstrated in at least 30% of patients. Etidronate disodium's reduction of abnormal bone resorption is responsible for its therapeutic benefit in hypercalcemia. Following successful treatment with etidronate disodium I.V. Infusion, which effectively reduces total and ionized serum calcium, etidronate disodium tablets help maintain clinically acceptable serum calcium levels.

STORAGE AND STABILITY

Store at controlled room temperature (15°C to 30°C). Protect from moisture.

SPECIAL HANDLING INSTRUCTIONS

Keep out of reach and sight of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage forms and availability

APO-ETIDRONATE 200 mg tablets: Each white, rectangular tablet, engraved "APO" on one side and "200" on the other side, contains 200 mg of etidronate disodium. Available in bottles of 100.

APO-ETIDRONATE 400 mg tablets: Each white to off-white, capsule-shaped, biconvex tablet, engraved "ETI" score "400" on one side, "APO" on the other side, contains 400 mg of etidronate disodium. Available in bottles of 100 and blisters of 100.

Composition

In addition to the active ingredient, etidronate disodium, each tablet contains crospovidone and magnesium stearate.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

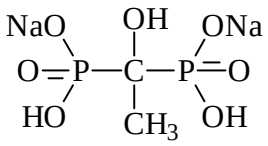
Drug Substance

Proper Name: Etidronate Disodium

Chemical Name: Disodium salt of (1-hyroxyethylidene) bisphosphonic acid.

Molecular formula and molecular weight: $C_2H_6P_2Na_2O_7$, 250.0 g/mol

Structural Formula:



Physicochemical properties:

Solution pH:	The pH of a 1.0% aqueous solution of etidronate disodium is 4.2 to 5.2.
Description:	Etidronate disodium is a white powder, highly soluble in water but insoluble in most other solvents. At temperatures above 250°C, etidronate disodium undergoes thermal decomposition.

CLINICAL TRIALS

Comparative Bioavailability

A randomized, single-dose, blinded standard 2-way crossover comparative bioavailability study, conducted under fasting conditions, was performed on healthy male volunteers. The results obtained from 40 volunteers who completed the study are summarized in the following table. The rate and extent of absorption of etidronate was measured and compared following a single oral dose (2 x 200 mg tablets) of APO-ETIDRONATE (etidronate disodium) 200 mg (Apotex Inc.) and DIDRONEL® (etidronate disodium) 200 mg tablets (Proctor and Gamble pharmaceuticals Canada Inc.).

Summary Table of the Comparative Bioavailability Data
Etidronate (Dose: 2 x 200 mg) From Measured Data – Under Fasting Conditions
Based on Etidronate

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**	90% Confidence interval (%)**
	Apo-Etidronate	Didronel® †		
AUC_T (ng•hr/mL)	1053 1193 (49)	1036 1248 (63)	101.6	88.9-116.2
AUC_I (ng•hr/mL)	1087 1230 (49)	1068 1285 (63)	101.8	89.1-116.3
C_{MAX} (ng/mL)	330 395 (59)	292 365 (69)	113.0	92.9-137.4
T_{MAX}^{*} (hr)	1.17 (93)	1.68 (76)	--	--
$T_{½}^{*}$ (hr)	4.41 (31)	4.19 (24)	--	--

* Arithmetic means (CV%).
** Based on the least squares estimate.
† Didronel® is marketed by Procter & Gamble Pharmaceuticals Canada Inc., Canada.

Paget's Disease

Etidronate disodium acts primarily on bone. It can modify the crystal growth of calcium hydroxyapatite by chemisorption onto the crystal surface. Depending on concentration, the drug may either inhibit crystal resorption or crystal growth. Etidronate disodium slows the rate of bone turnover (bone resorption and new bone accretion) in Pagetic bone lesions and in the normal remodeling process.

Paget's disease is an idiopathic bone disorder characterized by abnormal and accelerated bone resorption and formation in one or more bones. The extent and severity of the disease is highly variable. Characteristic symptoms may be bone pain, varying degrees of bone deformity, and vascular disorders, including abnormally elevated cardiac output secondary to the increased vascularity associated with Paget's disease.

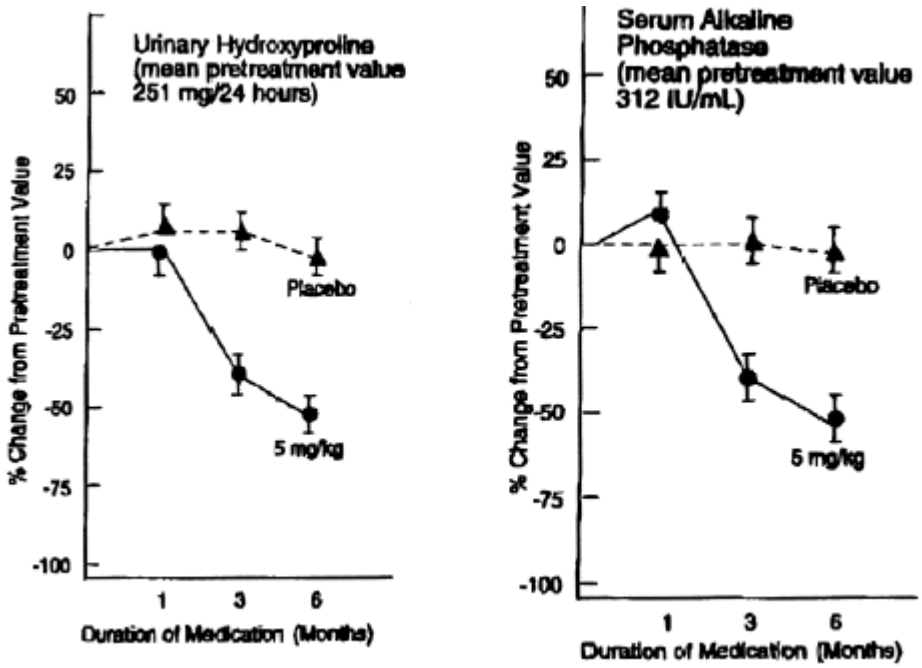
Serum phosphate elevations have been observed when etidronate disodium is administered at daily doses of 10 mg/kg body weight/day or above and occasionally at 5 mg/kg/day. This has not been found to be an indication for discontinuing therapy. This drug-related elevation appears to be the result of increased tubular reabsorption of phosphate by the kidney, and serum values in excess of 2.3 mmol/L (7 mg/100 mL) have been observed with high doses. No adverse effects of etidronate disodium - induced hyperphosphatemia have been found. Serum phosphate levels generally return to normal 2 to 4 weeks after stopping medication.

To elicit the bone effects of the drug, patients with Paget's disease of bone, myositis ossificans progressiva, as well as normal volunteers on prolonged bed rest, were studied. In general etidronate disodium, at a dose of 20 mg/kg/day, produced a reduction of approximately 50% in both mineral accretion rate and mineral resorption rate as measured by ^{47}Calcium kinetics methods. Patients generally showed an increased intestinal calcium absorption (and urinary calcium excretion) and a more positive calcium balance on the drug, but only a slight, clinically insignificant increase in serum calcium levels.

The first evidence of therapeutic response to etidronate disodium in Paget's patients, reduction of urinary hydroxyproline excretion, usually occurs after one to three months of medication. Average percent reductions of elevated hydroxyproline and alkaline phosphatase during etidronate disodium therapy at the recommended dose of 5 mg/kg/day for 6 months are shown in Figure 1.

Etidronate disodium's effectiveness has been demonstrated primarily in patients with polyostotic Paget's disease with symptoms of pain and with clinically significant elevations of urinary hydroxyproline and serum alkaline phosphatase. In patients treated with etidronate disodium at the dose of 5 mg/kg/day, the elevated urinary hydrxoxyproline and serum phosphatase decreased by 30% or more in about 80% of patients. Hydroxyproline and alkaline phosphatase either returned to normal or were decreased by at least half in about 60% and 50% of patients respectively.

FIGURE 1: Percentage Change In Elevated Biochemical Parameters (Patients Treated With Etidronate Disodium At 5 mg/kg/day In Double-Blind, Placebo-Controlled Studies)



In controlled studies of Paget's patients, approximately 60% of the patients experienced decreased pain and/or improved mobility. About 40% of the patients in the placebo group showed similar subjective improvement. Objective measurements in etidronate disodium-treated patients have shown reductions of elevated cardiac output in about 65% of the patients. Reductions in elevated skin temperature over Pagetic lesions have also been measured. The number of treated patients in these categories is still too small to predict with certainty how likely such a result will be in any given patient. Objective evidence of hearing improvement has not been demonstrated.

Histologic examination of Pagetic bone from patients treated with etidronate disodium shows a reduction in the excessive cellular activity, accompanied by a suppression of abnormal bone resorption and accretion. Marrow spaces become less vascular and normal fat and hematopoietic cellular elements replace the fibrous Pagetic marrow. Accumulation of unmineralized osteoid was frequently observed in patients treated with 20 mg etidronate disodium/kg/day for six months, and in some patients after longer periods of therapy at lower doses. This accumulation of osteoid is more marked in Pagetic bone than in the uninvolved portion of the skeleton. Withdrawal of the drug permits the osteoid to mineralize normally.

Impaired vitamin D metabolism could be associated with decreased calcium absorption. At a clinical dose of 20 mg/kg/day, etidronate disodium has been observed to increase intestinal calcium absorption. In addition, administration of vitamin D_3 or its active metabolite does not reverse etidronate disodium -induced inhibition of mineralization. This would seem to rule out any important effect of the drug on vitamin D metabolism at clinically employed doses.

Hypercalcemia of Malignancy
In a multicentre, randomized, double-blind study, patients with hypercalcemia due to malignant disease or with hypercalcemia due to primary hyperparathyroidism disease were treated with daily intravenous infusions of etidronate disodium I.V. Infusion plus saline or saline alone. All patients were eligible to receive up to 3 liters of additional saline and 80 mg furosemide daily during the I.V. treatment period.

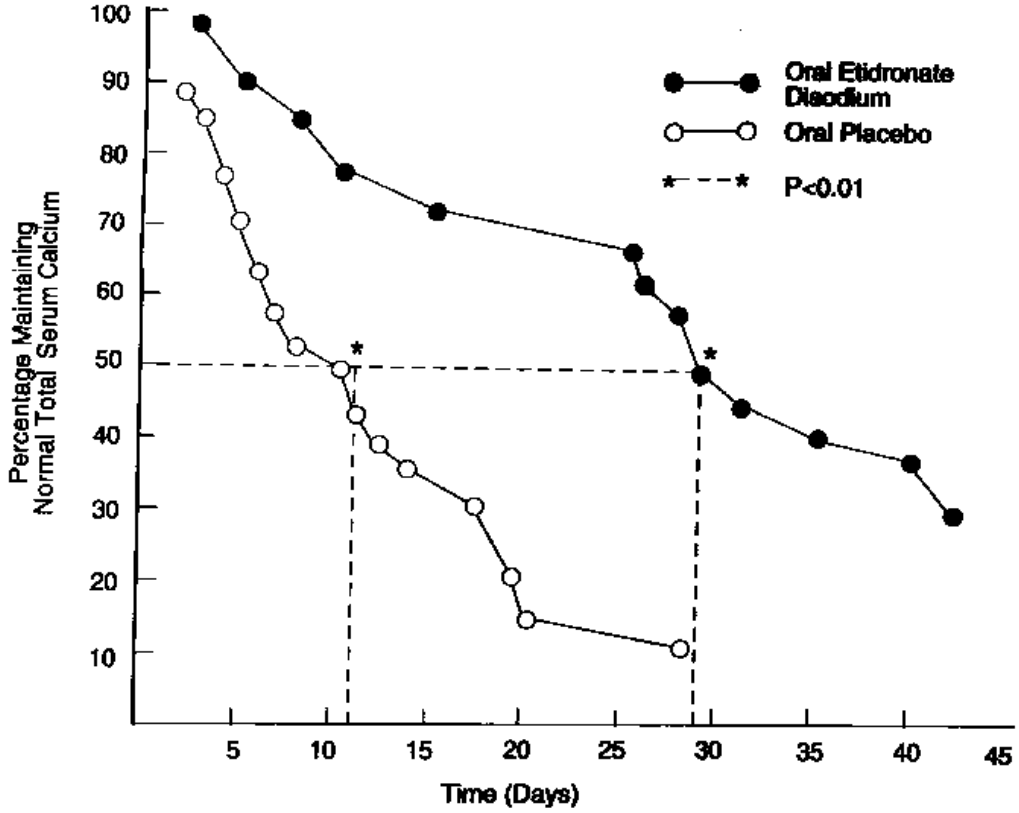
Patients in this study could participate in one or more of four treatment periods, which, in themselves, constituted individual studies. Three of the periods involved evaluating a response to IV infusion therapy; the other involved evaluating a response to maintenance therapy with oral etidronate disodium (blinded oral etidronate disodium or oral placebo).

In this trial, patients who had reductions in serum calcium to the normal range after the etidronate disodium I.V. therapy were randomized to receive either oral etidronate disodium at a dose of 20 mg/kg/day for 90 days, or a similar placebo regimen.

Eighty-one of the original 233 patients continued to the oral treatment period of the study, 63 of whom could be analyzed. Of these analyzable patients, about half were treated with oral etidronate disodium. A comparison of the duration of response between the two groups, using a lifetable analysis method, demonstrated a statistically significantly longer ($p<0.01$) median time of noromocalcemia for patients treated with oral etidronate disodium (29 days) versus placebo-treated patients (11 days) (Figure 2).

The success rates were 35% for oral etidronate disodium and 6% for placebo when total serum calcium was analyzed. The difference between the groups was statistically significant ($p<0.01$). Twenty patients were available for analysis of albumin adjusted serum calcium levels. The success rates were 38% and 0% respectively.

Figure 2: Percentage Of Patients With Hypercalcemia Of Malignancy Maintaining Normal Total Serum Calcium Levels Versus Time (Days).



DETAILED PHARMACOLOGY

Etidronate disodium chemisorbs onto hydroxyapatite (a calcium phosphate hydroxide) at physiological pH. This may be responsible for etidronate disodium's activity **in vivo** - at low doses, reduction of bone turnover (resorption and formation) and at high doses, inhibition of mineral accretion.

Following oral administration to animals the absorption of etidronate disodium varies from 3% in rats and rabbits to 5 to 21% in young dogs. In humans the absorption is 3 to 4% of the oral dose. The non-absorbed fraction of orally administered etidronate disodium is excreted unchanged in the feces; of the absorbed fraction, about half is deposited in the skeleton, while the remainder is rapidly excreted without metabolism in the urine. Based on non-compartmental pharmacokinetics in normal human subjects, the plasma half-life of etidronate disodium is between 1 to 6 hours.

The elimination of etidronate disodium from bone is slow (the half-life is approximately 120 days) and is controlled by the bone turnover rate, which in turn is influenced by metabolic conditions and specific bone types.

The pharmacologic conclusion from animal studies is that etidronate disodium significantly reduces the rate of bone turnover. The data supports a conclusion that the level of response to etidronate disodium can be controlled by modifying either the dose or the duration of dosing, or both. The effect of etidronate disodium on inhibition of mineralization is reversible when medication is stopped.

TOXICOLOGY

The acute oral toxicity of etidronate disodium is low relative to the clinical dosage. The oral LD_{50} is about 1300 mg/kg in rats and the emetic dose in dogs is approximately 85 mg/kg.

No significant adverse effects were seen in rats and dogs fed diets containing up to 1% etidronate disodium for two years other than a spontaneously remitting microcytic, hypochromic anemia in dogs during the first 6 months of the study. In rats treated by oral gavage for 1 year at dosages up to 216 mg/kg the primary effect was an extension of the pharmacology on the skeleton from long term continuous administration with subsequent secondary effects on organ systems.

Spontaneous fractures have occurred in dogs receiving etidronate disodium at doses of 2 mg/kg subcutaneously for 1 year and orally at 100 mg/day for 2 years. Higher doses completely inhibited bone mineral accretion and turnover, resulting in susceptibility to fractures after 9 to 12 months of continuous treatment. The spontaneous fractures healed normally when the drug was discontinued and at lower parenteral doses occurred and healed normally while etidronate disodium treatment continued. Subsequent studies of fracture healing in dogs and rats have demonstrated that when etidronate disodium is administered at low but not at high doses, the bone heals normally following fracture.

In order to study the effects of intravenous infusion followed by oral administration for the indication of hypercalcemia, etidronate disodium was administered intravenously to dogs at doses of 0, 10, or 20 mg/kg for 5 days (2 hr/day) followed by oral administration, 0 or 300 mg (ca.20 mg/kg), for either 7 (short cycle) or 21 (long cycle) days. This regimen was repeated three times. No compound related changes in the clinical chemistry, hematologic, or histologic parameters were observed in the 10 mg/kg IV/300mg PO long cycle group, or in those groups dosed with 0 mg/kg IV/300mg PO at both the long and short cycles. Chronic interstitial nephritis was observed in those long cycle groups dosed with 20 mg/kg IV/300mg PO, and in the short cycle groups dosed with either 10 or 20 mg/kg IV/0 or 300 mg PO.

Mutagenesis, Carcinogenesis, Impairment of Fertility

A two year feeding study in rats and five mutagenicity assays (dominant lethal assay in mice, two *Salmonella* microsomal point mutation assays, a micronucleus test in the bone marrow of the Chinese hamster, and an *in vitro Saccharomyces cerevisiae* MP-I point mutation assay) indicate that etidronate disodium is not carcinogenic or mutagenic.

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PART III: CONSUMER INFORMATION

[Pr]APO-ETIDRONATE
etidronate disodium tablets USP

This leaflet is part III of a three-part "Product Monograph" published when **APO-ETIDRONATE** was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about APO-ETIDRONATE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
- Treatment of symptomatic Paget's disease of the bone
- Short-term (30 to 90 days) maintenance of blood calcium levels following treatment with etidronate disodium I.V**.** Infusion for patients with hypercalcemia of malignancy (i.e. high blood calcium secondary to malignancy disease)

What it does:
To understand how the APO-ETIDRONATE therapy works, it is important to understand your bone health.

Bone is a living tissue that your body constantly renews. In this normal process, your body breaks down old bone tissue and replaces it with new bone. In Paget's disease, this process is abnormal and accelerated. APO-ETIDRONATE acts on bones by slowing the abnormal and accelerated rate of bone turnover in Paget's disease.

People with Paget's disease can experience bone pain, bone deformity and vascular disorder (i.e blood vessel disorder associated with Paget's disease). In research studies, etidronate disodium therapy improved Paget's symptoms including the reduction of bone pain in patients with Paget's disease.

APO-ETIDRONATE can also be used to treat hypercalcemia of malignancy or high blood calcium, which is a condition that occurs in 8 to 20% of patients with malignant diseases. By slowing the rate of bone turnover, APO-ETIDRONATE also reduces the release of calcium from the bones to the blood stream, which in turn reduces the blood calcium level to an acceptable level.

When it should not be used:
APO-ETIDRONATE is not suitable for everyone.

APO-ETIDRONATE should not be used:
- If you have unresolved osteomalacia, which is a condition of inadequate or delayed bone mineralization (formation).
- If you are allergic to APO-ETIDRONATE and any of its ingredients (see below).

What the medicinal ingredient is:
Etidronate disodium

What the nonmedicinal ingredients are:
Magnesium stearate and crospovidone.

What dosage forms it comes in:
Tablets, 200mg and 400 mg

WARNINGS AND PRECAUTIONS

Before you use APO-ETIDRONATE talk to your doctor or pharmacist if:

- You have unresolved osteomalacia, which is a condition of inadequate or delayed bone mineralization (formation).
- You have problems with your kidneys, stomach or intestines.
- You are pregnant or nursing.
- You are allergic to APO-ETIDRONATE and any of its ingredients.
- You have sores in the mouth. This can lead to osteonecrosis of the jaw.

  Your doctor may check if you:
  - smoke
  - have or have had teeth and/or gum disease
  - have dentures that do not fit well
  - have other relevant medical conditions at the same time, such as; low red blood cell count (called anemia) or if your blood cannot form clots in the normal way.

  Your doctor may tell you to stop taking APO-ETIDRONATE until all sores in your mouth are healed.
- You have one of the following risk factors: cancer; chemotherapy, radiotherapy of the head or neck, treatment with corticosteroids, or dental problems or dental infections. If so, a dental examination and any necessary dental procedures should be considered before you start treatment with APO-ETIDRONATE.

Be sure to tell your health care providers, including doctors and dentists, about all

medicines you are taking, including APO-ETIDRONATE.

Patients with Paget's disease of bone should maintain an adequate intake of calcium and vitamin D.

INTERACTIONS WITH THIS MEDICATION

If taken with some other medicines, the effects of APO-ETIDRONATE or the effects of other medicines may be changed. Please check with your doctor or pharmacist before taking other medications with APO-ETIDRONATE.

Drugs that may interact with APO-ETIDRONATE include corticosteroid, phosphate, calcitonin, furosemide, warfarin or mithramycin.

To maximize the absorption, the following foods and medicines should not be taken within 2 hours of taking APO-ETIDRONATE: Antacids, vitamins with mineral supplements such as iron, calcium supplements, laxatives containing magnesium and foods, especially food high in calcium, such as milk or milk products.

PROPER USE OF THIS MEDICATION

As with all medications, it is important to take as directed by your doctor.

Usual dose:

For Paget's disease, the recommended initial dose of APO-ETIDRONATE for most patients is 5 mg per kilogram of bodyweight per day, not to exceed a period of 6 months.

For hypercalcemia of malignancy, the recommended dose is 20 mg per kilogram of bodyweight per day for 30 days.

Overdose:

If you think you have taken too much APO-ETIDRONATE, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a day (or more) of the treatment, do not take 2 tablets the same day. Take 1 tablet on the day you remember and continue with the therapy.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

With any medication, there is some chance of side effects. The most common side effects observed with APO-ETIDRONATE are nausea and diarrhea.

Rarely reported side effects include confusion, a burning sensation of the tongue, hair loss, and a sensation of numbness, prickling or tingling.

In patients with Paget's disease, joint pain or new, increased or returning bone pain may occur. In some patients, the pain resolved while etidronate disodium was continued, but persisted for several months in others. On occasion, APO-ETIDRONATE may have to be stopped.

Ophthalmologic

Ocular disturbances including conjunctivitis, uveitis, episcleritis, iritis and scleritis have been reported with bisphosphonate use. There have been published reports of conjunctivitis with etidronate. Patients with ocular events other than uncomplicated conjunctivitis should be referred to an ophthalmologist for evaluation. Treatment may need to be discontinued.

Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. Poor healing of these fractures was also reported. Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered pending a risk/benefit assessment.

Very rarely patients have reported non-healing jaw wounds while receiving drugs in this class, such as etidronate disodium. Consult your doctor if you experience persistent pain in your mouth,

teeth or jaw, or if your gums or mouth heal poorly.

IMPORTANT SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and get immediate medical help.
	Only if severe	In all cases	
Uncommon (less than 1 in 100)			
Allergic reactions such as: hives; skin rash; itching			✓
Osteonecrosis of the jaw: (numbness or feeling of heaviness in the jaw, poor healing of the gums especially after dental work, loose teeth, exposed bone in mouth, pain in the mouth, teeth or jaw, sores or non-healing sores in the mouth or discharge, dry mouth, swelling or gum infections, bad breath)		✓	
Rare (less than 1 in 1000)			
Worsening of asthma			✓
Blood disorders with symptoms of bleeding, bruising and increased infections.		✓	
Skin reactions (rash, sores, blisters) involving mucous membranes			✓
Pain and swelling of the tongue or esophagus (tube connecting the mouth and stomach)			✓
Ophthalmologic ocular disturbances including conjunctivitis		✓	
Atypical, low energy or low trauma fractures of the femoral shaft		✓	
Very rare (less than 1 in 10,000)			
Worsening of stomach and intestinal ulcers			✓

This is not a complete list of side effects. For any unexpected effects while taking APO-ETIDRONATE, contact your doctor or pharmacist.

HOW TO STORE IT

Store at controlled room temperature (15°C to 30°C). Protect from moisture.

Keep out of reach and sight of children.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting DISpedia, Apotex's Drug Information Service, at

1-800-667-4708.

This leaflet can also be found at http://www.apotex.ca/products.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

Date of Revision: December 07, 2017