PRODUCT MONOGRAPH

PrDIDRONEL®

Etidronate Disodium Tablets, USP

200mg

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

Procter & Gamble
PHARMACEUTICALS

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Control# 097308

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[Pr]Didronel®

Etidronate Disodium tablets USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	etidronate disodium tablets 200 mg	No clinically relevant nonmedicinal ingredients *For a complete listing see Dosage Forms, Composition and Packaging Section*

INDICATIONS AND CLINICAL USE

Didronel is indicated for:

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

Pediatrics

The safety and effectiveness of Didronel in children has not been established.

Use in Osteoporosis

Etidronate disodium (200 mg) as a single ingredient, indicated for the treatment of Paget's disease and Hypercalcemia of Malignancy, should not be used for the management of osteoporosis.

CONTRAINDICATIONS

Didronel 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 Didronel.

WARNINGS AND PRECAUTIONS

General

The physician should adhere to the recommended dose regimen in order to avoid unnecessary overtreatment with Didronel (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, inclusing 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 hygeine). 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.

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

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

Musculoskeletal

Although there is no evidence of impaired fracture healing with Didronel, in case of spontaneous or pathological fractures occurring during Didronel 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, Didronel 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, Didronel 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 Didronel 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 Didronel.

Renal

Since absorbed Didronel 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.

Special Populations

Pregnant Women: Studies performed in rats and rabbits using orally administered Didronel 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: Didronel 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 Didronel 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 Didronel dose levels of 10 mg/kg/day or above may be suggestive of non-compliance.

Hyperphosphatemia: Didronel 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 Didronel I.V. Infusion therapy and/or oral Didronel 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 Didronel is administered at doses greater than 5 mg/kg/day. The incidence is approximately 20% in patients treated with 20 mg/kg/day of Didronel.

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 Didronel-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 Didronel 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, pre-existing 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 Didronel 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 Didronel 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 Didronel (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.

- Didronel 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 Didronel 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 Didronel therapy.

Retreatment Guidelines: Retreatment should be initiated only after:

1) A Didronel-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 3-6 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
Didronel tablets may be started on the day following the last dose of Didronel I.V. Infusion. The recommended oral dose of Didronel 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 Didronel, 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

Clinical experience with Didronel 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 4,000-6,000 mg (67-100 mg/kg) of Didronel 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

Didronel (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 Didronel is approximately 3.5%. The plasma half life ($t_{½}$) is between 1-6 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
Didronel 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 remodelling process. During treatment with Didronel 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.

Didronel 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. Didronel's reduction of abnormal bone resorption is responsible for its therapeutic benefit in hypercalcemia. Following successful treatment with Didronel I.V. Infusion, which effectively reduces total and ionized serum calcium, Didronel tablets help maintain clinically acceptable serum calcium levels.

STORAGE AND STABILITY

Store at controlled room temperature (15 - 30^{O}C).

DOSAGE FORMS, COMPOSITION AND PACKAGING

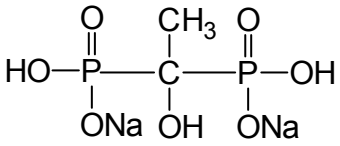
Didronel 200 mg (etidronate disodium) is supplied as a rectangular white tablet with “P&G” on one face and “402” on the other face in bottles of 60 tablets.

Each 200 mg Didronel tablet contains 200 mg etidronate disodium USP as active ingredient. Each tablet contains the following inactive ingredients: magnesium stearate, microcrystalline cellulose, and pregelatinized starch.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name:	Etidronate Disodium
Chemical Name:	Disodium salt of (1-hyroxyethylidene) bisphosphonic acid.
Structural Formula:	
Molecular Formula:	$C_2H_6P_2Na_2O_7$
Molecular Weight:	250.0
Solution pH:	The pH of a 1.0% aqueous solution of etidronate disodium is 4.2-5.2.
Description:	Etidronate disodium is a white powder, highly soluble in water but insoluble in most other solvents. At temperatures above 250^{o}C, etidronate disodium undergoes thermal decomposition.

CLINICAL TRIALS

Paget's Disease

Didronel 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. Didronel slows the rate of bone turnover (bone resorption and new bone accretion) in Pagetic bone lesions and in the normal remodelling 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.

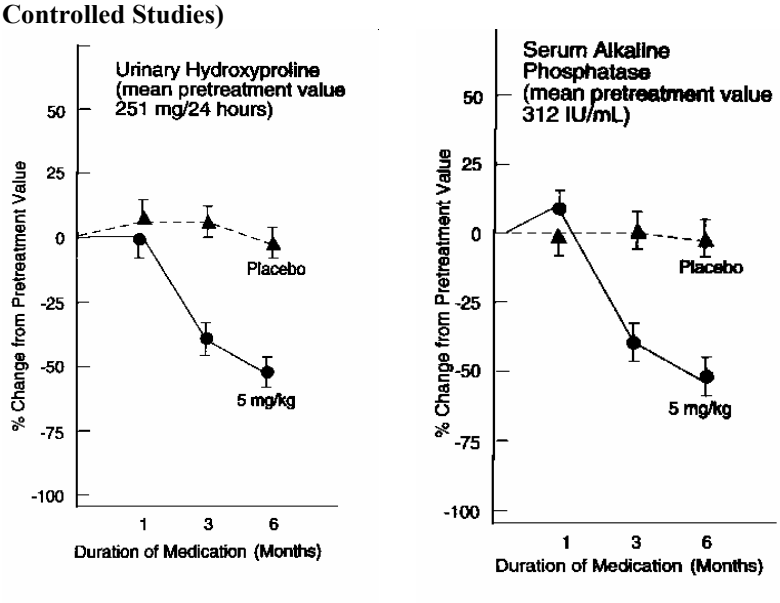
Serum phosphate elevations have been observed when Didronel is administered at daily doses of 10 mg/kg body weight/day or above and occasionally at 5 mg/kg/day. This has not been found to be an indication for discontinuing therapy. This drug-related elevation appears to be the result of increased tubular 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 Didronel-induced hyperphosphatemia have been found. Serum phosphate levels generally return to normal 2-4 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 Didronel 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 Didronel therapy at the recommended dose of 5 mg/kg/day for 6 months are shown in Figure 1.

Didronel'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 Didronel at the dose of 5 mg/kg/day, the elevated urinary hydroxyproline 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 Didronel 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 Didronel-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 Didronel 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, Didronel has been observed to increase intestinal calcium absorption. In addition, administration of vitamin D_3 or its active metabolite does not reverse Didronel-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 Didronel 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.

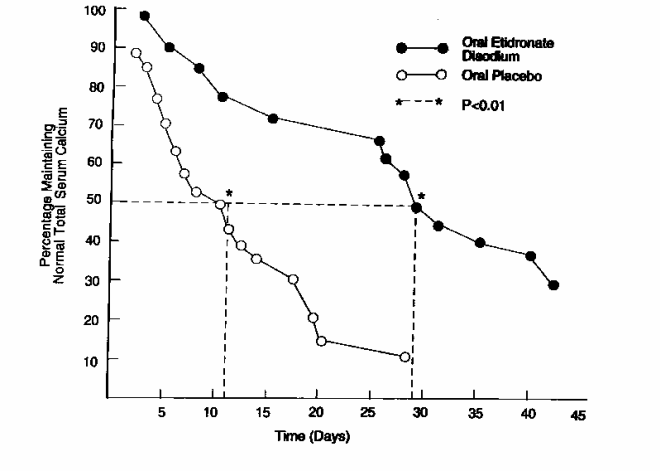
Patients in this study could participate in one or more of four treatment periods, which, in themselves, constituted individual studies. Three of the periods involved evaluating a response to IV infusion therapy; the other involved evaluating a response to maintenance therapy with oral etidronate disodium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

In this trial, patients who had reductions in serum calcium to the normal range after the Didronel 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 Didronel (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 Didronel'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 Didronel is between 1-6 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 9-12 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 Sacchromyces cerevisiae* MP-1 point mutation assay) indicate that Didronel is not carcinogenic or mutagenic.

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Paget's Disease

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PART III CONSUMER INFORMATION

Didronel®
etidronate disodium

This leaflet is part III of a three-part "Product Monograph" published when DIDRONEL was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about DIDRONEL. 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 (30-90 days) maintenance of blood calcium levels following treatment with Didronel I.V. Infusion for patients with hypercalcemia of malignancy (i.e. high blood calcium secondary to malignant disease)

What it does:
To understand how the Didronel 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. Didronel acts on bones by slowing the abnormal and accerelated 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, Didronel therapy improved Paget's symptoms including the reduction of bone pain in patients with Paget's disease.

Didronel can also be used to treat hypercalcemia of malignancy or high blood calcium, which is a condition that occurs in 8-20% of patients with malignant diseases. By slowing the rate of bone turnover, Didronel 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:
Didronel is not suitable for everyone. Didronel 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 Didronel and any of its ingredients (see below).

What the medicinal ingredient is:
Etidronate disodium

What the nonmedicinal ingredients are:
Magnesium stearate, microcrystalline cellulose, and pregelatinized starch.

What dosage forms it comes in:
Didronel 200 mg (etidronate disodium) is a rectangular white tablet with "P&G" on one face and "402" on the other face.

WARNINGS AND PRECAUTIONS

BEFORE you use Didronel 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 Didronel and any of its ingredients
- 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 Didronel

Be sure to tell your health care providers, including doctors and dentists, about all medicines you are taking, including Didronel.

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 Didronel or the effects of other medicines may be changed. Please check with your doctor or pharmacist before taking other medications with Didronel.

Drugs that may interact with Didronel 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 Didronel: Antacids, vitamins with mineral supplements such as iron, calcium supplements, laxative 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 Didronel 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 take too many tablets on any given day, contact your doctor immediately or go to the nearest emergency department.

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 Didronel 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 Didronel was continued, but persisted for several months in others. On occasion, Didronel may have to be stopped.

Very rarely patients have reported non-healing jaw wounds while receiving drugs in this class, such as Didronel. Consult your doctor if you experience persistent pain in your mouth, teeth or jaw, or if your gums or mouth heal poorly.

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

Symptom / Effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Uncommon (less than 1 in 100)			
Allergic reactions such as: hives; skin rash; itching			✓
Rare (less than 1 in 1000)			
Worsening of asthma			✓
Blood disorders with symptoms of bleeding, bruising and increased infection		✓	
Skin reactions (rash, sores, blisters) involving mucous membranes			✓
Pain and swelling of the tongue or esophagus (tube connecting the mouth & stomach)			✓
Very rare (less than 1 in 10,000)			
Worsening of stomach and intestinal ulcers			✓

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

HOW TO STORE IT

The Didronel therapy should be stored at room temperature (15 - 30°C). Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs . If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone:866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals is available by contacting the sponsor, Procter & Gamble Pharmaceuticals Canada Inc. at:
1-800-565-0814

This leaflet was prepared by Procter & Gamble Pharmaceuticals Canada Inc.

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