PRODUCT INFORMATION

DIDROCAL®

A Compliance Pack for Osteoporosis Therapy containing 28 tablets of disodium etidronate 200 mg and 76 tablets of calcium carbonate 1.25 g.

NAME OF THE MEDICINE

Non-proprietary name: **Disodium etidronate**

Chemical name: Disodium dihydrogen (1-hydroxyethylidene) diphosphonate

CAS No: 7414-83-7

\[
\text{ONa} \quad \text{OH} \quad \text{ONa} \\
\text{HO-P-C-P-OH} \\
\text{O} \quad \text{CH}_3 \quad \text{O}
\]

Non-proprietary name: **Calcium carbonate**

Chemical name: Calcium carbonate

CAS No: 471-34-1
**DESCRIPTION**

Disodium etidronate, often referred to in the literature as EHDP or disodium EHDP, is a white powder, highly soluble in water, with a molecular formula C$_2$H$_6$Na$_2$O$_7$P$_2$. The molecular weight is 250.

It is supplied in rectangular white tablets containing 200 mg of disodium etidronate for oral administration.

The light blue calcium carbonate tablets are a conventional oral formulation used as a supplement to dietary calcium for the formation of normal bone. Each tablet contains the equivalent of 500 mg of elemental calcium.

**PHARMACOLOGY**

Disodium etidronate acts primarily on bone. It can modify the crystal growth of calcium hydroxyapatite *in vitro* by chemisorption onto the crystal surface. Depending on concentration, the drug primarily inhibits either crystal resorption or crystal growth. The exact mechanism of *in vivo* activity is uncertain and may additionally involve direct effects on cellular metabolic processes.

Serum phosphate elevations have been observed when disodium etidronate 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. No adverse effects of etidronate-induced hyperphosphataemia have been found. Serum phosphate levels generally return to normal 2 - 4 weeks after stopping medication. Therapy with disodium etidronate alone is not accompanied by clinically significant changes in serum parathyroid hormone or serum calcium levels.

Disodium etidronate is not metabolised. After oral doses of up to 1600 mg of the disodium salt, the amount of drug absorbed is approximately 3 to 4%. In normal subjects, plasma half-life (t½) of etidronate, based on non-compartmental pharmacokinetics, is 6.0 ± 0.7 hours.

Within 24 hours about one-half of the absorbed dose is excreted in the urine. The remainder is chemically adsorbed on the bone and is slowly eliminated. Absorption varies appreciably between individuals. Unabsorbed drug is excreted in the faeces.

**Osteoporosis**

Osteoporosis is an age-related disorder characterised by a decrease in bone mass and an increased susceptibility to fracture. DIDROCAL is a non-hormonal treatment used to increase mineralised bone mass. By timing delivery and withdrawal, etidronate acts to modulate osteoclasts to reduce the mean resorption depth of the affected basic multicellular units. Two weeks of disodium etidronate treatment (400 mg/day) is repeated every 13 weeks. During the 11 week etidronate-free period adequate amounts of calcium are supplemented to ensure proper intake of this essential bone mineral. Reducing bone turnover and resorptive cavity depth results in the maintenance of existing trabecular structure.
CLINICAL TRIALS

The majority of clinical trials have been conducted in post menopausal females with osteoporosis. Controlled clinical trials have not been conducted in men with osteoporosis. However, data from uncontrolled studies indicate a similar effect of disodium etidronate on spinal mineral density in males and females, although no data on antifracture efficacy are available in males. Clinical trials examining the prevention of osteoporosis have also been conducted in both male and female patients on corticosteroid therapy.

Clinical trials in postmenopausal osteoporosis

Clinically, in responsive patients, DIDROCAL produces an increase in bone mass. Data (including limited data up to four years) demonstrate a reduced risk of vertebral fracture and slowing of the progression of vertebral deformity.

The long term effects of DIDROCAL therapy on bone structure, bone strength and fracture rates have not been determined fully.

Pivotal evaluable clinical trials of disodium etidronate intermittent cyclical therapy have been conducted in the USA and Europe. Administration of cyclical disodium etidronate for two years resulted in statistically significant increases in mean spinal bone mineral densities measured by DPA (Dual Photon Absorptiometry), ranging from approximately 2% to approximately 6% and did not occur in all subjects. Continuing the cyclical disodium etidronate for a further two to three years did not result in further significant increases measured by DPA or DEXA (Dual Energy X-ray Absorptiometry), although spinal mineral densities remained approximately 5-6% above baseline values after four years of cyclical etidronate. There are limited data from five to seven years of treatment. Increases in bone mineral density may be associated with a reduction in fracture rate. As all fractures in each treatment group had been recorded as a rate per treatment group, it does not follow that a lower rate per treatment group translates as a lower fracture risk per individual patient. There are insufficient data to establish whether a single course of treatment provides lasting benefits with respect to mineralisation and bone density.

Based on bone biopsy data, DIDROCAL intermittent cyclical therapy, beyond 16 cycles (4 years), was associated with an increased prevalence of mild to moderate osteomalacia and peritrabecular fibrosis. These changes have not been associated with any detectable clinical consequences.

The largest multicentre clinical trials of disodium etidronate intermittent cyclical therapy were conducted in the USA, initially under blinded conditions versus placebo calcium and/or phosphate supplements for three years. Nearly 500 patients with established postmenopausal osteoporosis were studied across all the placebo-controlled clinical trials for 3 years duration in both the USA and Europe.

The major US studies were first extended for two years during which all the patients received DIDROCAL therapy (open-label). At the end of Year 5, there were 125 patients from the US studies and 13 from Europe, who had been continuously on active treatment. Fifty-one of these and 42 patients from the original US control groups, continued on DIDROCAL in a two-year blinded second extension of the US multicentre study. The numbers available for analysis after Year 7 were 40 (on seven years of continuous active therapy) and 34 treated for only four years. Over the final two-year period, similar numbers were randomly allocated to
calcium supplement alone. Fracture data suggested reduced spinal fracture rates were evident during the first 4 years of treatment.

In the US studies, bone mass was also measured at three sites in the hip; the trochanter, Ward’s triangle and the femoral neck. DIDROCAL therapy produced an increase of 1 to 4% in bone mass at the three sites in the hip. On the other hand, calcium supplementation alone was unable to arrest bone loss at these sites. For the trochanter, the gain was statistically significant (p<0.05) compared to placebo. Such gains were maintained for up to 5 years of treatment.

**Clinical trials in corticosteroid-induced osteoporosis**

The efficacy of intermittent cyclical therapy with DIDROCAL in the prevention of corticosteroid-induced osteoporosis (CIO) was evaluated in 258 patients in two randomised, double-blind, placebo-controlled clinical trials. Patients were either currently initiating long-term, high-dose corticosteroid therapy (mean oral dose of ≥7.5 mg/day for the first 90 days followed by at least 12 months of ≥2.5 mg/day of prednisolone or its equivalent) or had commenced such therapy within the last 90 - 100 days. DIDROCAL was administered over four 90-day treatment cycles in which each received a 400 mg tablet of disodium etidronate or placebo daily during the first 14 days of each cycle, followed by 500 mg of elemental calcium for the remaining 76 days of each cycle.

The primary efficacy parameter in these studies was change in lumbar spine bone mineral density (BMD) from baseline to week 52 (endpoint). The results from the studies are listed in the table below.

<table>
<thead>
<tr>
<th>Study</th>
<th>Disodium etidronate</th>
<th>Placebo</th>
<th>Estimated Difference</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>0.30 ± 0.61</td>
<td>-2.79 ± 0.63</td>
<td>3.00 ± 0.84</td>
<td>0.004</td>
</tr>
<tr>
<td>Study 2</td>
<td>0.61 ± 0.54</td>
<td>-3.23 ± 0.6</td>
<td>3.72 ± 0.88</td>
<td>0.023</td>
</tr>
</tbody>
</table>

Study 2 allowed for a 12 month open-label extension in which those patients who completed the initial 12 month study were eligible to enrol. Of the 141 patients originally included in Study 2, 114 participated in the extension. Disodium etidronate therapy was discontinued for the extension study and all patients received 500 mg elemental calcium daily. The results from this 12 month extension indicated a small degree of bone loss in each group. However, compared with baseline, the beneficial effects of disodium etidronate therapy on the lumbar spine observed in the original 12 months were maintained into the second year.

**INDICATIONS**

1. Treatment of osteoporosis. Osteoporosis must be confirmed by the finding of low bone mass (at least two standard deviations below the gender-specific mean for young adults) or by the presence or history of osteoporotic fracture.
2. Prevention of bone loss in patients for whom long-term treatment with high-dose corticosteroids is either about to be commenced or has been recently initiated.

CONTRAINDICATIONS

DIDROCAL is contraindicated for patients with known hypersensitivity to either of the component tablets or their ingredients, and for patients suspected of having clinically overt osteomalacia, which should be treated prior to considering DIDROCAL therapy.

Heterotopic Ossification

Clinical trials have demonstrated no absolute contraindications.

Paget's Disease

At doses of 20 mg/kg/day, disodium etidronate usually stops mineralisation of the new bone in Pagetic lesions. Even on low dose therapy careful radiological studies indicate that osteolytic lesions may progress. Therefore, disodium etidronate should not be used in patients with significant lytic lesions or with lytic lesions involving crucially situated bones.

PRECAUTIONS

General

The physician should adhere to the recommended dose regimen in order to avoid overtreatment with disodium etidronate (see Adverse Effects).

It is most important that DIDROCAL be used in the manner described for intermittent cyclical therapy.

DIDROCAL therapy should be used to treat osteoporosis only after secondary causes, such as hypogonadism, have been excluded or identified and treated as far as possible.

Patients should maintain an adequate nutritional status, and particularly, an adequate intake of calcium and vitamin D.

Calcium can reduce the absorption of disodium etidronate. Therefore, supplemental calcium should not be given on the same days as disodium etidronate and foods high in calcium should be avoided within 2 hours of taking the disodium etidronate tablets (see also Dosage and Administration).

There are no data concerning patients with renal impairment. Disodium etidronate is not metabolised and is excreted intact via the kidney; therefore, treatment of patients with impaired renal function should be undertaken with due caution. Serum creatinine levels should be closely monitored in patients with renal impairment. Serum and urinary calcium should be measured before DIDROCAL is commenced and, if and when clinically indicated, during therapy to detect occurrence of hypercalcaemia or hypercalciuria.
Disodium etidronate has been reported to give rise to an increase in the frequency of bowel movements and diarrhoea. These effects were described at a dose of 20 mg/kg/day but may be seen occasionally at lower doses. The drug should therefore be used with caution in patients with inflammatory bowel disease.

Osteonecrosis of jaw

Osteonecrosis, primarily in the jaw, has been reported in patients treated with bisphosphonates. Most cases have been in cancer patients undergoing dental procedures such as tooth extraction, but some have occurred in patients with postmenopausal osteoporosis or other diagnoses. Most reported cases have been in patients treated with bisphosphonates intravenously but some have been in patients treated orally.

As long term safety data are not available, the need for treatment with DIDROCAL should be reviewed periodically.

Carcinogenicity, Mutagenicity and Impairment of Fertility

No evidence for a carcinogenic effect of disodium etidronate was found in long-term studies in mice and rats at oral doses of up to 50 and 20 mg/kg/day, respectively (ca. 30-40% of the maximum clinical dose based on body surface area).

Disodium etidronate was not genotoxic, as assessed in vitro for gene mutations and chromosomal aberrations. An in vivo assay of chromosomal damage (micronucleus test in Chinese hamsters) was also negative.

The effects of disodium etidronate on fertility have been studied in male and female rats. Treatment of male rats with disodium etidronate at oral doses greater than 100 mg/kg/day (ca. 1.6 times the maximum clinical dose based on body surface area) was associated with a decreased mating rate and an increased incidence of pre-implantation loss. The reproductive capacity of females was adversely affected following treatment with disodium etidronate at oral doses greater than 300 mg/kg/day (ca. 5 times the maximum clinical dose based on body surface area).

Use in Pregnancy (Category B3)

DIDROCAL is not intended for administration to pregnant women.

Reproduction studies have been performed in rats and rabbits. Treatment of pregnant rats with disodium etidronate was associated with embryofetal toxicity and fetal bone abnormalities at oral doses greater than 300 mg/kg/day (ca. 5 times the maximum clinical dose based on body surface area). In female rabbits, the conception rate was decreased at 100 mg/kg/day PO (ca. 3 times the maximum clinical dose based on body surface area). No teratogenic effects were observed in these studies.

There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed, when the potential benefit justifies the potential risk to the fetus.
Use in Lactation
DIDROCAL is not intended for administration during lactation. It is not known whether etidronate is excreted in human milk nor whether it has a harmful effect on the newborn.

Use in Children
DIDROCAL is not intended for administration to children. Safety and effectiveness in children have not been fully established.

Use in the Elderly
Special precautions related to the use of DIDROCAL in geriatric patients have not been identified.

Interactions with Other Medicines
Disodium etidronate is known to interact with calcium and other divalent or trivalent cations (see also Dosage and Administration). Calcium carbonate may interfere with the absorption of tetracycline given concomitantly.

Bone-active drugs which should not normally be administered concurrently with DIDROCAL include other bisphophonates and fluoride. If a patient receiving cyclical disodium etidronate requires imaging with bone-seeking isotopes, false negative bone scans may be obtained.

No data have been generated studying the possible interactions between disodium etidronate and fluoride, and the pivotal clinical trials in osteoporosis excluded patients taking concomitant fluoride therapy. As no controlled data exist on the effect of these two compounds taken together, it is recommended that their concomitant use be avoided.

Concomitant use of DIDROCAL with calcitriol has not been studied, however, due to the potential of excess intake of calcium during the “calcium” days 15-90 of the DIDROCAL cycle, it is recommended that DIDROCAL and calcitriol not be taken concomitantly.

Effects on Laboratory Tests
If a patient currently or recently treated with disodium etidronate requires imaging with bone-seeking isotopes, false negative bone scans may be obtained.

Information for Patients
The patient should adhere closely to the prescribed regimen. The response to intermittent cyclical therapy is one of slow onset and continues over time. To achieve and maintain therapeutic benefits, the regimen must be administered long-term.
ADVERSE EFFECTS

<table>
<thead>
<tr>
<th>Body system</th>
<th>Adverse Events</th>
<th>common (≥1/100)</th>
<th>uncommon (≥1/1000 and &lt;1/100)</th>
<th>rare &lt;1/1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Diarrhoea</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gastritis</td>
<td>x</td>
<td>x</td>
<td></td>
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<tr>
<td></td>
<td>Nausea</td>
<td>x</td>
<td>x</td>
<td></td>
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<tr>
<td></td>
<td>Glossitis</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Central/Peripheral nervous</td>
<td>Headache</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td></td>
<td>Leg cramps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paraesthesias, including peripheral neuropathy</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Musculo-skeletal</td>
<td>Arthralgia</td>
<td></td>
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<tr>
<td></td>
<td>Arthritis</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>Hypersensitivity, including skin rashes</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Blood</td>
<td>Leucopenia</td>
<td>x</td>
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<tr>
<td></td>
<td>Agranulocytosis</td>
<td>x</td>
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<tr>
<td></td>
<td>Pancytopenia</td>
<td>x</td>
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<tr>
<td>Respiratory</td>
<td>Exacerbation of asthma</td>
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<td>x</td>
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<tr>
<td>Psychiatric</td>
<td>Amnesia</td>
<td>x</td>
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<tr>
<td></td>
<td>Confusion</td>
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<tr>
<td></td>
<td>Depression</td>
<td>x</td>
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<tr>
<td></td>
<td>Hallucinations</td>
<td>x</td>
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<td></td>
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<tr>
<td>Skin/appendages</td>
<td>Alopecia</td>
<td>x</td>
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<tr>
<td></td>
<td>Erythema exudativum multiforme</td>
<td></td>
<td></td>
<td>x</td>
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</table>

The major side effect is diarrhoea affecting about 7% of placebo treated patients and 10% of patients at a dose of 5 mg/kg. This incidence rises to approximately 20% in patients at 20 mg/kg but can be reduced by dividing the dose.

In addition, four events, headache, gastritis, leg cramps and arthralgia, occurred with a significantly greater incidence in patients who received DIDROCAL cyclical therapy compared with those who received placebo. All episodes of leg cramps were transient in nature, most occurred at night, and most required no treatment. All patients with arthralgia reported joint discomfort or pain that was generally mild and related to underlying osteoarthritis.

Pain, flatulence, dyspepsia, constipation and vomiting occurred at an incidence comparable to placebo. Exacerbation of existing peptic ulcer with perforation has been reported in a few patients.

The effect of prolonged treatment on dentinogenesis has not been studied.

Reports of side effects have been collected in controlled clinical studies in females with postmenopausal osteoporosis and uncontrolled studies of men with osteoporosis. It should be
noted that long term safety data are not available at this time for males treated with cyclical disodium etidronate.

**DOSAGE AND ADMINISTRATION**

The disodium etidronate tablets should be taken as a single, oral dose at bedtime, preferably on an empty stomach. However, should gastrointestinal disturbance occur, the dose may be divided. To maximise absorption, patients should avoid taking the following within 2 hours of dosing:

- Foods, 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 aluminium.

**Intermittent Cyclical Therapy**

Two white tablets of disodium etidronate (400 mg/day; 5-10 mg/kg/day) for 14 days followed by a 76 day period of calcium (the minimum recommended supplement is 500 mg/day of elemental calcium). It is recommended that patients maintain an adequate intake of dietary calcium and vitamin D. However, calcium can reduce the absorption of disodium etidronate. Therefore, supplemental calcium should not be given on the same days as the tablets of disodium etidronate and foods high in calcium should be avoided within 2 hours of taking the white tablets.

Continued monitoring of efficacy (using bone densitometry where available) during treatment for osteoporosis is recommended. If this is done, then discontinuation of the therapy should be considered if the bone mass does not stabilise or increase after 8 cycles (2 years) of therapy. Patients who attain adequate response to treatment but discontinue treatment for other reasons should be monitored periodically.

**OVERDOSEAGE**

**Disodium etidronate**

Clinical experience with acute overdosage of disodium etidronate is extremely limited. Decreases in serum calcium following substantial overdosage may be expected in some patients. Signs and symptoms of hypocalcaemia may also occur in some of these patients. Some patients may develop vomiting. An 18-year-old female who ingested an estimated single dose of 4,000-6,000 mg (67-100 mg/kg) of disodium etidronate was reported to be mildly hypocalcaemic (7.52 mg/dL or 1.87 mmol/L) and to have experienced paraesthesia of the fingers. A 92-year-old female who accidentally received 1,600 mg of disodium etidronate per day for 3.5 days experienced marked diarrhoea and required treatment for electrolyte imbalance.

Overdose treatment is symptomatic and supportive. Standard procedures for treating hypocalcaemia, including the administration of Ca++ intravenously, would be expected to restore physiologic amounts of ionised calcium and to relieve signs and symptoms of
hypocalcaemia. Consider administration of activated charcoal in the event of a potentially toxic ingestion. Activated charcoal is most effective when administered within 1-hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected.

**Calcium carbonate**

Because of its limited intestinal absorption, overdosage with calcium carbonate is not likely. If mild hypercalcaemia were to occur, signs and symptoms could include polydipsia, polyuria, nausea, vomiting, constipation, abdominal pain, muscle weakness and confusion.

Serum calcium concentration can be safely and effectively lowered by haemodialysis in the management of hypercalcaemic crisis. Treatment of hypercalcaemia also includes cessation of all calcium supplements and Vitamin D.

Contact the Poisons Information Centre for advice on the management of an overdose.

**PRESENTATION**

**DIDROCAL Compliance Pack for Osteoporosis Therapy:** 28 white tablets of disodium etidronate 200 mg, which also contain magnesium stearate, microcrystalline cellulose and starch - pregelatinised maize, and 76 light blue tablets of calcium carbonate 1.25 g, each providing the equivalent of 500 mg calcium, which also contain starch - pregelatinised maize, sodium starch glycollate, magnesium stearate, macrogol 3350, hypromellose, polysorbate 80, indigo carmine CI 73015 and Opaspray blue colour coating dispersion K-1-4213 (ARTG No 1359).

**SPONSOR**

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