Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Didronel PMO.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

A two component therapy consisting of 14 Didronel 400mg tablets and 76 Cacit 500 mg effervescent tablets (equivalent to 500mg elemental calcium). Each Didronel tablet contains 400mg of Etidronate Disodium. Each Cacit 500mg effervescent tablet contains 1250mg of Calcium Carbonate which when dispersed in water provides 500 mg of elemental calcium as calcium citrate.

Excipients:

Each Cacit tablet contains 2 mg Sunset yellow FCF (E110)

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Didronel 400 mg: Tablet
Cacit: Effervescent tablet

Each Didronel 400mg tablet is white, capsule-shaped and marked with ‘NE’ on one face and ‘406’ on the other. Each Cacit 500 mg effervescent tablet is round, flat, white with pink speckles and has a distinctive orange flavour.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of osteoporosis and prevention of bone loss in postmenopausal women considered at risk of developing osteoporosis. Didronel PMO is particularly indicated in patients who are unable or unwilling to take oestrogen replacement therapy. Didronel PMO is also indicated for the prevention and treatment of corticosteroid - induced osteoporosis

4.2 Posology and method of administration

Didronel PMO therapy is a long-term cyclical regimen administered in 90-day cycles. Each cycle consists of Didronel 400mg tablets for the first 14 days, followed by Cacit 500mg tablets for the remaining 76 days.

***Didronel 400mg component:**
One tablet should be taken each day for 14 consecutive days on an empty stomach. It is recommended that patients take the tablet with water at the midpoint of a four hour fast (i.e. two hours before and two hours after food).

***Cacit 500mg component:**
Following 14 days treatment with Didronel 400mg tablets, one Cacit tablet should be dissolved daily in water and drunk immediately after complete dissolution.

Adults and Elderly
The patient should adhere to the prescribed regimen above. Modification of the dosage for the elderly is not required.

Children
No data exists in the use of this therapy in juvenile osteoporosis.

4.3 Contraindications

Known hypersensitivity to any of the ingredients. Treatment of patients with severe renal impairment. Patients with hypercalcaemia (e.g. due to hyperparathyroidism, hypervitaminosis D, decalcifying tumours, severe renal failure, bone metastases), hypercalciuria or renal calculi. Clinically overt osteomalacia. Use in pregnancy and lactation.

4.4 Special warnings and precautions for use

Clinicians should advise patients to adhere to the recommended treatment regimen, and compliance pack.

The majority of patients have been treated for three years. The optimum duration of treatment beyond this has not been established, although a limited number of patients have been treated up to seven years.

In clinical trials for osteoporosis, no clinical osteomalacia was observed with cyclical etidronate therapy. In small groups of patients these trials have continued over seven years.

Continuous administration of etidronate should be avoided.
Patients with significant chronic diarrhoeal disease may experience increased frequency of bowel movements and diarrhoea.

Didronel PMO therapy should be withheld from patients with enterocolitis because of increased frequency of bowel movements.

Caution should be taken in patients with impaired renal function, or a history of renal stone formation. In these patients serum and urinary calcium should be monitored regularly.

Etidronate disodium does not adversely affect serum levels of parathyroid hormone or calcium.

Hyperphosphataemia has been observed in patients receiving etidronate disodium, usually in association with doses of 10-20mg/kg/day. No adverse effects have been traced to this, and it does not constitute grounds for discontinuing therapy. It is apparently due to a drug-related increase in renal tubular re absorption of phosphate. Serum phosphate levels generally return to normal 2-4 weeks post therapy.

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer receiving treatment regimens including primarily intravenously administered bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, cortiscosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treament reduces risk of osteonecrosis of the jaw.
Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Food in the stomach or upper gastrointestinal tract, particularly materials with a high calcium content such as milk, may reduce absorption of etidronate disodium. Vitamins with mineral supplements such as iron, calcium supplements, laxatives containing magnesium, or antacids containing calcium or aluminium should not be taken within two hours of dosing etidronate disodium.

A small number of patients in clinical trials (involving more than 600 patients) received either thiazide diuretics or intravaginal oestrogen while on the Didronel PMO regimen. The concomitant use of either of these agents did not interfere with the positive effects of the Didronel PMO therapy on vertebral bone mass or fracture rates.

Calcium salts may reduce the absorption of some drugs, e.g. tetracyclines. It is therefore suggested that administration of Cacit tablets be separated from these products by at least three hours.

Vitamin D causes an increase in calcium absorption and plasma calcium levels may continue to rise after stopping vitamin D therapy. Concomitant administration of Cacit tablets and vitamin D should therefore be carried out with caution.

The effects of digoxin and other cardiac glycosides may be accentuated by calcium and toxicity may be produced, especially in combination with vitamin D therapy.

There have been isolated reports of patients experiencing changes in their prothrombin times when etidronate was added to warfarin therapy. 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 monitored.

4.6 Pregnancy and lactation

Contra-indicated.

4.7 Effects on ability to drive and use machines

Etidronate disodium does not interfere with the ability to drive or use machines.

4.8 Undesirable effects

Gastro-intestinal
In clinical studies of 2-3 years duration, the incidence of these events were comparable to placebo. The most common effects reported in order of incidence were diarrhoea, nausea, flatulence, dyspepsia, abdominal pain, gastritis, constipation and vomiting. Reports of exacerbation of peptic ulcer with complications in a few patients.

Dermatological/hypersensitivity
Hypersensitivity reactions including angio-oedema, urticaria, rash and/or pruritus have been reported rarely. The colouring agent E110 can cause allergic-type reactions including asthma. Allergy is more common in those people who are allergic to aspirin.

Nervous System
Headache, and rarely paresthesia, peripheral neuropathy and confusion.

Haematological
There have been rare reports of leucopenia, agranulocytosis and pancytopenia.

Other
Less common effects believed to be related to therapy include arthopathies (arthralgia and arthritis), and rarely burning of the tongue, alopecia, erythema multiforme and exacerbation of asthma.

Occasional mild leg cramps have been reported in less than 5% of patients on the Didronel PMO regimen. These cramps were transient, often nocturnal and generally associated with other underlying conditions

4.9 Overdose

Clinical experience of acute overdosage with etidronate is limited and unlikely with this compliance kit. Theoretically it would be manifested as the signs and symptoms of hypocalcaemia and possibly paresthesia of the fingers. Treatment would consist of gastric lavage to remove unabsorbed drug along with correction of hypocalcaemia with administration of Ca^{2+} intravenously.

Prolonged continuous treatment (chronic overdose) has been reported to cause nephrotic syndrome and fractures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Etidronate in an intermittent cyclical regimen, works indirectly to increase bone mass. By timing delivery and withdrawal, the etidronate disodium component acts to modulate osteoclasts and reduce the mean resorption depth of the affected basic multicellular units (BMU). Calcium is an essential element, which has been shown to help prevent bone loss.

5.2 Pharmacokinetic properties

Within 24 hours, about one half of the absorbed dose of etidronate is excreted in the urine. The remainder is chemically absorbed on bone and is slowly eliminated. Unabsorbed drug is excreted in the faeces. Etidronate disodium is not metabolised. After oral doses of up to 1600mg of the disodium salt, the amount of drug absorbed is approximately 3-4%. In normal subjects, plasma half life (t½) of etidronate, based on non-compartmental pharmacokinetics is 1-6 hours.

Calcium carbonate is converted into soluble calcium salts in the stomach under the influence of hydrochloric acid. 30-80% of orally ingested calcium is absorbed both by active transport (primarily in the upper small intestine) and by passive diffusion. The distribution of calcium in the body is subject to the mechanism of physiological regulation controlled by parathyroid hormone, calcitonin, calciferol and other hormones.

5.3 Preclinical safety data

In long-term studies in mice and rats, there was no evidence of carcinogenicity with etidronate disodium. All *in vitro* and *in vivo* assays conducted to assess the mutagenic potential of etidronate disodium have been negative.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Etidronate disodium tablets:

Microcrystalline cellulose
Pregelatinised maize starch
Magnesium stearate.

Cacit tablets:

Anhydrous citric acid
Saccharin sodium
Sodium cyclamate
Sunset yellow FCF (E110)
Orange flavouring.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 30°C. Keep the tube tightly closed.

6.5 Nature and contents of container

14 Didronel 400mg tablets in an opaque PVdC/foil blister plus four polypropylene tubes, each containing 19 Cacit 500 mg tablets, all packaged in a compliance kit.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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