Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Didronel 200mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200mg of Etidronate Disodium.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
White rectangular tablets marked with ‘P&G’ on one face and ‘402’ on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. Paget's disease of bone:
In the management of Paget’s disease of bone, particularly that of the polyostotic type with bone pain and significant elevations of urinary hydroxyproline and serum alkaline phosphatase, or in patients in danger of irreversible neurological damage, or with involvement of weight-bearing bone.

2. Heterotopic Bone Formation:
As a complication of hip replacement or when due to spinal cord injury.

4.2 Posology and method of administration

5mg/kg/day to 20mg/kg/day as detailed below.

Didronel should be given on an empty stomach. It is recommended that patients take the therapy with water, at the mid point of a four hour fast (ie. two hours before and two after food).

Daily Dosage Guide

Body Weight		Required Daily Regimen of 200mg Tablets		
Kilogrames	Stones	5mg/kg*	10mg/kg*	20mg/kg+
50	8	1	3	5
60	9.5	2	3	6
70	11	2	4	7
80	12.5	2	4	8
90	14	2	5	9

*Course of therapy - 6 months
+Course of therapy - 3 months

1. Paget's disease

Adults and Elderly:

The recommended initial dose of Didronel for most patients is 5mg/kg body weight/day, for a period not exceeding six months. Doses above 10mg/kg 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 10mg/kg/day should be approached cautiously and should not exceed three months duration. Doses in excess of 20mg/kg/day are not recommended.

Retreatment should be undertaken only after a drug-free period of at least three months and after it is evident that reactivation of the disease has occurred and biochemical indices of the disease have become substantially re-elevated or approach pre-treatment values (approximately twice the upper limit of normal or 75% of pre-treatment value). In no case should duration of treatment exceed the maximum duration of the initial treatment.

Premature retreatment should be avoided. In clinical trials the biochemical improvements obtained during drug therapy have generally persisted for a period of three months to 2 years after drug withdrawal.

Children:

Disorders of bone in children, referred to as juvenile Paget's disease, have been reported rarely. The relationship to adult Paget's disease has not been established. Didronel has not been studied in children for Paget's disease.

2. Heterotopic Bone Formation

In heterotopic ossification complicating hip replacement, the recommended adult dose is 20mg/kg/day for 1 month pre-operatively followed by 20mg/kg/day for 3 months post-operatively. The total treatment period is 4 months. There is no evidence that Didronel therapy will affect mature heterotopic bone.

In heterotopic ossification due to spinal cord injury the recommended adult dose of Didronel is 20mg/kg/day for 2 weeks followed by 10mg/kg/day for 10 weeks. The total treatment period is 12 weeks. The recommended dosage should be instituted as soon as is medically feasible following the injury, preferably prior to any radiographic evidence of heterotopic ossification.

4.3 Contraindications

Use in pregnancy and lactation. Retreatment within 3 months of a previous course.Known hypersensitivity to the drug. Clinically overt osteomalacia.

4.4 Special warnings and precautions for use

Didronel is not metabolised but excreted unchanged via the kidney; therefore, a reduced dose should be used in patients with mild renal impairment and treatment of patients with moderate to severe renal impairment should be avoided. Caution should be taken in patients with a history of renal stone formation. In patients with impaired renal function or a history of renal stone formation, serum and urinary calcium should be monitored regularly.

Etidronate disodium suppresses bone turnoner and may retard mineralisation of osteoid laid down during the bone accretion process. These effects are dose and time dependent. Osteoid, which may accumulate noticeably at doses of 10-20 mg/kg/day, mineralises normally post-therapy.

Patients in whom serum phosphate elevations are high and reductions of disease activity are low may be particularly prone to retarded mineralisation of new osteoid. In those cases where 200 mg per day (a single tablet) may be excessive, doses may be administered less frequently.

Patients with significant chronic diarrhoeal disease may experience increased frequency of bowel movements and diarrhoea, particularly at higher doses.

The risk of fracture may also be greater in patients with extensive and severe disease, a history of multiple fractures, and/or rapidly advancing osteolytic lesions. It is therefore recommended that the drug is discontinued when fractures occur and therapy not reinstated until the fracture healing is complete.

Patients with predominantly lytic lesions should be monitored radiographically and biochemically to permit termination of etidronate disodium in those patients unresponsive to treatment.

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.

4.5 Interaction with other medicinal products and other forms of interaction

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 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.

Concurrent administration with antacids may affect the activity of the etidronate disodium, while the latter in turn may affect responses to antiarrhythmics and cardiac glycosides.

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

Use is contraindicated in pregnancy and lactation (*See section 4.3, Contraindications*).

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

Gastrointestinal
The most common effects reported are diarrhoea and nausea. Reports of exacerbation of peptic ulcer with complications in few patients.

Nervous System
Paresthesia, confusion have been reported rarely.

Haematological
In patients receiving etidronate disodium, there have been rare reports of leucopenia, agranulocytosis and pancytopenia.

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

4.9 Overdose

Overdose would manifest as the signs and symptoms of hypocalcaemia. Treatment should involve cessation of therapy and correction of hypocalcaemia with administration of Ca^{2+} intravenously.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Starch
Magnesium stearate
Microcrystalline cellulose

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

4 years.

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

Supplied in high density polyethylene bottles with white polypropylene closures or in opaque PVDC/PE/PVC - aluminium foil blister packs; content 60 tablets.

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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