6 October 2010

Agreed Core Safety Profile

etidronate disodium

SECTIONS 4.3-4.9 AND SAFETY RELATED INFORMATION FROM SECTION 4.2 OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

4 CLINICAL PARTICULARS

4.2 Posology and method of administration*

A. General
Didronel should be administered as a single dose at least two hours before or after a meal. The dose may be taken with water. (see section 4.4, **Special warnings and special precautions for use**.)

B. Paget's disease indication
Retreatment: Therapy should only be initiated after an etidronate disodium-free period of at least 90 days and there is biochemical, symptomatic or other evidence of active disease process. For retreatment, the dose and duration of therapy are the same as for initial treatment.

Children
Didronel is not recommended for use in children due to insufficient data on safety and efficacy.

Elderly
There is no adjustment needed in dosage; dosages outside the recommended treatment regimen have not been studied.

Renal

A. General
Etidronate disodium is not metabolized and is excreted intact via the kidney. There is no experience specifically to guide the use of etidronate disodium in patients with impaired renal function. Patients with impaired renal function should have renal function monitored regularly.

B. Osteoporosis indication
Patients who are taking calcium supplementation should have serum and urine calcium and other relevant parameters monitored to prevent hypercalcemia or hypercalciuria. {Note: This should be included only in KIT products that contain etidronate in combination with calcium.}

Hepatic

Available safety information indicates there is no evidence to suggest that hepatotoxicity is associated with the use of etidronate disodium.

* Only safety related information

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients
Clinically overt osteomalacia.

4.4 Special warnings and precautions for use

A. General
Patients should maintain an adequate nutritional status and, particularly, an adequate intake of calcium and vitamin D. However, calcium can reduce the absorption of etidronate disodium and therefore should be avoided within 2 hours (before and after) of dosing with etidronate disodium.

The following should also be avoided within 2 hours of dosing with etidronate disodium: Foods, especially those high in calcium, such as milk or milk products; and vitamins with mineral supplements or antacids that are high in metals such as calcium, iron, magnesium, or aluminium.

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

Etidronate disodium is not metabolized and is excreted intact via the kidney. Due to the lack of clinical experience the treatment of patients with impaired renal function should be undertaken with due caution. The use of etidronate disodium is discouraged in patients with severely impaired kidney function.

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

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 bisphosphonates.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patient with concominant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, 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 treatment reduces risk of osteonecrosis of the jaw.

Clinical judgement of the treating physician should guide the management of each patient based on individual benefit/risk assessment.

B. Osteoporosis indication

The efficacy and safety of etidronate in the treatment of postmenopausal osteoporosis has been established using intermittent cyclical therapy. Continuous administration of etidronate should be avoided, as osteoid (demonstrating mineralization) may accumulate at doses of 10-20 mg/kg/day of chronic, continuous dosing.

C. Paget’s disease indication

Etidronate disodium suppresses bone turnover and may retard mineralization 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, mineralizes normally post therapy.

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 if fractures occur and that therapy not be reinstated until 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.

In Paget's patients, the response to therapy may be of slow onset and may continue for months after therapy has been discontinued. Dosage should not be increased prematurely. A drug-free interval of at least 90 days should be provided between courses of therapy.

Increased or recurrent bone pain at pagetic sites and/or the onset of pain at previously asymptomatic sites has been reported in approximately 10% of patients at 5mg/kg/day. At higher doses, the incidence rises to approximately 20%. When therapy continues, pain resolves in some patients but persists in others.

Osteogenic sarcoma is known to be increased in Paget's disease. With or without therapy, pagetic lesions may appear radiographically to progress markedly, possibly with some loss of definition of periosteal margins. Such lesions should be evaluated carefully to permit differentiation from osteogenic sarcoma.

The excretion of hydroxyproline and serum levels for alkaline phosphatase should be regularly monitored.

4.5 Interaction with other medicinal products and other forms of interaction

A. General
Etidronate disodium is known to interact with calcium and other divalent or trivalent cations (see section 4.4, **Special warnings and special precautions for use**.)

The diagnostic utility of bone-imaging agents may be impaired by current or recent etidronate use.

There have been isolated reports of patients experiencing increases 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.

B. Osteoporosis indication
Calcium carbonate may interfere with the absorption of tetracycline given concomitantly.
{Note: This should be included only in KIT products that contain etidronate in combination with calcium.}

4.6 Pregnancy and lactation

There are no adequate data from the use of Didronel in pregnant women.
Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.
Didronel should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

It is not known whether this drug passes into breast milk. It should therefore not be used during lactation period.

4.7 Effects on ability to drive and use machines

Didronel has no influence on the ability to drive and use machines

4.8 Undesirable effects

Adverse experiences from clinical trials and post-marketing data are listed below using the following conventions:
Very common (>1/10); common (>1/100; 1/10); uncommon (>1/1,000; <1/100); rare (>1/10,000; <1/1,000); very rare (<1/10,000).

MedDRA System organ class	
Blood and lymphatic system disorders	*Very Rare:* leukopenia, agranulocytosis & pancytopenia.

Psychiatric disorders	*Very Rare:* confusion
Nervous system disorders	*Uncommon:* headache *Rare:* paresthesias, peripheral neuropathy
Respiratory, thoracic and mediastinal disorders	*Rare:* exacerbation of asthma
Gastrointestinal disorders	*Common:* nausea; diarrhoea *Rare:* burning of the tongue; Exacerbations of peptic ulcer with complications; dyspepsia
Skin and subcutaneous tissue disorders	*Uncommon:* hypersensitivity reactions which include skin rashes (such as follicular eruption, macular rash, and maculopapular rash), angioedema/urticaria and pruritus; *Rare:* alopecia; erythema multiforme
Musculoskeletal and connective tissue disorders	*Uncommon:* arthropathies, including arthralgia, leg cramps *Very rare*: osteonecrosis of the jaw (see section 4.4 special warnings and precautions of use)

4.9 Overdose

A. General
Clinical experience with acute overdose of etidronate disodium is extremely limited. Decreases in serum calcium following substantial overdose may be expected in some patients. Signs and symptoms of hypocalcemia may also occur in some of these patients. Some patients may develop vomiting.

Gastric lavage may remove unabsorbed drug. Standard procedures have been effective for treating hypocalcemia, including the administration of calcium intravenously, would be expected to restore physiologic amounts of ionized calcium and to relieve signs and symptoms of hypocalcemia.

B. Osteoporosis indication
{The following statement should be included only in KIT products that contain calcium.}
Because of its limited intestinal absorption, overdosage with calcium carbonate is not likely. If mild hypercalcemia were to occur, signs and symptoms could include polydipsia, polyuria, nausea, vomiting, constipation, abdominal pain, muscle weakness, and confusion. Treatment of hypercalcemia includes cessation of all calcium and vitamin D. Supportive measures include rehydration with or without loop diuretics.