Zolena®

Zoledronic acid

4mg/5 mL vial concentrate sterile liquid for i.v. infusion

1. DESCRIPTION

Zoledronic acid is a bisphosphonate agent which is an inhibitor of osteoclastic bone resorption.

2. CLINICAL PHARMACOLOGY

2.1. Mechanism of Action

Zoledronic acid belongs to the class of bisphosphonates, which inhibits bone resorption via actions on osteoclasts or on osteoclast precursors. It binds to hydroxyapatite and accumulates in bone, thus inhibiting osteoclast migration and maturation. Zoledronic acid inhibits skeletal calcium release induced by tumors, and has a clinically significant impact on mixed and osteoblastic metastases in patients with breast or prostate cancer.

2.2. Pharmacokinetics

Plasma concentrations of zoledronate rise rapidly after the start of an intravenous infusion. Plasma protein binding is low; it has been variously reported as 22 or 56%. Zoledronate is not metabolized, and about 23 to 55% of the dose is excreted in the urine unchanged within 24 hours; the remainder is mainly sequestered to bone and only very slowly eliminated. Renal clearance is slower in patients with severe renal impairment. Despite the fact that renal clearance of zoledronic acid correlates to renal function, a pharmacokinetic study concluded that no dosage adjustment appeared necessary in patients with mild to moderate renal impairment (creatinine clearance 50 to 80 mL/minute, and 10 to 50 mL/minute, respectively).

3. INDICATIONS AND USAGE

Zoledronic acid is a bisphosphonate indicated for the treatment of:

- Hypercalcemia of malignancy
- Patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy.
- Important limitation of use: The safety and efficacy of Zoledronic acid has not been established for use in hyperparathyroidism or non-tumor-related hypercalcemia

4. CONTRAINDICATIONS

4.1. Hypersensitivity to Zoledronic Acid or Any Components

Hypersensitivity reactions including rare cases of urticaria and angioedema, and very rare cases of anaphylactic reaction/shock have been reported.

5. WARNINGS AND PRECAUTIONS

5.1. Hydration and Electrolyte Monitoring

Patients with hypercalcemia of malignancy must be adequately rehydrated prior to administration of Zoledronic acid. Loop diuretics should not be used until the patient is adequately rehydrated and should be used with caution in combination with Zoledronic acid in order to avoid hypocalcemia. Zoledronic acid should be used with caution with other nephrotoxic drugs.

Standard hypercalcemia-related metabolic parameters, such as serum levels of calcium, phosphate, and magnesium, as well as serum creatinine, should be carefully monitored following initiation of therapy with Zoledronic acid. If hypocalcemia, hypophosphatemia, or hypomagnesemia occur, short-term supplemental therapy may be necessary.

5.2. Renal Impairment

Zoledronic acid is excreted intact primarily via the kidney, and the risk of adverse reactions, in particular renal adverse reactions, may be greater in patients with impaired renal function. Safety and pharmacokinetic data are limited in patients with severe renal impairment and the risk of renal deterioration is increased. Preexisting renal insufficiency and multiple cycles of Zoledronic acid and other bisphosphonates are risk factors for subsequent renal deterioration with Zoledronic acid. Factors predisposing to renal deterioration, such as dehydration or the use of other nephrotoxic drugs, should be identified and managed, if possible.

Zoledronic acid treatment in patients with hypercalcemia of malignancy with severe renal impairment should be considered only after evaluating the risks and benefits of treatment. In the clinical studies, patients with serum creatinine >400 µmol/L or >4.5 mg/dL were excluded.

Zoledronic acid treatment is not recommended in patients with bone metastases with severe renal impairment. In the clinical studies, patients with serum creatinine >265 µmol/L or >3.0 mg/dL were excluded and there were only 8 of 564 patients treated with Zoledronic acid 4 mg by 15-minute infusion with a baseline creatinine >2 mg/dL. Limited pharmacokinetic data exists in patients with creatinine clearance <30 mL/min.

5.3. Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported predominantly in cancer patients treated with intravenous bisphosphonates, including Zoledronic acid. Many of these patients were also receiving chemotherapy and corticosteroids which may be risk factors for ONJ. Postmarketing experience and the literature suggest a greater frequency of reports of ONJ based on tumor type (advanced breast cancer, multiple myeloma), and dental status (dental extraction, periodontal disease, local trauma including poorly fitting dentures). Many reports of ONJ involved patients with signs of local infection including osteomyelitis.

Cancer patients should maintain good oral hygiene and should have a dental examination with preventive dentistry prior to treatment with bisphosphonates.

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop ONJ 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 the risk of ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

5.4. Musculoskeletal Pain

In postmarketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. This category of drugs includes Zoledronic acid. The time to onset of symptoms varied from one day to several months after starting the drug. Discontinue use if severe symptoms develop. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

5.5. Patients with Asthma

While not observed in clinical trials with Zoledronic acid, there have been reports of bronchoconstriction in aspirin sensitive patients receiving bisphosphonates.

5.6. Hepatic Impairment

Only limited clinical data are available for use of Zoledronic acid to treat hypercalcemia of malignancy in patients with hepatic insufficiency, and these data are not adequate to provide guidance on dosage selection or how to safely use Zoledronic acid in these patients.

6. DRUG INTERACTIONS

In-vitro studies indicate that zoledronic acid is approximately 22% bound to plasma proteins. In-vitro studies also indicate that zoledronic acid does not inhibit microsomal CYP450 enzymes. In-vivo studies showed that zoledronic acid is not metabolized, and is excreted into the urine as the intact drug. However, no in-vivo drug interaction studies have been performed.

6.1 Aminoglycosides

Caution is advised when bisphosphonates are administered with aminoglycosides, since these agents may have an additive effect to lower serum calcium level for prolonged periods. This effect has not been reported in Zoledronic acid clinical trials.

6.2 Loop Diuretics

Caution should also be exercised when Zoledronic acid is used in combination with loop diuretics due to an increased risk of hypocalcemia.

6.3 Nephrotoxic Drugs

Caution is indicated when Zoledronic acid is used with other potentially nephrotoxic drugs.

6.4 Thalidomide

In multiple myeloma patients, the risk of renal dysfunction may be increased when Zoledronic acid is used in combination with thalidomide.

7. USE IN SPECIFIC POPULATIONS

7.1. Pregnancy

Pregnancy Category D

ZOLEDRONIC ACID SHOULD NOT BE USED DURING PREGNANCY. There are no studies in pregnant women using Zoledronic acid. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

7.2. Nursing Mothers

It is not known whether Zoledronic acid is excreted in human milk. Because many drugs are excreted in human milk, and because Zoledronic acid binds to bone long term, Zoledronic acid should not be administered to a nursing woman.

7.3. Pediatric Use

Zoledronic acid is not indicated for use in children.

7.4. Geriatric Use

Clinical studies of Zoledronic acid in hypercalcemia of malignancy included 34 patients who were 65 years of age or older. No significant differences in response rate or adverse reactions were seen in geriatric patients receiving Zoledronic acid as compared to younger patients. Controlled clinical studies of Zoledronic acid in the treatment of multiple myeloma and bone metastases of solid tumors in patients over age 65 revealed similar efficacy and safety in older and younger patients. Because decreased renal function occurs more commonly in the elderly, special care should be taken to monitor renal function.

8. ADVERSE REACTIONS

hypophosphatemia, anaemia, influenza-like symptoms including bone pain, myalgia, arthralgia, fever and rigors; gastro-intestinal disturbances; atrial fibrillation; headache, dizziness, conjunctivitis, renal impairment (rarely acute renal failure); **less commonly** anorexia, taste disturbance, dry mouth, stomatitis, chest pain, hypertension, hypotension, dyspnea, cough, paresthesia, tremor, anxiety, lethargy, sleep disturbance, blurred vision, weight gain, pruritus, rash, sweating, muscle cramps, hematuria, proteinuria, urinary frequency, hypersensitivity reactions (including angioedema), asthenia, peripheral edema, thrombocytopenia, leucopenia, hypomagnesaemia, hypokalemia, also injection-site reactions; **rarely** bradycardia, confusion, hyperkaliemia, hypernatremia, pancytopenia, osteonecrosis of the jaw (see warnings and precautions); **very rarely** uveitis and episcleritis

9. OVERDOSAGE

Clinical experience with acute overdosage of Zoledronic acid is limited. Two patients received Zoledronic acid 32 mg over 5 minutes in clinical trials. Neither patient experienced any clinical nor laboratory toxicity. Overdosage may cause clinically significant hypocalcemia, hypophosphatemia,