Xoleron

Zoledronic Acid Injection

Lyophilized Powder for IV Injection

COMPOSITION

Xoleron Injection: Each vial contains Zoledronic Acid Monohydrate INN equivalent to Zoledronic Acid 4 mg as Lyophilized Powder.

DESCRIPTION

Zoledronic Acid, a bisphosphonic acid which is an inhibitor of osteoclastic bone resorption. Zoledronic Acid is designated chemically as (1-Hydroxy-2-imidazol-1-yl-phosphonoethyl) phosphonic acid monohydrate .

CLINICAL INFORMATION

The principal pharmacologic action of Zoledronic Acid is inhibition of bone resorption. Although the antiresorptive mechanism is not completely understood, several factors are thought to contribute to this action. In vitro, Zoledronic Acid inhibits osteoclastic activity and induces osteoclast apoptosis. Zoledronic Acid also blocks the osteoclastic resorption of mineralized bone and cartilage through its binding to bone. Zoledronic Acid inhibits the increased osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumors.

INDICATION & USES

Hypercalcemia of Malignancy : Xoleron is indicated for the treatment of hypercalcemia of malignancy.

Multiple Myeloma and Bone Metastases of Solid Tumors: Xoleron is indicated for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy.

The safety and efficacy of Xoleron in the treatment of hypercalcemia associated with hyperparathyroidism or with other nontumor-related conditions has not been established.

DOSAGE AND ADMINISTRATION

Hypercalcemia of Malignancy

The maximum recommended dose of Xoleron in hypercalcemia of malignancy is 4 mg. The 4-mg dose must be given as a single-dose intravenous infusion over no less than 15 minutes. Patients who receive Xoleron should have serum creatinine assessed prior to each treatment.

Patients should be adequately rehydrated prior to administration of Xoleron. Consideration should be given to the severity of, as well as the symptoms of, tumor-induced hypercalcemia when considering use of Xoleron. Vigorous saline hydration, an integral part of hypercalcemia therapy, should be initiated promptly and an attempt should be made to restore the urine output to about 2 L/day throughout treatment. Mild or asymptomatic hypercalcemia may be treated with conservative measures (i.e., saline hydration, with or without loop diuretics). Patients should be hydrated adequately throughout the treatment, but overhydration, especially in those patients who have cardiac failure, must be avoided. Diuretic therapy should not be employed prior to correction of hypovolemia.

Retreatment with Xoleron 4 mg may be considered if serum calcium does not return to normal or remain normal after initial treatment. It is recommended that a minimum of 7 days elapse before retreatment, to allow for full response to the initial dose. Renal function must be carefully monitored in all patients receiving Xoleron and serum creatinine must be assessed prior to retreatment with Xoleron.

Multiple Myeloma and Metastatic Bone Lesions of Solid Tumors

The recommended dose of Xoleron in patients with multiple myeloma and metastatic bone lesions from solid tumors for patients with creatinine clearance >60 mL/min is 4 mg infused over no less than 15 minutes every 3-4 weeks. The optimal duration of therapy is not known.

Upon treatment initiation, the recommended Xoleron doses for patients with reduced renal function (mild and moderate renal impairment) are listed as following. These doses are calculated to achieve the same AUC as that achieved in patients with creatinine clearance of 75 mL/min. Creatinine clearance (CrCl) is calculated using the Cockcroft-Gault formula.

Reduced Doses for patients with baseline CrCl ≤60 mL/min

Baseline Creatinine Clearance (mL/min)	Xoleron Recommended Dose*
>60	4 mg
50 - 60	3.5 mg
40 - 49	3.3 mg
30 - 39	3 mg
*Doses calculated assuming target AUC of 0.66(mgohr/L) (CrCl = 75 mL/min)	

During treatment, serum creatinine should be measured before each Xoleron dose and treatment should be withheld for renal deterioration.

Preparation of Solution

Xoleron Lyophilized powder for infusion must first be reconstituted in the vial using 5 mL water for injection. Dissolution must be complete before the solution is withdrawn. The required amount of the reconstituted solution is then further diluted with 100 mL of sterile 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP. Do not store undiluted concentrate in a syringe, to avoid inadvertent injection.

Preparing Reduced Doses for Patients with Baseline CrCl ≤60 mL/min

Withdraw the appropriate volume of the Xoleron concentrate from the vial for the dose required

Preparation of Reduced Doses

Xoleron Volume (mL)	Dose (mg)
4.4	3.5
4.1	3.3
3.8	3.0

The withdrawn concentrate must be diluted in 100 mL of sterile 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP.

If not used immediately after dilution with infusion media, for microbiological integrity, the solution should be refrigerated at 2^0C-8^0C. The refrigerated solution should then be equilibrated to room temperature prior to administration. The total time between dilution, storage in the refrigerator, and end of administration must not exceed 24 hours.

Xoleron must not be mixed with calcium or other divalent cation-containing infusion solutions, such as Lactated Ringer's solution, and should be administered as a single intravenous solution in a line separate from all other drugs.

Method of Administration

Due to the risk of clinically significant deterioration in renal function, which may progress to renal failure, single doses of Xoleron should not exceed 4 mg and the duration of infusion should be no less than 15 minutes. In the trials renal deterioration, progression to renal failure and dialysis, have occurred in patients, including those treated with the approved dose of 4 mg infused over 15 minutes. There have been instances of this occurring after the initial Zoledronic Acid dose.

CONTRAINDICATIONS

Hypersensitivity to Zoledronic Acid or any components of Xoleron.

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

WARNINGS AND PRECAUTIONS

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.

Renal Impairment

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.

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.

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.

Musculoskeletal Pain

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.

Patients with Asthma

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

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.

ADVERSE REACTIONS

Renal Toxicity

Administration of Zoledronic Acid 4 mg given as a 5-minute intravenous infusion has been shown to result in an increased risk of renal toxicity, as measured by increases in serum creatinine, which can progress to renal failure. The incidence of renal toxicity and renal failure has been shown to be reduced when Zoledronic Acid 4 mg is given as a 15-minute intravenous infusion. Zoledronic Acid should be administered by intravenous infusion over no less than 15 minutes.

Acute Phase Reaction-like Events

Symptoms consistent with acute phase reaction (APR) can occur with intravenous bisphosphonate use. Fever has been the most commonly associated symptom, occurring in patients treated with Zoledronic Acid 4 mg. Occasionally, patients experience a flu-like syndrome consisting of fever, chills, flushing, bone pain and/or arthralgias, and myalgias.

Mineral and Electrolyte Abnormalities

Electrolyte abnormalities, most commonly hypocalcemia, hypophosphatemia and hypomagnesemia, can occur with bisphosphonate use.

Injection Site Reactions

Local reactions at the infusion site, such as redness or swelling, were observed infrequently. In most cases, no specific treatment is required and the symptoms subside after 24-48 hours.

Ocular Adverse Events

Ocular inflammation such as uveitis and scleritis can occur with bisphosphonate use. No cases of iritis, scleritis or uveitis were reported.

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.

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.

Loop Diuretics

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

Nephrotoxic Drugs

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

Thalidomide

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Xoleron 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.

Nursing Mothers

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

Pediatric Use

Xoleron is not indicated for use in children.

Geriatric Use

No significant differences in response rate or adverse reactions were seen in geriatric patients receiving Xoleron as compared to younger patients. Because decreased renal function occurs more commonly in the elderly, special care should be taken to monitor renal function.

OVERDOSAGE

Clinical experience with acute overdosage of Xoleron is limited. Overdosage may cause clinically significant hypocalcemia, hypophosphatemia, and hypomagnesemia. Clinically relevant reductions in serum levels of calcium, phosphorus, and magnesium should be corrected by intravenous administration of calcium gluconate, potassium or sodium phosphate, and magnesium sulfate, respectively.

PHARMACEUTICAL INFORMATION

Storage Conditions

Store the vial in original carton below 30°C. Protect from light. Keep out of the reach of the children.

Presentation & Packaging

Xoleron Injection: Each commercial box contains one vial of Zoledronic Acid Monohydrate INN equivalent to Zoledronic Acid 4 mg as Lyophilized Powder.

Manufactured By
BEACON Pharmaceuticals Limited
Mymensingh, Bangladesh

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