Dromezon®

Zoledronic Acid

FORMS AND PRESENTATION
Dromezon®: 4mg/5ml; Concentrate for solution for infusion; 1 Vial.
COMPOSITION
Dromezon®: Each 5ml vial contains Zoledronic acid Monohydrate, corresponding to 4 mg Zoledronic acid on an anhydrous basis.
Excipients: Mannitol, tri sodium citrate dihydrate.
PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: Drugs for treatment of bone diseases, bisphosphonates, ATC code: M05BA08.
Zoledronic acid belongs to the class of bisphosphonates and acts primarily on bone. It is an inhibitor of osteoclastic bone resorption.
The selective action of bisphosphonates on bone is based on their high affinity for mineralised bone, but the precise molecular mechanism leading to the inhibition of osteoclastic activity is still unclear. In long-term animal studies, zoledronic acid inhibits bone resorption without adversely affecting the formation, mineralisation or mechanical properties of bone.
In addition to being a potent inhibitor of bone resorption, zoledronic acid also possesses several anti-tumour properties that could contribute to its overall efficacy in the treatment of metastatic bone disease. The following properties have been demonstrated in preclinical studies:
- *In vivo*: Inhibition of osteoclastic bone resorption, which alters the bone marrow microenvironment, making it less conducive to tumour cell growth, anti-angiogenic activity and anti-pain activity.
- *In vitro*: Inhibition of osteoblast proliferation, direct cytostatic and pro-apoptotic activity on tumour cells, synergistic cytostatic effect with other anti-cancer drugs, anti-adhesion/invasion activity.
Pharmacokinetic properties
Absorption
After initiating the infusion of Zoledronic Acid, the plasma concentrations of Zoledronic Acid rapidly increased, achieving their peak at the end of the infusion period, followed by a rapid decline to < 10% of peak after 4 hours and < 1% of peak after 24 hours, with a subsequent prolonged period of very low concentrations not exceeding 0.1% of peak prior to the second infusion of Zoledronic Acid on day 28.
Elimination
Intravenously administered Zoledronic Acid is eliminated by a triphasic process: rapid biphasic disappearance from the systemic circulation, with half-lives of $t_{1/2}\alpha$ 0.24 and $t_{1/2}\beta$ 1.87 hours, followed by a long elimination phase with a terminal elimination half-life of $t_{1/2}\gamma$ 146 hours. There was no accumulation of Zoledronic Acid in plasma after multiple doses given every 28 days. Zoledronic acid is not metabolised and is excreted unchanged via the kidney. Over the first 24 hours, 39 ± 16% of the administered dose is recovered in the urine, while the remainder is principally bound to bone tissue. From the bone tissue it is released very slowly back into the systemic circulation and eliminated via the kidney. The total body clearance is 5.04 ± 2.5 l/h, independent of dose, and unaffected by gender, age, race, and body weight. Increasing the infusion time from 5 to 15 minutes caused a 30% decrease in Zoledronic Acid concentration at the end of the infusion but had no effect on the area under the plasma concentration versus time curve.
INDICATIONS
Dromezon® 4mg/5ml solution for injection is indicated for the:
- Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in adult patients with advanced malignancies involving bone.
- Treatment of adult patients with tumour-induced hypercalcaemia (TIH).
CONTRAINDICATIONS
- Hypersensitivity to the active substance, to other bisphosphonates or to any of the excipients listed.
- Breast-feeding
PRECAUTIONS
General
- Patients must be assessed prior to administration of Dromezon® to ensure that they are adequately hydrated. Overhydration should be avoided in patients at risk of cardiac failure.
- Standard hypercalcaemia-related metabolic parameters, such as serum levels of calcium, phosphate and magnesium, should be carefully monitored after initiating Dromezon® therapy. If hypocalcaemia, hypophosphataemia, or hypomagnesaemia occurs, short-term supplemental therapy may be necessary. Careful renal function monitoring should be considered.
- Patients being treated with Dromezon® should not be treated with Aclasta or any other bisphosphonate concomitantly, since the combined effects of these agents are unknown.
Renal insufficiency
- Patients with TIH and evidence of deterioration in renal function should be appropriately evaluated with consideration given as to whether the potential benefit of treatment with Zoledronic acid outweighs the possible risk.
- The decision to treat patients with bone metastases for the prevention of skeletal related events should consider that the onset of treatment effect is 2–3 months.
- Zoledronic acid has been associated with reports of renal dysfunction. While the risk is reduced with a dose of 4 mg zoledronic acid administered over 15 minutes, deterioration in renal function may still occur. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of 4 mg zoledronic acid. Increases in serum creatinine also occur in some patients with chronic administration of Zoledronic acid at recommended doses for prevention of skeletal related events, although less frequently.
- Patients should have their serum creatinine levels assessed prior to each dose of Zoledronic acid. Upon initiation of treatment in patients with bone metastases with mild to moderate renal impairment, lower doses of zoledronic acid are recommended. In patients who show evidence of renal deterioration during treatment, Zoledronic acid should be withheld. Zoledronic acid should only be resumed when serum creatinine returns to within 10% of baseline. Zoledronic acid treatment should be resumed at the same dose as that given prior to treatment interruption.
- The use of Zoledronic acid is not recommended in patients with severe renal impairment.
Hepatic insufficiency
- As only limited clinical data are available in patients with severe hepatic insufficiency, no specific recommendations can be given for this patient population.
Osteonecrosis of the jaw (ONJ)
Osteonecrosis of the jaw (ONJ) has been also reported uncommonly.
The start of treatment or of a new course of treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth, except in medical emergency situations. A dental examination with appropriate preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with bisphosphonates in patients with concomitant risk factors.
The following risk factors should be considered when evaluating an individual's risk of developing ONJ:
- Potency of the bisphosphonate (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose.
- Cancer, co-morbid conditions (e.g. anaemia, coagulopathies, infection), smoking.
- Concomitant therapies: chemotherapy, angiogenesis inhibitors, radiotherapy to neck and head, corticosteroids.
- History of dental disease, poor oral hygiene, periodontal disease, invasive dental procedures (e.g. tooth extractions) and poorly fitting dentures.
Osteonecrosis of other anatomical sites
Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections.
Additionally, there have been sporadic reports of osteonecrosis of other sites, including the hip and femur, reported predominantly in adult cancer patients treated with Zoledronic acid.
Musculoskeletal pain
Severe and occasionally incapacitating bone, joint, and/or muscle pain have been reported in patients taking Zoledronic acid. However, such reports have been infrequent. The time to onset of symptoms varied from one day to several months after starting treatment.
Atypical fractures of the femur
Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. Fractures are often bilateral; therefore, the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment.
Hypocalcaemia
Hypocalcaemia has been reported in patients treated with Zoledronic acid. Cardiac arrhythmias and neurologic adverse events (including convulsions, hypoaesthesia and tetany) have been reported secondary to cases of severe hypocalcaemia. Cases of severe hypocalcaemia requiring hospitalisation have been reported. In some instances, the hypocalcaemia may be life-threatening. Caution is advised when Zoledronic acid is administered with medicinal products known to cause hypocalcaemia, as they may have a synergistic effect resulting in severe hypocalcaemia. Serum calcium should be measured and hypocalcaemia must be corrected before initiating Zoledronic acid therapy. Patients should be adequately supplemented with calcium and vitamin D.
Effects on ability to drive and use machines
Adverse reactions, such as dizziness and somnolence, may have influence on the ability to drive or use machines, therefore caution should be exercised with the use of Zoledronic acid along with driving and operating of machinery.
FERTILITY, PREGNANCY AND LACTATION
Pregnancy: Zoledronic acid should not be used during pregnancy. Women of child-bearing potential should be advised to avoid becoming pregnant.
Breast-feeding: Zoledronic acid is contraindicated in breast-feeding women.
Fertility: Results in pre-clinical studies precluded determining a definitive effect of zoledronic acid on fertility in humans.
DRUG INTERACTIONS
- In clinical studies, Zoledronic acid has been administered concomitantly with commonly used anticancer agents, diuretics, antibiotics and analgesics without clinically apparent interactions occurring. Zoledronic acid shows no appreciable binding to plasma proteins and does not inhibit human P450 enzymes in vitro, but no formal clinical interaction studies have been performed.
- Caution is advised when bisphosphonates are administered with aminoglycosides, calcitonin or loop diuretics, since these agents may have an additive effect, resulting in a lower serum calcium level for longer periods than required.
- Caution is indicated when Zoledronic acid is used with other potentially nephrotoxic medicinal products. Attention should also be paid to the possibility of hypomagnesaemia developing during treatment.
- In multiple myeloma patients, the risk of renal dysfunction may be increased when Zoledronic acid is used in combination with thalidomide.
- Caution is advised when Zoledronic acid is administered with anti-angiogenic medicinal products, as an increase in the incidence of ONJ has been observed in patients treated concomitantly with these medicinal products.
ADVERSE EFFECTS
Within three days after Zoledronic Acid administration, an acute phase reaction has commonly been reported, with symptoms including bone pain, fever, fatigue, arthralgia, myalgia and rigors; these symptoms usually resolve within a few days. The following are the important identified risks with Zoledronic Acid in the approved indications: Renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, ocular adverse events, atrial fibrillation, anaphylaxis.
The adverse reactions are displayed by system organ class. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness: Very common (1/10), common (1/100 to 1/10), uncommon (1/1000 to 1/100), rare (1/10000 to 1/1000), very rare (<1/10,000) and not known (cannot be estimated from the available data).
- Blood and lymphatic system disorders: Anaemia (common), thrombocytopenia, leucopenia (uncommon), pancytopenia (rare).
- Immune system disorders: Hypersensitivity reaction (uncommon), angioneurotic oedema (rare).
- Psychiatric disorders: Anxiety, sleep disturbance (uncommon), confusion (rare).
- Nervous system disorders: Headache (common), dizziness, paraesthesia, taste disturbance, hypoaesthesia, hyperaesthesia, tremor, somnolence (uncommon), seizures, numbness and tetany (very rare).

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- Eye disorders: Conjuctivitis (common), blurred vision, scleritis and orbital inflammation (uncommon), uveitis, episcleritis (very rare).
- Cardiac disorders: Hypertension, hypotension, atrial fibrillation, hypotension leading to syncope or circular collapse (uncommon), bradycardia (rare), cardiac arrhythmia (very rare).
- Respiratory, thoracic and mediastinal disorders: Dyspnoea, cough, bronchoconstriction (uncommon), interstitial lung disease (rare).
- Gastrointestinal disorders: Nausea, vomiting, anorexia (common), diarrhea, constipation, abdominal pain, dyspepsia, stomatitis, dry mouth (uncommon).
- Skin and subcutaneous tissue disorders: Pruritus, rash including erythematous and macular rash, increased sweating (uncommon).
- Musculoskeletal and connective tissue disorders: Bone pain, myalgia, arthralgia, generalized pain (common), muscle cramps, osteonecrosis of the jaw (uncommon).
- Renal and urinary disorders: Renal impairment (common), acute renal failure, hematuria, proteinuria (uncommon).
- General disorders and administration site conditions: Fever, flu-like syndrome (including fatigue, rigors, malaise and flushing) (common), asthenia, peripheral oedema, injection site reactions (including pain, irritation, swelling, induration), chest pain, weight increase, anaphylactic reaction/shock, urticaria (uncommon).
- Investigations: Hypophosphataemia (very common), blood creatinine and urea incresead, hypocalcaemia (common), hypomagnesaemia, hypokalaemia (uncommon), hyperkalaemia and hypernatraemia (rare).

DOSAGE AND ADMINISTRATION

Dromezon® must only be prescribed and administered to patients by healthcare professionals experienced in the administration of intravenous bisphosphonates.

Posology

Prevention of skeletal related events in patients with advanced malignancies involving bone

Adults and older people

- The recommended dose in the prevention of skeletal related events in patients with advanced malignancies involving bone is 4 mg zoledronic acid every 3 to 4 weeks.
- Patients should also be administered an oral calcium supplement of 500 mg and 400 IU vitamin D daily.
- The decision to treat patients with bone metastases for the prevention of skeletal related events should consider that the onset of treatment effect is 2-3 months.

Treatment of TIH

Adults and older people

- The recommended dose in hypercalcaemia (albumin-corrected serum calcium ≥ 12.0 mg/dl or 3.0 mmol/l) is a single dose of 4 mg zoledronic acid.

Renal impairment

TIH:

- Dromezon® treatment in TIH patients who also have 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. No dose adjustment is necessary in TIH patients with serum creatinine < 400 µmol/l or < 4.5 mg/dl.

Prevention of skeletal related events in patients with advanced malignancies involving bone:

- When initiating treatment with Dromezon® in patients with multiple myeloma or metastatic bone lesions from solid tumours, serum creatinine and creatinine clearance (CLcr) should be determined. CLcr is calculated from serum creatinine using the Cockcroft-Gault formula. Dromezon® is not recommended for patients presenting with severe renal impairment prior to initiation of therapy, which is defined for this population as CLcr < 30 ml/min. In clinical trials with Dromezon®, patients with serum creatinine > 265 µmol/l or > 3.0 mg/dl were excluded.
- In patients with bone metastases presenting with mild to moderate renal impairment prior to initiation of therapy, which is defined for this population as CLcr 30–60 ml/min, the following Dromezon® dose is recommended:

Baseline creatinine clearance (ml/min)	Dromezon® recommended dose*
> 60	4.0 mg Zoledronic Acid
50-60	3.5 mg* Zoledronic Acid
40-49	3.3 mg* Zoledronic Acid
30-39	3.0 mg* Zoledronic Acid

* Doses have been calculated assuming target AUC of 0.66 (mg•hr/l) (CLcr = 75 ml/min). The reduced doses for patients with renal impairment are expected to achieve the same AUC as that seen in patients with creatinine clearance of 75 ml/min.

Following initiation of therapy, serum creatinine should be measured prior to each dose of Dromezon® and treatment should be withheld if renal function has deteriorated. In the clinical trials, renal deterioration was defined as follows:

- For patients with normal baseline serum creatinine (< 1.4 mg/dl or < 124 µmol/l), an increase of 0.5 mg/dl or 44 µmol/l;
- For patients with abnormal baseline creatinine (> 1.4 mg/dl or > 124 µmol/l), an increase of 1.0 mg/dl or 88 µmol/l.

In the clinical studies, Zoledronic acid treatment was resumed only when the creatinine level returned to within 10% of the baseline value. Dromezon® treatment should be resumed at the same dose as that given prior to treatment interruption.

Paediatric population: The safety and efficacy of zoledronic acid in children aged 1 year to 17 years have not been established.

Method of administration

Intravenous use.

Dromezon® 4 mg concentrate for solution for infusion, further diluted in 100 ml, should be given as a single intravenous infusion in no less than 15 minutes.

In patients with mild to moderate renal impairment, reduced Dromezon® doses are recommended.

Instructions for preparing reduced doses of Dromezon®

Withdraw an appropriate volume of the concentrate needed, as follows:

- 4.4 ml for 3.5 mg dose
- 4.1 ml for 3.3 mg dose
- 3.8 ml for 3.0 mg dose

For instructions on the dilution of the medicinal product before administration. The withdrawn amount of concentrate must be further diluted in 100 ml of sterile 0.9% w/v sodium chloride solution or 5% w/v glucose solution. The dose must be given as a single intravenous infusion over no less than 15 minutes.

Dromezon® concentrate 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 separate infusion line.

Patients must be maintained well hydrated prior to and following administration of Dromezon®.

OVERDOSAGE

Patients who have received doses higher than those recommended should be carefully monitored, since renal function impairment (including renal failure) and serum electrolyte (including calcium, phosphorus and magnesium) abnormalities have been observed. In the event of hypocalcaemia, calcium gluconate infusions should be administered as clinically indicated.

Special precautions for disposal and other handling

• Prior to administration, 5.0 ml concentrate from one vial or the volume of the concentrate withdrawn as required must be further diluted with 100 ml of calcium-free infusion solution (0.9% w/v sodium chloride solution or 5% w/v glucose solution).
• Aseptic techniques must be followed during the preparation of the infusion. For single use only.
• Only clear solution free from particles and discolouration should be used.
• Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
• After dilution: From a microbiological point of view, the diluted solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C – 8°C. The refrigerated solution should then be equilibrated to room temperature prior to administration.

STORAGE CONDITIONS

Store below 25°C.
Keep in original pack in intact conditions.

Date of Revision: April 2019.

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

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