45 mm

45 mm

ZOLASTA
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80 mm

● Product Name

ZOLASTA (Zoledronic Acid Concentrate for Solution for Infusion 4 mg/5 ml)

● Name and Strength of Active Substance

Each 5 ml contains:

Zoledronic acid monohydrate 4.26 mg eq. to Zoledronic acid anhydrous 4 mg

List of excipients:

Mannitol Sodium citrate

Water for injections

● Product Description

Description of unopened vial (before dilution): A clear, colourless solution filled in a clear vial, when examined under suitable condition visibly; it is free from foreign particles.

Description after dilution (Diluent: 0.9% w/v sodium chloride solution for Injection or 5% w/v glucose solution): A clear, colourless solution free from visible particulate matter.

● Pharmacodynamics/ Pharmacokinetics

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. Zoledronic acid inhibits bone resorption without adversely affecting the formation, mineralization 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

Biotransformation

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 t½α 0.24 and t½β 1.87 hours, followed by a long elimination phase with a terminal elimination half-life of t½γ 146 hours. Zoledronic acid is not metabolized 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. Increasing the infusion time from 5 to 15 minutes causes 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.

No pharmacokinetic data for zoledronic acid are available in patients with hypercalcaemia or in patients with hepatic insufficiency. Zoledronic acid does not inhibit human P450 enzymes and the administered dose was recovered in the feces, suggesting no relevant role of liver function in the pharmacokinetics of zoledronic acid.

The renal clearance of zoledronic acid was correlated with creatinine clearance. Only limited pharmacokinetic data are available in patients with severe renal insufficiency.

Zoledronic acid showed low affinity for the cellular components of human blood, with a mean blood to plasma concentration ratio of 0.59 in a concentration range of 30 ng/ml to 5000 ng/ml. The plasma protein binding is low, with the unbound fraction ranging from 60% at 2 ng/ml to 77% at 2000 ng/ml of zoledronic acid.

Special populations

Paediatric patients

Limited pharmacokinetic data in children with severe osteogenesis imperfecta suggest that zoledronic acid pharmacokinetics in children aged 3 to 17 years are similar to those in adults at a similar mg/kg dose level.

● Indication

- 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).

● Recommended Dosage

Zoledronic Acid Injection 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 Elderly people

The recommended dose in the prevention of skeletal related events in patients with advanced malignancies involving bone is 4 mg Zoledronic Acid Injection 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 Tumour-Induced Hypercalcaemia (TIH)

Adults and Elderly 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 Injection.

Renal impairment

Tumour-Induced Hypercalcaemia (TIH):

Zoledronic Acid Injection treatment in Tumour-Induced Hypercalcaemia (TIH) patients who also have severe renal impairment should be considered only after evaluating the risks and benefits of treatment. No dose adjustment is necessary in Tumour-Induced Hypercalcaemia (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 Zoledronic Acid Injection 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. Zoledronic Acid Injection 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 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 Zoledronic Acid Injection dose is recommended:

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

* 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 zoledronic acid and treatment should be withheld if renal function has deteriorated. 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.

Zoledronic Acid Injection treatment should be resumed at the same dose as that given prior to treatment interruption.

Paediatric population

The safety and efficacy of Zoledronic Acid Injection in children aged 1 year to 17 years have not been established.

● Instructions for Use

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).

Additional information on handling of Zoledronic Acid Concentrate for Solution for Infusion 4mg/5ml, including guidance on preparation of reduced doses, is provided in section Posology and Method of Administration.

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.

Posology and Method of Administration

Intravenous use.

Zoledronic Acid concentrate for solution for infusion 4mg/5ml, 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 Zoledronic acid doses are recommended.

Instructions for preparing reduced doses of Zoledronic acid

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

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.

Patients must be maintained well hydrated prior to and following administration of Zoledronic acid.

Healthcare professionals are advised not to dispose of unused Zoledronic Acid via the domestic sewage system.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Incompatibilities

Zoledronic acid 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.

● Contraindications

Contraindicated in pregnancy, in breast-feeding women, patients with clinically significant hypersensitivity to zoledronic acid or other biphosphonates or any of the excipients in the formulation

● Warnings and Precautions

General

Patients must be assessed prior to administration of zoledronic acid 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 zoledronic acid therapy. If hypocalcaemia, hypophosphataemia, or hypomagnesaemia occurs, short-term supplemental therapy may be necessary. Untreated hypercalcaemia patients generally have some degree of renal function impairment, therefore careful renal function monitoring should be considered.

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. Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of zoledronic acid and other bisphosphonates as well as use of other nephrotoxic medicinal products. 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.

In view of the potential impact of zoledronic acid on renal function, the lack of clinical safety data in patients with severe renal impairment (in clinical trials defined as serum creatinine ≥ 400 µmol/l or ≥ 4.5 mg/dl for patients with TIH and ≥ 265 µmol/l or ≥ 3.0 mg/dl for patients with cancer and bone metastases, respectively) at baseline and only limited pharmacokinetic data in patients with severe renal impairment at baseline (creatinine clearance < 30 ml/min), 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

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) has been reported uncommonly in patients receiving Zoledronic Acid.

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 of bisphosphonate.
- 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.

All patients should be encouraged to maintain good oral hygiene, undergo routine dental check- ups and immediately report any oral symptoms such as dental mobility, pain or swelling, or non- healing of sores or discharge during treatment with Zoledronic Acid.

While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to zoledronic acid administration. 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 the risk of osteonecrosis of the jaw.

The management plan for patients who develop ONJ should be set up in close collaboration between the treating physician and a dentist or oral surgeon with expertise in ONJ. Temporary interruption of zoledronic acid treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.

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. Most patients had relief of symptoms after stopping treatment. A subset had recurrence of symptoms when rechallenged with zoledronic acid or another bisphosphonate.

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. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures,

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weeks to months before presenting with a completed femoral fracture. 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.

During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.

Hypocalcaemia

Hypocalcaemia has been reported in patients treated with zoledronic acid. Cardiac arrhythmias and neurologic adverse events (including convulsions, hypoasthesia 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 Zolendronc 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.

● Interactions with Other Medicaments

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.

● Pregnancy and Lactation

Pregnancy

There are no adequate data on the use of zoledronic acid in pregnant women. The potential risk for humans is unknown. Zoledronic acid should not be used during pregnancy. Women of child- bearing potential should be advised to avoid becoming pregnant.

Breast-feeding

It is not known whether zoledronic acid is excreted into human milk. Zoledronic acid is contraindicated in breast feeding women.

● Adverse Effects/ Undesirable Effects

Summary of the safety profile

Within three days after zoledronic acid administration, an acute phase reaction has commonly been reported, with symptoms including bone pain, fever, fatigue, arthralgia, myalgia, rigors and arthritis with subsequent joint swelling; these symptoms usually resolve within a few days (see description of selected adverse reactions).

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, atrial fibrillation, anaphylaxis, interstitial lung disease. The frequencies for each of these identified risks are shown in below Table.

Blood and lymphatic system disorders	
Common:	Anaemia
Uncommon:	Thrombocytopenia, leukopenia
Rare:	Pancytopenia
Immune system disorders	
Uncommon:	Hypersensitivity reaction
Rare:	Angioneurotic oedema
Psychiatric disorders	
Uncommon:	Anxiety, sleep disturbance
Rare:	Confusion
Nervous system disorders	
Common:	Headache
Uncommon:	Dizziness, paraesthesia, dysgeusia, hypoaesthesia, hyperaesthesia, tremor, somnolence
Very rare:	Convulsions, hypoaesthesia and tetany (secondary to hypocalcaemia)
Eye disorders	
Common:	Conjunctivitis
Uncommon:	Blurred vision, scleritis and orbital inflammation
Rare:	Uveitis
Very rare:	Episcleritis
Cardiac disorders	
Uncommon:	Hypertension, hypotension, atrial fibrillation, hypotension leading to syncope or circulatory collapse
Rare:	Bradycardia, cardiac arrhythmia (secondary to hypocalcaemia)
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Dyspnoea, cough, bronchoconstriction
Rare:	Interstitiel lung disease
Gastrointestinal disorders	
Common:	Nausea, vomiting, decreased appetite
Uncommon:	Diarrhoea, constipation, abdominal pain, dyspepsia, stomatitis, dry mouth
Skin and subcutaneous tissue disorders	
Uncommon:	Pruritus, rash (including erythematous and macular rash), increased sweating
Musculoskeletal and connective tissue disorders	
Common:	Bone pain, myalgia, arthralgia, generalised pain
Uncommon:	Muscle spasms, osteonecrosis of the jaw
Very rare:	Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction) and other anatomical sites including femur and hip
Renal and urinary disorders	
Common:	Renal impairment
Uncommon:	Acute renal failure, haematuria, proteinuria
Rare:	Acquired Fanconi syndrome
General disorders and administration site conditions	
Common:	Fever, flu-like syndrome (including fatigue, rigors, malaise and flushing)
Uncommon:	Asthenia, peripheral oedema, injection site reactions (including pain, irritation, swelling, induration), chest pain, weight increase, anaphylactic reaction/shock,urticaria
Rare:	Arthritis and joint swelling as a symptom of acute phase reaction
Investigations	
Very common:	Hypophosphataemia
Common:	Blood creatinine and blood urea increased, hypocalcaemia
Uncommon:	Hypomagnesaemia, hypokalaemia
Rare:	Hyperkalaemia, hypernatraemia

● Overdose and Treatment

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.

● 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 Zolasta along with driving and operating of machinery

● Storage Conditions

Unopened vials Store below 30°C.

Diluted preparation

For storage conditions after dilution of the medicinal product, *see Section: Shelf Life*.

● Shelf life

Unopened vials

36 months.

Diluted preparation

Chemical and physical in-use stability has been demonstrated for 24 hours at 2 – 8 °C.

After dilution: From a microbiological point of view, the product 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 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

● Dosage forms and packaging available

Pack size: 1 x 5ml vials

Each carton contains 1 vial of 5 ml

5 ml/20 mm ready to use cyclo olefin copolymer (COC) colourless vial stoppered with 20mm grey fluorotec plus rubber stopper and sealed with 20mm flip off aluminium violet coloured seal.

1 x 5ml vial is packed in a secondary carton along with the package insert.

● Name and address of product registration holder

Accord Healthcare Sdn Bhd (1035160 D)
Suite 12A-15, Level 12A, Wisma Zelan, No 1 Jalan Tasik Permaisuri 2, Bandar Tun Razak, 56000 Kuala Lumpur

● Name and address of product manufacturer

Intas Pharmaceuticals Limited
Plot Numbers 457, 458 & 191/218P, Sarkhej-Bavla Highway, Matoda, Sanand, Ahmedabad, Gujarat, IN-382210, India

● Date of revision of PI
25 July 2022

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