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New Launching Product

210mm

# ZIVALO®

**Solution for Infusion**

(Zoledronic Acid)

**For I.V. use only**

## QUALITATIVE AND QUANTITATIVE COMPOSITION

**ZIVALO® 5mg/100ml Solution for Infusion**
Each 100ml contains:
Zoledronic Acid Monohydrate BP
eq. to Zoledronic Acid.....5mg

## PHARMACEUTICAL FORM

Solution for infusion

## CLINICAL PARTICULARS

**THERAPEUTIC INDICATIONS:**

- Treatment of osteoporosis in post-menopausal women and adult men (at increased risk of fracture, including those with a recent low-trauma hip fracture).
- Prevention of osteoporosis in postmenopausal women.
- Treatment of osteoporosis associated with long-term systemic glucocorticoid therapy in post-menopausal women and adult men (at increased risk of fracture).
- Treatment of Paget's disease of the bone in adults.

**Important Limitations of Use:** All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis. Patients at low-risk for fracture should be considered for drug discontinuation after 3 to 5 years of use. Patients who discontinue therapy should have their risk for fracture re-evaluated periodically.

**POSOLOGY AND METHOD OF ADMINISTRATION:**

**Posology:** Patients must be appropriately hydrated prior to administration of zoledronic acid. This is especially important for the elderly (≥65 years) and for patients receiving diuretic therapy.
Adequate calcium and vitamin D intake are recommended in association with zoledronic acid administration.

***Osteoporosis:***

- For the treatment of post-menopausal osteoporosis, osteoporosis in men and the treatment of osteoporosis associated with long-term systemic glucocorticoid therapy, the recommended dose is a single intravenous infusion of 5mg zoledronic acid administered once a year.
- In patients with a recent low-trauma hip fracture, it is recommended to give the zoledronic acid infusion at least two weeks after hip fracture repair. In patients with a recent low-trauma hip fracture, a loading dose of 50,000 to 125,000 IU of vitamin D given orally or via the intramuscular route is recommended prior to the first zoledronic acid infusion.

***Paget's disease:***

- For the treatment of Paget's disease, zoledronic acid should be prescribed only by physicians with experience in the treatment of Paget's disease of the bone. The recommended dose is a single intravenous infusion of 5mg zoledronic acid.
- In patients with Paget's disease, it is strongly advised that adequate supplemental calcium corresponding to at least 500mg elemental calcium twice daily is ensured for at least 10 days following zoledronic acid administration.
- Re-treatment of Paget's disease: After initial treatment with zoledronic acid in Paget's disease, an extended remission period is observed in responding patients.
- Re-treatment consists of an additional intravenous infusion of 5mg zoledronic acid after an interval of one year or longer from initial treatment in patients who have relapsed. Limited data on re-treatment of Paget's disease are available.

**Special populations:**
***Renal impairment:*** Contraindicated in patients with creatinine clearance <35ml/min. No dose adjustment is necessary in patients with creatinine clearance ≥ 35 ml/min.
***Hepatic impairment:*** No dose adjustment is required.
***Elderly (≥ 65 years):*** No dose adjustment is necessary since bioavailability, distribution and elimination were similar in elderly patients and younger subjects.
***Paediatric population:*** Should not be used in children and adolescents below 18 years of age.
***Method of administration:*** For intravenous use. Zoledronic acid (5mg in 100ml ready-to-infuse solution) is administered via a separate vented infusion line and given slowly at a constant infusion rate; do not mix with calcium containing solutions.
The infusion time must not be less than 15 minutes.

**CONTRAINDICATIONS:**

- Hypersensitivity to the active substance, or to any bisphosphonates.
- Patients with hypocalcaemia.
- Severe renal impairment with creatinine clearance < 35ml/min.
- Pregnancy and breast-feeding.

**SPECIAL WARNINGS AND PRECAUTIONS FOR USE:**

**Renal function:** Use in patients with severe renal impairment (creatinine clearance < 35ml/min) is contraindicated due to an increased risk of renal failure in this population.
Renal impairment is known to occur following the administration of zoledronic acid especially in patients with pre-existing renal dysfunction, advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy, or dehydration occurring after administration.
The following precautions should be taken into account to minimize the risk of renal adverse reactions:

- Creatinine clearance should be calculated, monitoring of serum creatinine should be considered in at-risk patients.
- Should be used with caution when concomitantly used with other medicinal products that could impact renal function.
- Patients, especially elderly patients and those receiving diuretic therapy, should be appropriately hydrated.
- Single dose should not exceed 5mg and the duration of infusion should be at least 15 minutes.

**Hypocalcaemia:** Pre-existing hypocalcaemia and other disturbances of mineral metabolism must be treated before initiating therapy (e.g. diminished parathyroid reserve, intestinal calcium malabsorption). Physicians should consider clinical monitoring for these patients.
Elevated bone turnover is a characteristic of Paget's disease of the bone. Due to the rapid onset of effect of zoledronic acid on bone turnover, transient hypocalcaemia, sometimes symptomatic, may develop and is usually maximal within the first 10 days after infusion of zoledronic acid.
Adequate calcium and vitamin D intake are recommended in association with zoledronic acid administration. It is strongly advised that adequate supplemental calcium corresponding to at least 500mg elemental calcium twice daily is ensured for at least 10 days following zoledronic acid administration. Measurement of serum calcium before infusion of zoledronic acid is recommended for patients with Paget´s disease.
Severe and occasionally incapacitating bone, joint and/or muscle pain have been infrequently reported in patients taking bisphosphonates, including zoledronic acid.
**Osteonecrosis of the jaw (ONJ):** ONJ is known to occur in the post-marketing setting in patients receiving zoledronic acid for osteoporosis.
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. A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with zoledronic acid in patients with concomitant risk factors.
The following should be considered when evaluating a patient's risk of developing ONJ.

- Potency of the medicinal product that inhibits bone resorption (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapy.
- Cancer, co-morbid conditions (e.g. anemia, coagulopathies, infection), smoking.
- Concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck.
- Poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures, e.g. tooth extractions. 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, non-healing of sores or discharge during treatment with zoledronic acid.
- While on treatment, invasive dental procedures should be performed with caution and avoided in close proximity to zoledronic acid treatment. Temporary interruption of zoledronic acid treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.

**Osteonecrosis of the external auditory canal:** 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.
**Atypical fractures of the femur:** Atypical sub trochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis.
Some patients experience thigh or groin pain, often associated with imaging features of stress fractures, 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. 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.

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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.
**Acute phase reactions:** Acute phase reactions (APRs) or post-dose symptoms such as fever, myalgia, flu-like symptoms, arthralgia and headache have been observed, the majority of which occurred within three days following zoledronic acid administration. APRs may sometimes be serious or prolonged in duration. It is also advisable to postpone treatment if the patient is clinically unstable due to an acute medical condition and an APR could be problematic.
**General:** Other products containing zoledronic acid as an active substance are available for oncology indications. Patients being treated with zoledronic acid should not be treated with such products or any other bisphosphonate concomitantly, since the combined effects of these agents are unknown.
This medicinal product contains less than 1mmol sodium (23mg) per 100ml vial of zoledronic acid, i.e. essentially "sodium free".

**INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:**
Zoledronic acid is not systemically metabolized and does not affect human cytochrome P450 enzymes in vitro.
Zoledronic acid is not highly bound to plasma proteins (approximately 43-55% bound) and interactions resulting from displacement of highly protein-bound medicinal products are therefore unlikely.
Zoledronic acid is eliminated by renal excretion. Caution is indicated when zoledronic acid is administered in conjunction with medicinal products that can significantly impact renal function (e.g. aminoglycosides or diuretics that may cause dehydration). In patients with renal impairment, the systemic exposure to concomitant medicinal products that are primarily excreted via the kidney may increase.

**FERTILITY, PREGNANCY AND LACTATION:**
**Fertility:** Results precluded a definitive effect of zoledronic acid on fertility in humans.
**Pregnancy:** ***Pregnancy Category C:*** There are no adequate and well-controlled studies in pregnant women. Zoledronic acid is contraindicated during pregnancy. Studies in animals with zoledronic acid have shown reproductive toxicological effects including malformations. The potential risk for humans is unknown.
**Breast-feeding:** Zoledronic acid is contraindicated during breast-feeding. It is unknown whether zoledronic acid is excreted into human milk.
**Women of childbearing potential:** Zoledronic acid is not recommended in women of childbearing potential.

**EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:**
Adverse reactions, such as dizziness, may affect the ability to drive or use machines.

**UNDESIRABLE EFFECTS:**
**Very common:** Pyrexia.
**Common:** Hypocalcaemia, headache, dizziness, ocular hyperaemia, atrial fibrillation, nausea, vomiting, diarrhoea, myalgia, arthralgia, bone pain, back pain, pain in extremity, influenza-like illness, chills, fatigue, asthenia, pain, C-reactive protein increased.
**Uncommon:** Influenza, nasopharyngitis, anaemia, decreased appetite, lethargy, paraesthesia, somnolence, tremor, syncope, dysgeusia, conjunctivitis, eye pain, vertigo, palpitations, hypertension, flushing, cough, dyspnea, dyspepsia, abdominal pain upper, abdominal pain, gastro-oesophageal reflux disease, constipation, dry mouth, oesophagitis, toothache, gastritis, rash, hyperhydrosis, pruritus, erythema, neck pain, musculoskeletal stiffness, joint swelling, muscle spasms, musculoskeletal chest pain, blood creatinine increased, pollakiuria, proteinuria malaise, infusion site reaction, blood calcium decreased.
**Rare:** Hypophosphataemia, uveitis, episcleritis, iritis, muscular weakness.

**OVERDOSE:**
Patients who have received doses higher than those recommended should be carefully monitored. In the event of overdose leading to clinically significant hypocalcaemia, reversal may be achieved with supplemental oral calcium and/or an intravenous infusion of calcium gluconate.

## PHARMACOLOGICAL PROPERTIES
**PHARMACODYNAMIC PROPERTIES:**
**Pharmacotherapeutic group:** Drugs for treatment of bone diseases, bisphosphonates, **ATC code:** M05BA08
**Mechanism of action:** Belongs to the class of nitrogen-containing bisphosphonates and acts primarily on bone. It is an inhibitor of osteoclast-mediated bone resorption.
**Pharmacodynamic effects:** The selective action of bisphosphonates on bone is based on their high affinity for mineralized bone.
Main molecular target of zoledronic acid in the osteoclast is the enzyme farnesyl pyrophosphate synthase. The long duration of action is attributable to its high binding affinity for the active site of farnesyl pyrophosphate (FPP) synthase and its strong binding affinity to bone mineral.
Zoledronic acid treatment rapidly reduced the rate of bone turnover from elevated post-menopausal levels with the nadir for resorption markers observed at 7 days, and for formation markers at 12 weeks. Thereafter bone markers stabilised within the pre-menopausal range. There was no progressive reduction of bone turnover markers with repeated annual dosing.

**PHARMACOKINETIC PROPERTIES:**
Single and multiple 5 and 15-minute infusions of 2, 4, 8 and 16mg zoledronic acid in 64 patients yielded the following pharmacokinetic data, which were found to be dose independent.
**Distribution:** After initiation of the zoledronic acid infusion, plasma concentrations of the active substance increased rapidly, 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 levels.
**Elimination:** Intravenously administered zoledronic acid is eliminated by a triphasic process: rapid biphasic disappearance from the systemic circulation, with half-lives of t½ α 0.24 and t½ β1.87 hours, followed by a long elimination phase with a terminal elimination half-life of t½ γ 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. This uptake into bone is common for all bisphosphonates and is presumably a consequence of the structural analogy to pyrophosphate.
As with other bisphosphonates, the retention time of zoledronic acid in bones is very long. 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 or body weight. The inter- and intra-subject variation for plasma clearance of zoledronic acid was shown to be 36% and 34%, respectively. 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.

## SHELF LIFE
See expiry on the pack.

## AVAILABILITY
**ZIVALO®** 5mg/100ml solution for infusion in a pack of 1's

## INSTRUCTIONS
**Dosage:** As advised by the physician.
To be sold on the prescription of registered medical practitioner only.
Keep out of reach of children.
Do not store over 30°C, and protect from heat and freezing.
Improper storage may deteriorate the medicine.
Stable for 24 hours at 2 - 8°C, after opening.
If refrigerated, allow the refrigerated solution to reach room temperature before administration.

Injection should not be used if container is leaking, solution is cloudy or it contains undissolved particle(s).

# زیوالو®
سلوشن برائے انفیوژن
(زولی ڈرونک ایسڈ)

## ہدایات:
**خوراک:** ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔
دوا کو ۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں،
گرمی اور منجمد ہونے سے محفوظ رکھیں ورنہ دوا خراب ہو جائیگی۔
انجکشن کھولنے کے بعد ۲ سے ۸ ڈگری سینٹی گریڈ پر ۲۴ گھنٹے کے اندر استعمال کرلیں۔
انجکشن کے لیک ہونے، دُھندلا ہونے یا اس میں کوئی غیر حل پزیر شے نظر آنے کی صورت میں ہرگز استعمال نہ کریں۔

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