LEDRONIC IV Infusion

(Zoledronic Acid)

لیڈرونک آئی وی انفیوژن

(زولیڈرونک ایسڈ)

COMPOSITION: Each 100ml contains:
Zoledronic Acid monohydrate eq. to Zoledronic Acid … 5mg. [Innovator's Specification]

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

CONTRA-INDICATIONS: Hypersensitivity to the active or to any bisphosphonates or to any of the components of the product. Patients with hypocalcaemia. Severe renal impairment with creatinine clearance < 35ml/min. Pregnancy and breast-feeding.

PHARMACOLOGY:

MECHANISM OF ACTION: Zoledronic Acid belongs to the class of nitrogen-containing bisphosphonates and acts primarily on bone. It is an inhibitor of osteoclast-mediated bone resorption. The selective action of bisphosphonates on bone is based on their high affinity for mineralised bone. The main molecular target of Zoledronic Acid in the osteoc last is the enzyme farnesyl pyrophosphate synthase. The long duration of action of Zoledronic Acid is attributable to its high binding affinity for the active site of farnesyl pyrophosphate (FPP) synthase and its strong binding affinity to bone mineral.

PHARMACOKINETIC:

Distribution: 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. 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.

Excretion: 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 the active substance in plasma after multiple doses given every 28 days. The early disposition phases (α and β, with $t_{1/2}$ values above) presumably represent rapid uptake into bone and excretion via the kidneys. 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. 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.

DOSAGE AND ADMINISTRATION: Patients must be appropriately hydrated prior to administration of **Ledronic** IV Infusion (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 **Ledronic** IV Infusion (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 **Ledronic** IV Infusion (Zoledronic Acid) administered once a year. In patients with a recent low-trauma hip fracture, it is recommended to give the **Ledronic** IV Infusion (Zoledronic Acid) two or more 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 **Ledronic** IV Infusion (Zoledronic Acid) infusion.

Paget's disease: For the treatment of Paget's disease, **Ledronic** IV Infusion (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 **Ledronic** IV Infusion (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 **Ledronic** IV Infusion (Zoledronic Acid) administration.

Re-treatment of Paget's disease: After initial treatment with **Ledronic** IV Infusion (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 **Ledronic** IV Infusion (Zoledronic Acid) after an interval of one year or longer from initial treatment in patients who have relapsed.

Special populations: Renal impairment: Ledronic IV Infusion (Zoledronic Acid) is contra-indicated in patients with creatinine clearance < 35ml/min. No dose adjustment is necessary in patients with creatinine clearance ≥ 35ml/min.

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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: The safety and efficacy of **Ledronic** IV Infusion (Zoledronic Acid) in children and adolescents below 18 years of age have not been established. No data are available.
Method of administration: Intravenous use. **Ledronic** IV Infusion (Zoledronic Acid) (5mg in 100ml ready-to-infuse solution) is administered via a vented infusion line and given at a constant infusion rate. The infusion time must not be less than 15 minutes.

OVERDOSAGE: Clinical experience with acute overdose is limited. 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.

WARNINGS & PRECAUTIONS:
Renal function: The use of Zoledronic Acid in patients with severe renal impairment (creatinine clearance < 35ml/min) is contra-indicated due to an increased risk of renal failure in this population. Renal impairment has been observed in patients after a single administration. Patients, especially elderly patients and those receiving diuretic therapy, should be appropriately hydrated prior to administration of Zoledronic Acid.
Hypocalcaemia: Pre-existing hypocalcaemia must be treated by adequate intake of calcium and vitamin D before initiating therapy with Zoledronic Acid. Other disturbances of mineral metabolism must also be effectively treated (e.g. diminished parathyroid reserve, intestinal calcium malabsorption). Physicians should consider clinical monitoring for these patients. 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 has been reported 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.

DRUG INTERACTIONS: No interaction studies with other medicinal products have been performed. Zoledronic Acid is not systemically metabolised 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 drugs 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:
Women of childbearing potential: Zoledronic Acid is not recommended in women of childbearing potential.
Pregnancy: Zoledronic Acid is contraindicated during pregnancy. There are no adequate data on the use of Zoledronic Acid in pregnant women.
Breast-feeding: Zoledronic Acid is contraindicated during breast-feeding. It is unknown whether Zoledronic Acid is excreted into human milk.
Fertility: Zoledronic Acid was evaluated in rats for potential adverse effects on fertility of the parental and F1 generation. This resulted in exaggerated pharmacological effects considered related to the compound's inhibition of skeletal calcium mobilisation, resulting in periparturient hypocalcaemia, a bisphosphonate class effect, dystocia and early termination of the study. Thus these results precluded determining a definitive effect of Zoledronic Acid on fertility in humans.
Effects on ability to drive and use machines: Adverse reactions, such as dizziness, may affect the ability to drive or use machines.

ADVERSE REACTIONS: The following side effects are common (occurring in greater than 30%) for patients taking Zoledronic Acid: Ostealgia, nausea, fever usually mild and short lived, fatigue, anemia, vomiting, constipation. Flu-like symptoms; mild fever sometimes accompanied by malaise, chills, fatigue and flushing. Usually occurs with first treatment with Zoledronic Acid only. These are less common side effects (occurring in 10-29%) for patients receiving Zoledronic Acid: Shortness of breath, diarrhea, weakness, myalgia (muscle pain), loss of appetite, cough, lower extremity swelling, arthralgia (joint pain), headache, dizziness, decreased kidney function, trouble sleeping, abdominal pain, weight loss, paresthesia (abnormal sensation, typically tingling or prickling), anxiety, depression, dehydration, urinary tract infection, confusion, hypophosphatemia (low phosphorus in the blood), hypoesthesia (reduced sense of touch or sensation), hair loss, low potassium in the blood, low blood counts, candidiasis (yeast infection), bone pain, low blood pressure, chills, rash, low magnesium in the blood, cold symptoms (upper respiratory infection), heart burn, chest pain, hypocalcemia (low calcium in the blood), trouble swallowing, mouth sores, infection (non-specific).

INSTRUCTIONS: Store below 30°C. Protect from heat and light. Keep out of the reach of children.

PRESENTATION: Ledronic IV Infusion (Zoledronic Acid) is available in pack size of 1 vial of 100ml.

ہدایات: ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔ روشنی اور گرمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔

Manufactured By:
Surge Laboratories (Pvt.) Ltd.
10th KM, Faisalabad Road, Bikhi, District Sheikhupura - Pakistan.
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