Zoleron
(Zoledronic Acid)

5mg/100mL Solution For I.V. Infusion

زولیرون انفیوژن
۵ ملی گرام/۱۰۰ ملی لیٹر

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100mL contains:

Zoledronic acid monohydrate eq. to Zoledronic acid…. 5mg

Innovator's Specs.

DESCRIPTION:

Zoleron contains 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-phosphonoeth-yl) phosphonic acid monohydrate. Zoledronic acid monohydrate is a white crystalline powder. Its molecular formula is $C_5H_{10}N_2O_7P_2.H_2O$ and a molar mass of 290.1 g/Mol.

CLINICAL 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.

Pharmacodynamics: 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 osteoclast is the enzyme farnesyl pyrophosphate synthase. 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.

Pharmacokinetics: Pharmacokinetic data in patients with osteoporosis and Paget's disease of bone are not available.

Distribution: Plasma concentrations of the active substance increases rapidly after administration, 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.

Metabolism: Zoledronic acid does not inhibit human P450 enzymes in vitro. Zoledronic acid does not undergo biotransformation in vivo.

Excretion: The cumulative percent of drug excreted in the urine over 0-24 hours was independent of dose. The balance of drug not recovered in urine over 0-24 hours, representing drug presumably bound to bone, is slowly released back into the systemic circulation, giving rise to the observed prolonged low plasma concentrations. The 0-24 hour renal clearance of zoledronic acid was 3.7 ± 2.0 L/h. Zoledronic acid clearance was independent of dose but dependent upon the patient's creatinine clearance.

INDICATIONS AND USAGE:

Treatment and Prevention of Osteoporosis in Postmenopausal Women, Osteoporosis in Men (including Glucocorticoid-Induced Osteoporosis) and Paget's Disease of Bone.

Contraindications: Hypersensitivity to the active substance, to any bisphosphonates or to any of the excipients.

- Patients with hypocalcaemia.
- Severe renal impairment with creatinine clearance < 35 ml/min.
- Pregnancy and breast-feeding

INTERACTIONS: DRUG INTERACTIONS

Aminoglycosides: Zoledronic acid administered with aminoglyco-sides, may have an additive effect to lower serum calcium level for prolonged periods.

Loop Diuretics: Caution should also be exercised when Zoleron is used in combination with loop diuretics due to an increased risk of hypocalcemia.

Nephrotoxic Drugs: Caution is indicated when Zoleron is used with other potentially nephrotoxic drugs such as nonsteroidal anti-inflammatory drugs.

Drugs Primarily Excreted by the Kidney: Renal impairment has been observed following the administration of zoledronic acid in patients with pre-existing renal compromise or other risk factors.

Use in Specific Population:

Conception And Contraception: Contra-indicated in women of child-bearing potential.

Pregnancy: Avoid—toxicity in animal studies.

Breast Feeding: Avoid—no information available.

Hepatic Impairment: Caution in severe hepatic impairment—limited information available.

Renal Impairment: Avoid in tumour-induced hypercalcaemia if serum creatinine above 400 micromol/litre. Avoid in advanced malignancies involving bone if eGFR less than 30 mL/minute/1.73m2 (or if serum creatinine greater than 265 micromol/litre). Avoid in Paget's disease, treatment of postmenopausal osteoporosis and oste-oporosis in men if eGFR less than 35 mL/minute/1.73m2.

Dose adjustments In advanced malignancies involving bone, if eGFR 50–60 mL/minute/1.73m2 reduce dose to 3.5 mg every 3–4 weeks; if eGFR 40–50 mL/minute/1.73m2 reduce dose to 3.3mg every 3–4 weeks; if eGFR 30–40 mL/minute/1.73m2 reduce dose to 3 mg every 3–4 weeks; if renal function deteriorates in patients with bone metastases, withhold dose until serum creatinine returns to within 10% of baseline value.

Monitoring Requirements:

• Correct disturbances of calcium metabolism (e.g. vitamin D deficiency, hypocalcaemia) before starting. Monitor serum electrolytes, calcium, phosphate and magnesium. • Monitor renal function in patients at risk, such as those with pre-existing renal impairment, those of advanced age, those taking concomitant nephrotoxic drugs or diuretics, or those who are dehydrated.

PRECAUTIONS:

IMPORTANT SAFETY INFORMATION MHRA/CHM ADVICE: BISPHOSPHONATES: ATYPICAL FEMORAL FRACTURES (JUNE 2011): Atypical femoral fractures have been reported rarely with bisphosphonate treatment, mainly in patients receiving long-term treatment for osteoporosis. The need to continue bisphosphonate treatment for osteoporosis should be re-evaluated periodically based on an assessment of the benefits and risks of treatment for individual patients, particularly after 5 or more years of use.

Patients should be advised to report any thigh, hip, or groin pain during treatment with a bisphosphonate. Dis-continuation of bisphosphonate treatment in patients suspected to have an atypical femoral fracture should be considered after an assessment of the benefits and risks of continued treatment.

MHRA/CHM ADVICE: BISPHOSPHONATES: OSTEONECROSIS OF THE JAW (NOVEMBER 2009) AND INTRAVENOUS BISPHOSPHONATES: OSTEONECROSIS OF THE JAW—FUR-THER MEASURES TO MINIMISE RISK (JULY 2015): The risk of osteonecrosis of the jaw is substantially greater for patients receiving intravenous bisphosphonates in the treatment of cancer than for patients receiving oral bisphosphonates for osteoporosis or Paget's disease. Risk factors for developing osteonecrosis of the jaw that should be considered are: potency of bisphosphonate (highest for zoledronate), route of administration, cumulative dose, duration and type of malignant disease, concomitant treatment, smoking, comorbid conditions, and history of dental disease. All patients should have a dental check-up (and any necessary remedial work should be performed) before bisphosphonate treatment, or as soon as possible after starting treatment. Patients should also maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain, or swelling, non-healing sores or discharge to a doctor and dentist during treatment. Before prescribing an intravenous bisphosphonate, patients should be given a patient reminder card and informed of the risk of osteonecrosis of the jaw. Advise patients to tell their doctor if they have any problems with their mouth or teeth before starting treatment, and if the patient wears dentures, they should make sure their dentures fit properly. Patients should tell their doctor and dentist that they are receiving an intravenous bisphosphonate if they need dental treatment or dental surgery.

Bisphosphonates: Dental Clinical Guidance, Scottish Dental Clinical Effectiveness Programme, April 2011

MHRA/CHM ADVICE: BISPHOSPHONATES: OSTEONECROSIS OF THE EXTERNAL AUDITORY CANAL (DECEMBER 2015)

Benign idiopathic osteonecrosis of the external auditory canal has been reported very rarely with bisphospho-nate treatment, mainly in patients receiving long-term therapy (2 years or longer). 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, or suspected cholesteatoma. Risk factors for developing osteonecrosis of the external auditory canal include: steroid use, chemotherapy, infection, an ear operation, or cottonbud use. Patients should be advised to report any ear pain, discharge from the ear, or an ear infection during treatment with a bisphosphonate.

cardiac disease: (avoid fluid overload).

Hypocalcemia and Mineral Metabolism: Clinical monitoring of calcium and mineral levels is highly recommended in patients with Pre-existing hypocalcemia and disturbances of mineral metabolism (e.g., hypoparathyroidism, thyroid surgery, parathyroid surgery; malabsorption syndromes, excision of small intestine).

Renal Impairment: should be used with caution in patients with chronic renal impairment. Use with caution for concomitant medicines that affect renal function.

Musculoskeletal Pain: Consider withholding future Zoleron treatment if severe symptoms develop.

Patients with Asthma: Use Zoleron with caution in aspirin-sensitive patients. NICE decisions • Bisphosphonates for treating osteoporosis (updated February 2018) NICE TA464: **This technology appraisal guidance should be applied clinically in conjunction with:**

• NICE guideline on assessing the risk of fragility fractures (CG146), which defines who is eligible for osteoporotic fracture risk assessment. • NICE quality standard on osteoporosis (QS149), which defines the clinical intervention thresholds for the 10-year fracture probability of a major osteoporotic fracture, in those patients who have undergone fracture risk assessment. Zoledronic acid is recommended as an option for treating osteoporosis in patients, only if: • The person is eligible for risk assessment as defined in the full NICE guideline on osteoporosis, and the 10-year probability of osteoporotic fragility fracture is at least 10%, or the 10-year probability of osteoporotic fragility fracture is at least 1% and the person has difficulty taking oral bisphosphonates (alendronic acid, ibandronic acid or risedronate sodium) or these drugs are contra-indicated or not tolerated. Patients whose treatment was started within the NHS before this guidance was published should have the option to continue treatment, without change to their funding arrangements, until they and their NHS clinician consider it appropriate to stop.

DOSAGE AND ADMINISTRATION:

Treatment of Paget's Disease of Bone: • By Intravenous Infusion-Adult: 5 mg as a single dose, to be administered over at least 15 minutes, at least 500mg elemental calcium twice daily (with vitamin D) for at least 10 days is recommended following infusion.

Re-treatment of Paget's Disease After a single treatment with Zoleron in Paget's disease an extended remission period is observed. However, re-treatment with Zoleron may be considered in patients who have relapsed, based on increases in serum alkaline phosphatase, or in those patients who failed to achieve normalization of their serum alkaline phosphatase, or in those patients with symptoms, as dictated by medical practice. Treatment of Postmenopausal Osteoporosis And Osteoporosis In Men (including corticosteroid-induced osteoporosis): • By Intravenous Infusion-Adult: 5 mg once yearly as a single dose, to be administered over at least 15 minutes, in patients with a recent low-trauma hip fracture, the dose should be given 2 or more weeks following hip fracture repair; before first infusion give 50 000–125 000 units of vitamin D. **Prevention of Postmenopausal Osteoporosis:** 5mg infusion given once every 2 years intravenously over no less than 15 minutes. **Scottish Medicines Consortium (SMC) Decisions:** The Scottish Medicines Consortium has advised (February 2008) that in postmenopausal women zoledronic acid is accepted for restricted use within the NHS Scotland for the treatment of osteoporosis in those for whom oral treatment options for osteoporosis are inappropriate and when initiated by a specialist.

DIRECTIONS FOR ADMINISTRATION:

Zoleron injection must be administered as an intravenous infusion over no less than 15 minutes. Patients must be appropriately hydrated prior to administration. The I.V. infusion should be followed by a 10 mL normal saline flush of the intravenous line. Zoleron must not be allowed to come in contact with any calcium or other divalent cation-containing solutions, and should be administered as a single intravenous solution through a separate vented infusion line. Administration of acetaminophen following Zoleron administration may reduce the incidence of acute-phase reaction symptoms.

Overdosage: Clinical experience with acute overdosage of zoledronic acid solution for intravenous infusion is limited. Patients who have received doses higher than those recommended should be carefully monitored. Overdosage may cause clinically significant renal impairment, 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. 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.

ADVERSE REACTIONS:

• Common or very common: Appetite decreased. chills. Flushing.

• Uncommon: Anxiety. arrhythmias. chest pain. circulatory collapse. cough. drowsiness. dry mouth. dyspnoea. electrolyte imbalance. haematuria. hyperhidrosis. hypertension. hypotension. leukopenia. muscle spasms. orbital inflammation. proteinuria. respiratory disorders. sensation abnormal. sleep disorder. stomatitis. syncope. thrombocytopenia. tremor. vision blurred. weight increased • Rare or very rare: Confusion. Fanconi syndrome acquired. osteonecrosis. pancytopenia • Frequency not known: Acute phase reaction

INSTRUCTIONS

Dosage as directed by the physician. Store at 25°C, excursions permitted to 15°C - 30°C. Protect from sunlight. Do not freeze. Keep all medicines out of the reach of children. To be sold on the prescription of a registered medical practitioner only. Infusion should not be used if container is leaking, solution is cloudy or it contains un-dissolved particles. If refrigerated, allow the refrigerated solution to reach room temperature before administration.After opening, the solution is stable for 24 hours at 2°C - 8°C.

PRESENTATION

Zoleron (Zoledronic Acid) Infusion 5mg/100mL is available in 1x100mL clear glass vial with insert.

علامات/طریقہ استعمال:

زولیرون انفیوژن کا استعمال اوسٹیوپوروسس کے مریضوں میں ہڈیوں کے بھربھرے پن اور ہڈیوں کی کمزوری کے علاج کے لیے تجویز کردہ ہے۔

مضر اثرات:

بھوک میں کمی، سردی لگنا، جلد کا سرخ ہونا، بے چینی، کھانسی، منہ خشک ہونا، پٹھوں میں کھچاؤ، وزن بڑھنا، سینے کا درد، دھندلا پن۔

احتیاطی تدابیر:

حاملہ خواتین اور دودھ پلانے والی ماؤں میں زولیرون کا استعمال ممنوع ہے۔

جگر اور گردے کے مریضوں میں دوا کا استعمال صرف ڈاکٹر کے مشورے سے کریں۔

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

۲۵ ڈگری سینٹی گریڈ پر رکھیں، محفوظ رکھنے کی حد ۱۵ سے ۳۰ ڈگری سینٹی گریڈ ہے۔

سورج کی روشنی سے محفوظ رکھیں۔ منجمد ہونے سے بچائیں۔

تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔ صرف رجسٹرڈ ڈاکٹر کے نسخہ پر فروخت کریں۔

انفیوژن کے لیک، مجلوں کے دھندلا ہونے یا کسی بھی قسم کے غیر حل پزیر شے نظر آنے کی صورت میں ہرگز استعمال نہ کریں۔

کھلنے کے بعد سلوشن کو ۲۴ گھنٹوں تک ۲-۸ ڈگری سینٹی گریڈ پر استعمال کیا جاسکتا ہے۔

For detailed information please contact:

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