SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Zoledronic acid 4 mg/vial concentrate for solution for infusion
Zolova 4

2. Qualitative and quantitative composition

Each vial of solution contains 4 mg of zoledronic acid.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Concentrate for solution for injection.

A white or yellowish lyophilized mass.

4. Clinical particulars

4.1 Therapeutic indications

Zoledronic acid is indicated for the treatment of hypercalcemia of malignancy and the treatment of bone metastases in patients with multiple myeloma and solid tumours in conjunction with anti-neoplastic therapy.

Patients with prostate cancer should have progressed after therapy with at least one hormonal agent.

4.2 Posology and method of administration

For the treatment of hypercalcemia of malignancy:
For hypercalcemia of malignancy (albumin-corrected serum calcium equal to or greater than 12 mg/dL), the maximum recommended dose of zoledronic acid is 4mg, given as a single dose intravenous infusion over a minimum of 15 minutes. Adequate rehydration of patients should precede the administration of zoledronic acid. The patient may be retreated with zoledronic acid 4 mg if serum calcium does not return to or remains higher than the normal range after initial treatment. It is recommended that a minimum of 7 days be allowed to pass between treatments, in order to allow for a full initial response. If patients with a normal serum creatinine before treatments have an increase of 0.5 mg/dL or if patients with a serum creatinine prior to treatment have an increase of 1mg/dL from baseline within 2 weeks of their next dose, zoledronic acid should be withheld until the serum creatinine is within 10% of baseline.

For the treatment of bone metastases:
For the treatment of bone lesions associated with multiple myeloma and bone metastases from solid tumours, the recommended dose is 4 mg intravenously over 15 minutes every 3 or 4 weeks for patients with creatinine clearance of greater than 60 mL/min, in conjunction with standard antineoplastic therapy. Concomitant oral calcium (500 mg) and vitamin D supplementation (400 international units) are also recommended.

Dose Modifications
Serum creatinine (Scr) should be measured prior to each zoledronic acid dose. Patients with hypercalcemia, malignancy and deterioration of renal function should be evaluated regarding risk versus benefit for continued zoledronic acid therapy. Patients with bone metastases and deterioration of renal function should have zoledronic acid therapy withheld until serum creatinine (Scr) values return to within 10% of baseline.

Reconstitution
Reconstitute the content of the vial with 5 ml of sterile water for injection and shake gently to dissolve it completely. The reconstituted solution should immediately be diluted in 100 ml of sterile 0.9% w/v sodium chloride injection or 5% w/v dextrose injection. The dose must be given as a single intravenous infusion over no less than 15 minutes. Reconstituted and diluted solution should be used immediately or within 24 hours if stored under refrigeration at 2-8°C the refrigerated solution should then be equilibrated to room temperature prior to administration. Do not mix with calcium-containing infusion solution viz., Ringer's solution and should be administered as a single intravenous solution in a line separate from all other drugs. Inspect the reconstituted solution visually for particulate matter and decolouration prior to administration.

4.3 Contraindications
- Prior hypersensitivity to zoledronic acid, its excipients or other bisphosphonates.
- Patients with bone metastases and severe renal impairment; serum creatinine >3mg/dL.
- Pregnancy.

4.4 Special warnings and precautions for use
- Renal impairments (renaly eliminated; possibility of enhanced toxicity).
- History of hypoparathyroidism; risk of hypocalcemia.
- Concomitant administrations of loop diuretics, aminoglycosides or other nephrotoxic drugs.
- History of aspirin-sensitive asthma.
- Dose > 4 mg and infusion time less than 15 minutes have increased risk for renal toxicity. Due to the risk of renal toxicity, including renal failure, avoid intravenous administration over less than 15 minutes or doses greater than 4 mg.
- Monitor renal function prior to and during treatment, especially in patients with preexisting renal impairment. Re-treatment should be delayed in patients who develop increased serum creatinine following the initial dose. The risk of zoledronic acid treatment must be carefully considered in patients with renal failure or impairment.
- Caution is recommended when zoledronic acid is administered to elderly patients. Since these patients have a greater frequency of decreased renal function and concomitant disease states or other drug therapy.
- Standard hypocalcemia-related metabolic parameters, such as serum level of calcium, phosphate and magnesium, as well as serum creatinine, should be monitored during treatment with zoledronic acid.
- Zoledronic acid should not be used in patients with preexisting hypocalcemia. If electrolyte imbalance (i.e., hypocalcemia, hypomagnesemia or hypophosphatemia) occurs during therapy, short-term supplementation may be necessary.
- Dehydration or hypovolemia should be corrected during the treatment of hypercalcemia and prior to beginning zoledronic acid therapy; maintain a urine output of 2 L/day during the treatment of hypercalcemia.

4.5 Interaction with other medicinal products and other forms of interaction
Loop diuretics should be used with caution in combination with zoledronic acid in order to avoid hypocalcemia. The initial treatment of hypercalcemia typically includes the use of loop diuretics, in combination with saline hydration. However, diuretic therapy should not be employed prior to the correction of hypovolemia and dehydration.

Caution is recommended when bisphosphonate is administered with aminoglycosides since these agents may have an additive effect of lowering serum calcium levels for a prolonged period.

4.6 Fertility, pregnancy and lactation
Zoledronic acid is classified as FDA pregnancy risk category D.

In animal studies, administration of zoledronic acid was associated with increased pre and post-implantation losses and stillbirths; decreased neonatal survival; skeletal, visceral and external malformation and adverse maternal effects including periparturient mortality. Because no adequate and well-controlled studies of zoledronic acid have been conducted in pregnant women, the drug should be avoided during pregnancy whenever possible.

4.7 Effects on the ability to drive and use machines
Adverse reactions such as dizziness and somnolence, may influence the ability to drive or use machines. Therefore, caution should be exercised with the use of zoledronic acid along with driving and operating machinery.

4.8 Undesirable effects
Adverse effects include bone pain, nausea, constipation, fatigue, confusion, hallucination, anaemia, muscle pain, vomiting, weakness, anorexia, fever, dyspnea, eye irritation, hypocalcemia, headache, diarrhoea and hypophosphatemia.

Administration is most commonly associated with fever (44.2%). Occasionally, patients experience a flu-like syndrome consisting of fever chills, bone pain and /or arthralgias (10%) and myalgia.

Gastrointestinal reactions such as nausea/vomiting (29%/14%) and anorexia (9%) have been reported following administration. Injection site reactions, such as erythema, redness or swelling, were observed infrequently and resolved in most cases without treatment within 24-48 hours.

Azotemia (2%) has been reported during therapy with zoledronic acid; serum creatinine should be monitored.

Electrolyte imbalances may occur during treatment with zoledronic acid. Hypocalcemia (1.2%), hypomagnesemia (10%) and hypophosphatemia (52%) have been reported. Monitor serum calcium, phosphate and magnesium during therapy; short-term supplementation of this electrolyte may be necessary.

Rare cases of rash (unspecified), pruritus and chest pain (unspecified) have been reported. As with other bisphosphonates, cases of conjunctivitis and bronchospasm have been reported following treatment with zoledronic acid.

Other adverse events that have been reported in > 1% of patients include abdominal pain, agitation, anaemia, anxiety, confusion, constipation, cough, diarrhoea, dyspnoea, hypotension, insomnia, candidiasis and urinary tract infection.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the e-PV desktop applications (https://drive.google.com/file/d/16hwTz0587ZWtSWadbBAMwQPOD_KSExZP/view) or search for e-PV Mobile applications on the Google Play or Apple App Store.

4.9 Overdose
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.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacological classification: 31. Miscellaneous.

Mechanism of Action
Zoledronic acid inhibits bone resorption by altering osteoclast activity and by inhibiting normal endogenous, as well as tumour-induced, mediators of bone degradation. Like other bisphosphonates, zoledronic acid binds to hydroxyapatite crystals in mineralised bone matrix. The binding to calcium phosphate slows the dissolution of hydroxyapatite crystals, as well as inhibiting the formation and aggregation of these crystals. Zoledronic acid is incorporated into osteoclastic bone surfaces where it inhibits bone resorption by inhibiting osteoclastic activity and osteoclastic apoptosis.

The presence of bisphosphonate in the bone structure appears to prevent acid extrusion, an important step stimulated by osteoclasts during the bone resorption process.

Following subsequent resorption, bone tissue surrounding the bisphosphonate-containing bone tends to lack ruffled borders and has fewer vacuoles, which are changes consistent with lower resorptive capacity.

Zoledronic acid affects chemical and hormonal mediators of bone degradation. Zoledronic acid inhibits the increased osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumours. This may be due to the mediation of the release of interleukin (IL)-1beta, IL-6, and tumour necrosis factor (TNF) by monocytes. These cytokines are involved in osteoclast recruitment and activation. Zoledronic acid appears to have direct anti-tumour effects in specific types of cancer cells. Although the exact mechanism is unknown, zoledronic acid has been demonstrated to inhibit cell growth and induce apoptosis in human myeloma, breast cancer and prostate cancer cell lines.

5.2 Pharmacokinetic properties

Zoledronic acid is administered by intravenous infusion. Human oral absorption data for zoledronic acid are unavailable. Other bisphosphonates are poorly absorbed (e.g., less than 5% of a dose for alendronate, tiludronate, etidronate), and absorption is further retarded by administration with food or calcium or other divalent cations. After intravenous infusion, zoledronic acid distributes primarily to the bone in a triphasic process. Zoledronic acid does not undergo biotransformation. Zoledronic acid does not inhibit P450 enzymes *in vitro*. Zoledronic acid plasma concentrations are dose-proportional.

Plasma protein binding is approximately 22% and independent of zoledronic acid concentration. More than 95% of zoledronic acid is excreted unchanged, via the kidney. The elimination is triphasic, with an alpha early distribution half-life of 0.23 hours, a beta half-life of 1.75 hours and a terminal elimination half-life of 167 hours, with low plasma concentrations observed up to 28 days post-dose.

5.3 Preclinical safety data

Acute toxicity

The highest non-lethal single intravenous dose was 10 mg/kg body weight in mice and 0.6 mg/kg in rats.

Subchronic and chronic toxicity

Zoledronic acid was well tolerated when administered subcutaneously to rats and intravenously to dogs at doses up to 0.02 mg/kg daily for 4 weeks. Administration of 0.001 mg/kg/day subcutaneously in rats and 0.005 mg/kg intravenously once every 2– 3 days in dogs for up to 52 weeks was also well tolerated.

The most frequent finding in repeat-dose studies consisted of increased primary spongiosa in the metaphyses of long bones in growing animals at nearly all doses, a finding that reflected the compound's pharmacological antiresorptive activity.

The safety margins relative to renal effects were narrow in the long-term repeat-dose parenteral animal studies but the cumulative no adverse event levels (NOAELs) in the single dose (1.6 mg/kg) and multiple-dose studies of up to one month (0.06–0.6 mg/kg/day) did not indicate renal effects at doses equivalent to or exceeding the highest intended human therapeutic dose. Longer-term repeat administration at doses bracketing the highest intended human therapeutic dose of zoledronic acid produced toxicological effects in other organs, including the gastrointestinal tract, liver, spleen and lungs, and at intravenous injection sites.

Reproduction toxicity

Zoledronic acid was teratogenic in the rat at subcutaneous doses _J 0.2 mg/kg. Although no teratogenicity or foetotoxicity was observed in the rabbit, maternal toxicity was found. Dystocia was observed at the lowest dose (0.01 mg/kg body weight) tested in the rat.

Mutagenicity and carcinogenic potential

Zoledronic acid was not mutagenic in the mutagenicity tests performed and carcinogenicity testing did not provide any evidence of carcinogenic potential.

6. Pharmaceutical particulars

6.1 List of excipients
Mannitol
Sodium citrate
Water for injection

6.2 Incompatibilities
This medicinal product must not be allowed to come into contact with any calcium-containing solutions and it must not be mixed or given intravenously with any other medicinal product in the same infusion line.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store below 30 °C.

6.5 Nature and contents of the container
A tubular USP type I glass vial closed with a 20 mm grey butyl rubber plug and a 20 mm flip-off lavender seal.

Fill weight: 4 mg.
Pack size: 1 vial per carton.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT
Innovata Pharmaceuticals
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Johannesburg 2091
South Africa

8. MANUFACTURERS
Venus Remedies Limited
Hill Top Industrial Estate, Jharmajri EPIP, Phase-I, (Extn.), Bhatoli Kalan, Baddi
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9. REGISTRATION DETAILS
Zimbabwe registration number: 2023/31/6483
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10. DATE OF REVISION OF THE TEXT
November 2023