PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ZOBONE SOLUTION FOR INFUSION

(Concentrate for solution for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL vial concentrate contains 4,264 mg zoledronic acid (as monohydrate), equivalent to 4 mg zoledronic acid anhydrous.

One mL concentrate contains approximately 0, 8 mg zoledronic acid (anhydrous).

This medicine contains 24 mg sodium per vial

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZOBONE SOLUTION FOR INFUSION is indicated for:

- Treatment of tumour-induced hypercalcaemia (TIH).
- ZOBONE SOLUTION FOR INFUSION slows progression of skeletal conditions in adult patients when used in conjunction with appropriate antineoplastic therapy in patients with advanced carcinoma of the breast, prostate, lung and myeloma.

4.2 Posology and method of administration

Posology

For the treatment of:

Skeletal conditions in patients with advanced malignancies involving bone:

Adults and elderly:

The recommended dose in the treatment of the above, is 4 mg ZOBONE SOLUTION FOR INFUSION solution, which should be further diluted with 100 mL *0,9 % w/v* sodium chloride or *5 % w/v* glucose solution, given as a 15-minute intravenous infusion 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:

The recommended dose in hypercalcaemia (albumin-corrected serum calcium ≥ 12,0 mg/dL or 3,0 mmol/L) is 4 mg, which should be diluted with 100 mL sterile 0,9 % w/v sodium chloride or 5 % w/v glucose solution, given as a single 15-minute intravenous infusion.

Patients must be maintained well-hydrated prior to and following administration of ZOBONE SOLUTION FOR INFUSION.

Special populations

Renal impairment

Adjustment of dosage or infusion time is not required in patients with mild or moderate renal impairment (serum creatinine less than 400 µmol/L or less than 4,5 mg/dL, or calculated creatinine clearance by Cockcroft-Gault formula of more than 30 mL/min).

Patients with HCM:

ZOBONE SOLUTION FOR INFUSION treatment in patients with hypercalcaemia of malignancy (HCM) and who also have severe renal impairment should be considered only after evaluating the risks and benefits of treatment.

In the clinical studies, patients with serum creatinine > 400 micromol/L or > 4,5 mg/dL were excluded. No dose adjustment is necessary in HCM patients with serum creatinine < 400 micromol/L or < 4,5 mg/dl (see section 4.4)

Skeletal related events in patients with advanced malignancies involving bone.

Skeletal-related events (SREs) are complications associated with bone metastases and may include fractures, spinal cord compression, bone pain, and frequently hypercalcemia. They are associated with intractable 275 bone pain, fractures, bladder and bowel disturbances, anxiety, depression, and decreased survival.

When initiating treatment with ZOBONE SOLUTION FOR INFUSION in patients with multiple myeloma or metastatic bone lesions from solid tumours, serum creatinine levels and creatinine clearance (CrCl) should be determined. CrCl is calculated from serum creatinine levels using the Cockcraft-Gault formula. ZOBONE SOLUTION FOR INFUSION is not recommended for patients presenting with severe renal impairment prior to initiation of therapy, which is defined for this population as CrCl < 30 mL/min. In clinical trials with ZOBONE SOLUTION FOR INFUSION, patients with Serum creatinine >265 micromol/L or > 3,0 mg/dL were excluded.

In patients with bone metastases presenting with mild to moderate renal impairment prior to initiation of therapy, which is defined for this population as CrCl 30 – 60 mL/min, the following ZOBONE SOLUTION FOR INFUSION dose is recommended (see also section 4.4).

Table 1.

Baseline Creatinine Clearance (mL/min)	**ZOBONE SOLUTION FOR INFUSION Recommended Dose ***
< 60	4,0 mg
50 to 60	3.5 mg*
40 to 49	3.3 mg*
30 to 39	3.0 mg*

**Doses have been calculated assuming target AUC of 0,66 (mg.hr/L) (CrCl = 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 ZOBONE SOLUTION FOR INFUSION and treatment should be withheld if renal function has deteriorated. In the clinical trials, renal deterioration was defined as follows:

- For patients with normal baseline serum creatinine (< 1,4 mg/dL or 123,76 mmol/L), an increase of ≥0,5 mg/dl or 44,2 mmol/L.

- For patients with an abnormal baseline creatinine (> 1,4 mg/dL or 123,76 mmol/L), an increase of ≥1,0 mg/dL or 88,4 mmol/L. It is reported that, ZOBONE SOLUTION FOR INFUSION treatment should be resumed only when the creatinine level returned to within 10 % of the baseline value (see section 4.4). ZOBONE SOLUTION FOR INFUSION should be resumed at the same dose as that prior to treatment interruption.

Paediatric population

The safety and efficacy of ZOBONE SOLUTION FOR INFUSION in children aged less than 18 years has not been established.

Instructions for preparing reduced dose of ZOBONE SOLUTION FOR INFUSION:

Withdraw an appropriate volume of the reconstituted solution

(4 mg/5 mL) as needed:

4,4 mL for 3,5 mg dose

4,1 mL for 3,3 mg dose

3,8 mL for 3,0 mg dose

For information on the reconstitution and dilution of ZOBONE SOLUTION FOR INFUSION see Instructions for use and handling.

The withdrawn amount of liquid 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 of no less than 15 minutes.

In patients with mild to moderate renal impairment, reduced doses are recommended (see section “Posology” above and section 4.4).

If refrigerated, the solution must be allowed to reach room temperature before administration (see section 6.6).

4.3 Contraindications

ZOBONE SOLUTION FOR INFUSION is contraindicated in the following:

- Patients with clinically significant hypersensitivity to zoledronic acid, other bisphosphonates or any of the excipients listed in section 6.1.

- Severe impairment of renal function.
- Pregnancy and lactation. (see section 4.6).

4.4 Special warnings and precautions for use

General

Patients should be assessed prior to administration of ZOBONE SOLUTION FOR INFUSION to assure adequate hydration. Over-hydration should be avoided in patients at risk of cardiac failure.

Standard hypercalcaemia-related metabolic parameters, such as serum levels of calcium, phosphate, magnesium, as well as serum creatinine should be carefully monitored after initiating ZOBONE SOLUTION FOR INFUSION therapy. If hypocalcaemia, hypophosphataemia, or hypomagnesaemia occur, short-term supplemental therapy may be necessary.

Renal insufficiency

Bisphosphonates as a class, including zoledronic acid as in ZOBONE SOLUTION FOR INFUSION, have been associated with reports of renal dysfunction. Renal function should be monitored appropriately during therapy with ZOBONE SOLUTION FOR INFUSION considering individual risk factors, and patients with evidence of deterioration in renal dysfunction should be appropriately evaluated with consideration given as to whether the potential benefit of continued treatment with ZOBONE SOLUTION FOR INFUSION 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 as in ZOBONE SOLUTION FOR INFUSION has been associated with reports of renal dysfuction. Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of Zoledronic acid as in ZOBONE SOLUTION FOR INFUSION, and other bisphosphonates as well as use of other nephrotoxic medicines. While the risk is reduced with a dose of 4 mg zoledronic acid (as in ZOBONE SOLUTION FOR INFUSION) 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 ZOBONE SOLUTION FOR INFUSION. Increases in serum creatinine also occur in some patients with chronic administration of ZOBONE SOLUTION FOR INFUSION 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 ZOBONE SOLUTION FOR INFUSION. Upon initiation of treatment in patients with bone metastases with mild to moderate renal impairment, lower doses of ZOBONE SOLUTION FOR INFUSION are recommended. In patients who report renal deterioration during treatment, ZOBONE SOLUTION FOR INFUSION should be withheld. ZOBONE SOLUTION FOR INFUSION should only be resumed when serum creatinine returns to within 10 % of baseline. ZOBONE SOLUTION FOR INFUSION treatment should be resumed at the same dose as that given prior to treatment interruption.

In view of the potential impact of bisphosphonates, including ZOBONE SOLUTION FOR INFUSION, on renal function, the use of ZOBONE SOLUTION FOR INFUSION is not recommended in this population (see section 4.3).

Hepatic insufficiency

In patients with severe hepatic insufficiency, no specific recommendations can be given for this patient population. Increases in serum creatinine also occur in some patients with chronic administration of ZOBONE SOLUTION FOR INFUSION at recommended doses.

Osteonecrosis

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) has been reported uncommonly in clinical studies with patients receiving zoledronic acid as in ZOBONE SOLUTION FOR INFUSION. Post-marketing reports and published literature suggest a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma). In the reported study, ONJ was higher in myeloma patients when compared to other cancers.

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 (see section 4.5), 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 ZOBONE SOLUTION FOR INFUSION. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to ZOBONE SOLUTION FOR INFUSION 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 reported 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 ZOBONE SOLUTION FOR INFUSION 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 as in ZOBONE SOLUTION FOR INFUSION.

Musculoskeletal pain

In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain have been

reported in patients taking zoledronic acid as in ZOBONE SOLUTION FOR INFUSION. However, such reports have relief of symptoms after stopping treatment. A subset had recurrence of symptoms when rechallenged with zoleronic acid as in ZOBONE SOLUTION FOR INFUSION, 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, 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 cardiac arrhythmias and neurologic adverse events (including convulsions, hypoaesthesia 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 (see section 4.8).
Caution is advised when ZOBONE SOLUTION FOR INFUSION is administered with medicines known to cause hypocalcaemia, as they may have a synergistic effect resulting in severe hypocalcaemia (see section 4.5).

Serum calcium should be measured and hypocalcaemia must be corrected before initiating ZOBONE SOLUTION FOR INFUSION therapy. Patients should be adequately supplemented with calcium and vitamin D.

ZOBONE SOLUTION FOR INFUSION contains sodium

This medicine contains 24 mg sodium per vial equivalent to 1,2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Paediatric population

The safety and efficacy of ZOBONE SOLUTION FOR INFUSION in paediatric patients have not been established.

4.5 Interaction with other medicines and other forms of interaction

ZOBONE SOLUTION FOR INFUSION can be administered concomitantly with commonly used anticancer medicines, diuretics, antibiotics and analgesics without apparent interactions occurring. Zoledronic acid shows no appreciable binding to plasma proteins and human P450 enzymes in vitro. Caution is advised when ZOBONE SOLUTION FOR INFUSION is administered with aminoglycosides, calcitonin or loop diuretics, since these medicines may have an additive effect, resulting in a lower serum calcium level for longer periods than required (see section 4.4). Caution is advised when ZOBONE SOLUTION FOR INFUSION is used with other potentially nephrotoxic medicines. 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 ZOBONE SOLUTION FOR INFUSION is used in combination with thalidomide. Caution is advised when ZOBONE SOLUTION FOR INFUSION is administered with anti-angiogenic medicines, as an increase in the incidence of ONJ has been reported in patients treated concomitantly with these medicines.

In clinical studies, ZOBONE SOLUTION FOR INFUSION has been administered concomitantly with analgesics without clinically apparent interactions occurring. ZOBONE SOLUTION FOR INFUSION shows no appreciable binding to plasma proteins and does not inhibit human P450 enzymes *in vitro* (see section 5.2), but no formal clinical interaction studies have been performed. No dose adjustment for ZOBONE SOLUTION FOR INFUSION is needed when co-administered with thalidomide, except in patients with mild to moderate renal impairment at baseline (see section 4.2).

Co- administration of thalidomide (100 or 200 mg once daily) with ZOBONE SOLUTION FOR INFUSION (4 mg given as a 15 minute infusion) did not significantly change the pharmacokinetics of zoledronic acid and the creatinine clearance of patients with multiple myeloma.

4.6 Fertility, pregnancy and lactation

The use of ZOBONE SOLUTION FOR INFUSION during pregnancy and lactation is not recommended as safety and efficacy have not been established. ZOBONE SOLUTION FOR INFUSION should not be used during pregnancy (see section 4.3).

Pregnancy

There are no adequate data that have been reported on the use of ZOBONE SOLUTION FOR INFUSION acid in pregnant women. Animal reproduction studies with zoledronic acid as in ZOBONE SOLUTION FOR INFUSION have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. ZOBONE SOLUTION FOR INFUSION should not be used during pregnancy. Women of child-bearing potential should be advised to avoid becoming pregnant.

Breast-feeding

It is not reported whether zoledronic acid as in ZOBONE SOLUTION FOR INFUSION is excreted into human milk. ZOBONE SOLUTION FOR INFUSION is contraindicated in breast-feeding women (see section 4.3).

Fertility

Zoledronic acid as in ZOBONE SOLUTION FOR INFUSION was reported to be evaluated in rats for potential adverse effects on fertility of the parental and F1 generation. This resulted in exaggerated pharmacological effects considered to be related to the compound's inhibition of skeletal calcium metabolisation, resulting in periparturient hypocalcaemia, a bisphosphonate class effect, dystocia and early termination of the reported study. Thus reported results precluded determining a definitive effect of zoledronic acid on fertility in humans.

4.7 Effects on the ability to drive and use machines

Adverse reactions, such as dizziness, blurred vision and somnolence, may have influence on the ability to drive or use machines, therefore caution should be exercised with the use of ZOBONE SOLUTION FOR INFUSION along with driving and operating of machinery (see section 4.8).

4.8 Undesirable effects

a) Summary of the safety profile

Within three days after zoledronic acid (as in ZOBONE SOLUTION FOR INFUSION) 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.

The following are the important identified risks with ZOBONE SOLUTION FOR INFUSION in the approved indications:

Renal function impairment, osteonecrosis of the jaw, acute, phase reaction, hypocalcaemia, atrial fibrillation, anaphylaxis interstitial lung disease.

b) Tabulated list of adverse reactions

The following side-effects may occur with the use of ZOBONE SOLUTION FOR INFUSION:

Blood and lymphatic system disorders	
Frequent	Thrombocytopenia, anaemia, pancytopenia
Frequency not known	Leucopenia
Immune system disorders	
Frequent	Hypersensitivity reaction, angioedema
Psychiatric disorders	
Frequent	Anxiety, sleep disturbance
Frequency not known	Confusion
Nervous system disorders	
Frequent	Headache, dizziness, paraesthesia, hypoaesthesia
Less frequent	Taste disturbance, somnolence
Frequency not known	Hyperaesthesia, tremor, convulsions, tetany (secondary to hypocalcaemia)
Eye disorders	
Less frequent	Scleritis and orbital inflammation, uveitis, episcleritis
Frequency not known	Conjunctivitis, blurred vision
Cardiovascular disorders	

Less frequent	Bradycardia, hypertension, hypotension, atrial fibrillation, hypotension leading to syncope or circulatory collapse, cardiac arrhythmia (secondary to hypocalcaemia)
Respiratory, thoracic and mediastinal disorders	
Frequent	Dyspnoea, cough, interstitial lung disease
Frequency not known	Bronchoconstriction in acetylsalicylic acid-sensitive asthmatic patients
Gastrointestinal disorders	
Frequent	Nausea, vomiting, anorexia, diarrhoea, abdominal pain, constipation, dry mouth
Frequency not known	Dyspepsia, stomatitis
Skin and subcutaneous tissue disorders	
Frequent	Increased sweating, rash (including erythematous and macular rash).
Less frequent	Pruritus
Musculoskeletal, connective tissue and bone	
Frequent	Bone pain, myalgia, arthralgia, muscle cramps, generalised pain
Less frequent	Muscle spasms, osteonecrosis of the jaw, osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction) and other anatomical sites including femur and hip
Renal and urinary disorders	
Frequent	Painful or difficult urination, haematuria, acquired Fanconi syndrome
Frequency not known	Renal impairment, acute renal failure, proteinuria
General disorders and administration site conditions	
Frequent	Fever, flu-like syndrome (including fatigue, rigors, malaise and flushing), asthenia, chest pain
Less frequent	Anaphylactic reaction/shock, urticaria, arthritis and joint swelling as a symptom of acute phase reaction
Frequency not known	Peripheral oedema, injection site reactions (including pain, irritation, swelling, induration), weight increase
Laboratory abnormalities	

Frequent	Hypophosphataemia, hypocalcaemia, hypomagnesaemia, hypokalaemia
Frequency not known	Increased blood creatinine and blood urea, hyperkalaemia, hypernatraemia.

Description of selected adverse reactions

Renal function impairment

Zoledronic acid has been reported to be associated with renal dysfunction. In a pooled analysis for the prevention of skeletal-related events in patients with advanced malignancies involving bone, the frequency of renal impairment adverse events suspected to be related to zoledronic acid (adverse reactions) was as follows: multiple myeloma (3,2 %), prostate cancer (3,1 %), breast cancer (4,3 %), lung and other solid tumours (3,2 %). Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of zoledronic acid or other bisphosphonates, as well as concomitant use of nephrotoxic medicines or using a shorter infusion time than currently recommended. 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 (see section 4.4).

Osteonecrosis of the jaw

Cases of osteonecrosis of the jaw have been reported, predominantly in cancer patients treated with medicines that inhibit bone resorption, such as zoledronic acid (see section 4.4). Many of these patients were also receiving chemotherapy and corticosteroids and had signs of local infection including osteomyelitis. The majority of the reports refer to cancer patients following tooth extractions or other dental surgeries.

Atrial fibrillation

In a reported 3-year study, zoledronic acid 5 mg once yearly for treatment of postmenopausal osteoporosis (PMO), resulted the overall incidence of atrial fibrillation 2,5 % and 1,9 % in patients receiving zoledronic acid 5 mg and placebo, respectively. The reported rate of atrial fibrillation serious adverse events was 1,3 % and 0,6 % in patients receiving zoledronic acid 5 mg and placebo, respectively. The reported imbalance in the study has not been reported in other studies with zoledronic acid, including those with zoledronic acid 4 mg every 3-4 weeks in oncology patients. The mechanism behind the increased incidence of atrial fibrillation in this clinical study is unknown.

Acute phase reaction

This adverse drug reaction consists of a constellation of symptoms that includes fever, myalgia, headache, extremity

pain, nausea, vomiting, diarrhoea arthralgia and arthritis with subsequent joint swelling. The onset time is ≤ 3 days post-zoledronic acid infusion, and the reaction is also referred to using the terms “flu-like” or “post-dose” symptoms.

Atypical fractures of the femur

During post-marketing experience, the following reactions have been reported (frequency rare): Atypical subtrochanteric and diaphyseal femoral fractures (bisphopsphonate class adverse reaction).

Hypocalcaemia-related ADRs

Hypocalcaemia is an important identified risk with zoledronic acid in the approved indications. Based on the review of both clinical study and post-marketing cases, there is sufficient evidence reported to support an association between zoledronic acid therapy, the reported event of hypocalcaemia, and the secondary development of cardiac arrhythmia. Furthermore, there is evidence of an association between hypocalcaemia and secondary neurological events reported in these cases including; convulsions, hypoaesthesia and tetany.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications:

https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

There is no reported evidence of acute intoxication with ZOBONE SOLUTION FOR INFUSION. Patients who have received doses higher than those recommended should be carefully monitored. In the event of clinically significant hypocalcaemia, reversal may be achieved with an infusion of calcium gluconate.

Treatment should be supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A34 Other

Pharmacotherapeutic group: Drugs for treatment of bone diseases, bisphosphonates, ATC code: M05BA08.

Mechanism of action

Zoledronic acid is a bisphosphonate which primarily acts on the bone by inhibiting osteoclastic bone resorption (process by which osteoclasts break down bone tissues and release the minerals, resulting in a transfer of calcium from bone tissue to the blood) without adversely affecting the formation, mineralisation or mechanical properties of bone. The selective action of zoledronic acid on bone is based on the affinity for mineralised bone, but the precise molecular mechanism leading to the inhibition of osteoclastic activity is still unclear. In addition to inhibiting osteoclastic bone resorption, zoledronic acid exerts direct anti-tumour effects on cultured human myeloma and breast cancer cells, inhibiting proliferation and inducing apoptosis. It also reported to inhibit human endothelial cell proliferation *in vitro*.

5.2 Pharmacokinetic properties:

Absorption

Single and multiple 5- and 15-minute infusions of 2, 4, 8 and 16 mg zoledronic acid in patients with bone metastases reported the following pharmacokinetic data, which is dose independent. 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. Intravenously administered zoledronic acid is eliminated by a triphasic process: rapid biphasic disappearance from the systemic circulation, with half-lives of $t_{½\alpha}$ 0.24 and $t_{½\beta}$ 187 hours, followed by a long elimination phase with a terminal elimination half-life of t½γ 146 hours. There was no accumulation of zoledronic acid in plasma after multiple doses given every 28 days.

Metabolism and Elimination

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. From the bone tissue it is released very slowly back into the systemic circulation and eliminated via the kidney with a half-life of at least 167 hours. The total body clearance is 5,04 ± 2,5 L/h, independent of dose, and unaffected by gender, age, race, and body weight. 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.

The interpatient variability in pharmacokinetic parameters for zoledronic acid was high, as reported with other bisphosphonates.

No pharmacokinetic data for zoledronic acid have been reported in patients with hypercalcaemia or in patients with hepatic insufficiency. It has been reported that zoledronic acid does not inhibit human P450 enzymes in vitro, reported no biotransformation and in animal studies < 3 % of the administered dose was recovered in the faeces, suggesting no relevant role of liver function in the pharmacokinetics of zoledronic acid.

The renal clearance of zoledronic acid was reported to be correlated with creatinine clearance, renal clearance representing 75 ± 33 % of the creatinine clearance, which showed a mean of 84 ± 29 mL/min (range 22 to 143 mL/min) in cancer patients. Population analysis has reported that for a patient with creatinine clearance of 20 mL/min (severe renal impairment), or 50 mL/min (moderate impairment), the corresponding predicted clearance of zoledronic acid would be 37 % or 72 %, respectively, of that of a patient showing creatinine clearance of 84 mL/min. Only limited pharmacokinetic data are available in patients with severe renal insufficiency (creatinine clearance < 30 mL/min).

Distribution

Zoledronic acid is approximately 22% bound to plasma proteins. Zoledronic acid shows low affinity or no affinity for the cellular components of blood and plasma protein binding is approximately 56 % and independent of the concentration of zoledronic acid.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, Sodium citrate, Water for injection

6.2 Incompatibilities

To avoid potential incompatibilities, ZOBONE SOLUTION FOR INFUSION concentrate is to be diluted with *0,9 % w/v* sodium chloride solution or *5 % w/v* glucose solution.

This medicine 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.

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

ZOBONE SOLUTION FOR INFUSION: 24 months.

Store at or below 25 °C. Do not refrigerate.

ZOBONE SOLUTION FOR INFUSION is stable when exposed to light before use.

KEEP OUT OF REACH OF CHILDREN.

Dilution instructions:

The Zoledronic acid SUN solution is stable for 24 hours at 2 °C– 8 °C after further dilution in 100 ml physiological saline or *5% w/v* glucose solution.

After aseptic dilution, from a microbiological point of view, the medicine should be used immediately. If not used immediately, the total time between dilution, storage in a refrigerator at 2 °C- 8 °C and end of administration must not exceed 24 hours.

The refrigerated solution should then be equilibrated to room temperature prior to administration.

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

For storage conditions of the diluted solution for infusion, see section 6.3.

ZOBONE SOLUTION FOR INFUSION can withstand the effects of high (40 °C) and low (-10 °C to -20 °C) temperature variations that may be encountered during shipping and handling, for 24 hours.

After dilution:

Chemical and physical in-use stability has been demonstrated for 24 hours at 2 to 8 ºC.

The stability has been demonstrated throughout the entire concentration range (between 38,1 µg/mL and 28,9 µg/mL) for 24 hours at 2-8 °C.

The diluted solution is stable for 24 hours stored at 2-8 °C when reconstituted (see section 6.3).

6.5 Nature and contents of container

ZOBONE SOLUTION FOR INFUSION:

Clear colourless solution in 5 mL colourless tubular glass vial with grey rubber stopper sealed with baby blue flip top aluminum seal.

Vial: 5 ml clear Type-I Neutral glass vial.

Stopper: Grey bromobutyl flange rubber stopper.

Seal: White aluminium seal and baby blue flip top aluminium seal.

Pack size: Packed in unit pack containing 1x 5 ml single vial.

6.6 Special precautions for disposal and other handling

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 ZOBONE SOLUTION FOR INFUSION, including guidance on preparation of reduced doses, is provided in section 4.2.

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.

Healthcare professionals are advised not to dispose of unused ZOBONE SOLUTION FOR INFUSION via the domestic sewage system.

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

After aseptic dilution, it is preferable to use the diluted medicine immediately. If not used immediately, the duration and conditions of storage prior to use are the care provider's responsibility. The total time between dilution, storage in a refrigerator at 2-8 °C and end of administration must not exceed 24 hours. Do not freeze the reconstituted solution.

7. Marketing authorisation holder

RANBAXY PHARMACEUTICALS (Pty) Ltd

(a Sun Pharma company)

14 Lautre Road, Stormill, Ext. 1,

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8. Marketing authorisation number(s)

47/34/1168

9. Date of first authorisation/renewal of the authorisation

10 August 2022

10. Date of revision of the text