Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ZOBONE, 4 mg/vial powder for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 4 mg zoledronic acid (as zoledronic acid monohydrate).

Excipients with known effect:

Contains sugar alcohol (220 mg mannitol per vial).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

White to off-white lyophilised cake in 5 mL vial.

The pH of the solution is between 5,7 and 6,7.

The osmolality is between 280 and 330 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of tumour-induced hypercalcaemia (TIH).

ZOBONE slows progression of skeletal conditions in adult patients when used in conjunction with appropriate anti neoplastic therapy in patients with advanced carcinoma of the breast, prostate, lung and myeloma.

4.2 Posology and method of administration

Posology

Skeletal conditions in patients with advanced malignancies involving bones:

Adults and elderly patients:

The recommended dose is 4 mg. The 4 mg dose of ZOBONE powder for solution for infusion must be further diluted with 100 mL sterile 0,9 % *w/v* sodium chloride or 5 % *w/v* glucose solution~~)~~ and 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.

For the treatment of tumour-induced hypercalcaemia (TIH):

Adults and elderly patients:

The recommended dose in hypercalcaemia (albumin-corrected serum calcium ≥ 12,0 mg/dL or 3,0 mmol/L) is 4 mg. ZOBONE powder for solution for infusion must be diluted with 100 mL sterile 0,9 % w/v sodium chloride or 5 % w/v glucose solution and given as a single intravenous infusion in no less than 15 minutes. Patients must be maintained well hydrated prior to and following administration of ZOBONE.

Special populations

Treatment of patients with renal impairment:

Patients with HCM:

ZOBONE 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.

No dose adjustment is necessary in HCM patients with serum creatinine < 400 micromol/1 or< 4,5 mg/di (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 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 CockcraftGault formula. ZOBONE 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 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 dose is recommended (see also section 4.4).

Table 1:

Baseline creatinine clearance (mL/min)	ZOBONE 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·h/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 and treatment should be withheld if renal function has deteriorated.

- For patients with normal baseline serum creatinine (< 1,4 mg/dL or 123,76 mmol/L), an increase of 2 0,5 mg/di or 44,2 mmol/L.
- For patients with an abnormal baseline creatinine (> 1,4 mg/dL or 123,76 mmol/L), an increase of 2 1,0 mg/dL or 88,4 mmol/L.

ZOBONE treatment was resumed only when the creatinine level returned to within 10 % of the baseline value (see section 4.4). ZOBONE should be resumed at the same dose as that prior to

treatment interruption.

Paediatric population

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

Method of administration

ZOBONE 4 mg powder for solution for infusion is for intravenous use only.

Instructions on reconstitution, dilution and the administration of a dose of 8 mg have been included in section 6.6.

Instructions on preparing reduced doses of ZOBONE:

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, *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.

4.3 Contraindications

- 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

It is important to ensure adequate hydration before and after administration of ZOBONE as dehydration predisposes to deterioration in renal function.

In patients with cardiac disease over-hydration should be avoided, especially in elderly patients.

ZOBONE should not be given together with other bisphosphonates since the combined effects of these medicines are unknown. After initiating ZOBONE treatment, serum levels of calcium, phosphate, magnesium as well as serum creatinine should be carefully monitored as standard metabolic parameters of hypercalcaemia. Short-term supplemental therapy may be necessary if hypocalcaemia, hypophosphataemia or hypomagnesaemia occur. Untreated hypercalcaemia patients generally have some degree of renal function impairment, therefore careful renal function monitoring should be considered.

Renal impairment:

Patients with HCM with evidence of deterioration in renal function should be appropriately evaluated with consideration given as to whether the potential benefit of continued treatment with ZOBONE 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 to 3 months.

Bisphosphonates as a class, including ZOBONE, have been associated with reports of renal dysfunction. Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of ZOBONE or other bisphosphonates as well as use of nephrotoxic medicines or using a shorter infusion time than currently recommended. While the risk is reduced with a dose of ZOBONE administered over no less than 15 minutes, deterioration in renal function may still occur.

Increases in serum creatinine also occurred in some patients with chronic administration of ZOBONE at recommended doses for prevention of skeletal related events, although less frequently. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of ZOBONE.

Patients should have their serum creatinine levels assessed prior to each dose of ZOBONE. Upon initiation of treatment in patients with bone metastases with mild to moderate renal impairment, lower doses of ZOBONE are recommended.In patients who show evidence of renal deterioration during treatment, ZOBONE should be withheld. ZOBONE should only be resumed when the

creatinine level returns to within 10 % of the baseline value (see section 4.2). Zoledronic acid 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 on renal function, the lack of extensive clinical safety data in patients with severe renal impairment (serum creatinine ≥ 400 µmol/L or ≥ 4,5 mg/dL for patients with HCM and ≥ 265 µmol/L or ≥ 3,0 mg/dl for patients with cancer and bone metastases, respectively) at baseline and only limited pharmacokinetic data in patients with severe renal impairment at baseline (creatinine clearance less than 30 mL/min), the use of ZOBONE is not recommended (see section 4.3).

Hepatic insufficiency:

In view of the limited clinical data available in patients with severe hepatic insufficiency, no specific recommendations can be given for this patient population (see section 4.3).

Osteonecrosis

Osteonecrosis of the jaw (ONJ):

Osteonecrosis of the jaw (ONJ) has been reported predominantly in patients with cancer receiving treatment regimens including bisphosphonates such as ZOBONE. Many of these patients were also receiving chemotherapy and corticosteroids. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection including osteomyelitis.

Post-marketing experience and the literature suggest a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma), and dental status (dental extraction, periodontal disease, local trauma including poorly fitting dentures).

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.

Patients should maintain good oral hygiene and should have dental examination with preventive dentistry prior to treatment with bisphosphonates.

Patients should be advised of the reports of osteonecrosis of the jaw so that dental symptoms developing during treatment can be fully assessed before commencing dental procedures.

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy (e.g. ZOBONE), dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment (e.g. ZOBONE) 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 zoledronic acid 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 includes 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.

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 patients treated with ZOBONE, who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of ZOBONE 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 ZOBONE 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

Musculoskeletal pain:

In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain have been reported in patients taking bisphosphonates, including ZOBONE. However, such reports have been infrequent. The time to onset of symptoms varied from one day to several months after starting treatment. Most patients had relief of symptoms after stopping treatment. A subset had recurrence of symptoms when rechallenged with the same medicine or another bisphosphonate.

Hypocalcaemia:

Hypocalcaemia has been reported in patients treated with ZOBONE. Cardiac dysrhythmias and neurological adverse events (seizures, tetany and numbness) have been reported secondary to cases of severe hypocalcaemia. In some instances, the hypocalcaemia may be life-threatening. Caution is advised when ZOBONE is administered with other hypocalcaemia-causing medicines, 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 therapy. Patients should be adequately supplemented with calcium and vitamin D. While not observed with ZOBONE, administration of bisphosphonates as a class has been associated with bronchoconstriction in acetylsalicylic acid-sensitive asthmatic patients.

Atrial fibrillation:

There are reports of atrial fibrillation in post-menopausal women.

Acute phase reaction:

Acute phase reaction consists of a constellation of symptoms that includes fever, myalgia, headache, extremity pain, nausea, vomiting, diarrhoea and arthralgia. The onset time is ≤ 3 days post-ZOBONE, and the reaction is also referred to using the terms “flu-like” or “post-dose” symptoms.

Elderly patients:

Clinical studies of ZOBONE in hypercalcemia of malignancy, multiple myeloma and bone metastases included patients who were 65 years of age or older. No significant differences in response rate or adverse reactions were seen in elderly patients receiving ZOBONE as compared to younger adult patients. Because decreased renal function occurs with bisphosphonates, including ZOBONE, more commonly in the elderly, special care should be taken to monitor renal function.

Paediatric population:

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

ZOBONE contains sodium:

This medicine contains less than 1 mmol sodium (23 mg) per unit volume, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicines and other forms of interaction

Concomitant use of ZOBONE and loop diuretics, calcitonin or aminoglycosides, since both medicines may have an additive effect, resulting in a lower serum calcium level for prolonged

periods than required. The concomitant use of these medicines with ZOBONE may cause an increased risk of hypocalcaemia. Medicines exhibiting nephrotoxicity should be used with caution during and after ZOBONE treatment. Attention should also be paid to the possibility of hypomagnesaemia developing during treatment.

Individual benefit/risk needs to be assessed in patients on chemotherapy and/or corticosteroid treatment with concomitant use of ZOBONE as they may be at risk for osteonecrosis of the jaw. The increase in incidence of osteonecrosis of the jaw has been observed in patients treated concomitantly with anti-angiogenic medicines (see section 4.4). In multiple myeloma patients, the risk of renal dysfunction may be increased when intravenous bisphosphonates, such as ZOBONE, are used in combination with thalidomide.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential should be advised to avoid becoming pregnant and advised of the potential hazard to the foetus while receiving ZOBONE. There may be a risk of fetal harm (e.g. skeletal and other abnormalities) if a woman becomes pregnant (see section 4.3) while receiving bisphosphonate therapy. Animal studies have shown teratogenicity at doses of ≥ 0,2 mg/kg in rats. No teratogenicity or fetotoxicity was observed in rabbits, however maternal toxicity was observed in rabbits.

Pregnancy:

The safety of ZOBONE in pregnant women has not been established (see section 4.3).

ZOBONE should not be used during pregnancy**.**

Breastfeeding:

The safety of ZOBONE in lactating women has not been established (see section 4.3). ZOBONE should not be used during breastfeeding.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Undesirable effects such as dizziness and somnolence reported with the use of ZOBONE may

influence the ability to drive or use machinery and caution is therefore necessary. The patients should therefore be careful when driving, using machinery or performing other tasks that need full attention. It is not always possible to predict to what extent ZOBONE may interfere with the daily activities of a patient. Patients should ensure that they do not engage in the above activities until they are aware of the extent to which ZOBONE affects them.

4.8 Undesirable effects

a. Summary of the safety profile

Within three days after ZOBONE administration, an acute phase reaction has frequently 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 (see section 4.4).

The following are the important identified risks with ZOBONE in the approved indications: Renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, atrial fibrillation, anaphylaxis, interstitial lung disease.

b. Tabulated summary of adverse reactions

The following adverse drug reactions, listed below, have been accumulated from clinical studies and post-marketing reports following predominantly chronic treatment with ZOBONE.

MedDRA System Organ Class	**Frequency**	**Adverse reaction**
Blood and lymphatic system disorders	*Frequent*	Anaemia.
	Less frequent	Thrombocytopenia, leukopenia, pancytopenia.
Immune system disorders	*Less frequent*	Hypersensitivity reaction, angioneurotic-oedema.
Psychiatric disorders	*Less frequent*	Anxiety, sleep disturbance, confusion.
Nervous system disorders	*Frequent*	Headache
	Less frequent	Dizziness, paraesthesia, taste disturbance (dysgeusia), hypaesthesia, hyperaesthesia,

		tremor, somnolence,convulsion, tetany (secondary to hypocalcaemia).
Eye disorders	*Frequent*	Conjunctivitis
	Less frequent	Blurred vision, scleritis, orbital inflammation, uveitis, episcleritis.
Cardiac disorders	*Less frequent*	Bradycardia, cardiac dysrhythmia (secondary to hypocalcaemia), atrial fibrillation, hypertension, hypotension, hypotension leading to syncope or circulatory collapse.
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Dyspnoea, cough, bronchoconstriction, interstitial lung disease.
Gastrointestinal disorders	*Frequent*	Nausea, vomiting, anorexia, decreased appetite.
	Less frequent	Diarrhoea, constipation, abdominal pain, dyspepsia, stomatitis, dry mouth.
Skin and subcutaneous tissue disorders	*Less frequent*	Pruritus, rash (including erythematous and macular rash), increased sweating (hyperhidrosis).
Musculoskeletal and connective tissue disorders	*Frequent*	Bone pain, myalgia, arthralgia, generalised pain, joint stiffness.
	Less frequent	Muscle cramps, 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*	Renal impairment.

	Less frequent	Acute renal failure, haematuria, proteinuria, acquired Fanconi syndrome.
	Frequency unknown	Tubulointerstitial nephritis
General disorders and administration site conditions	*Frequent*	Fever, flu-like syndrome (including fatigue, rigors, malaise, flushing).
	Less frequent	Asthenia, peripheral oedema, injection site reactions (including pain, irritation, swelling, induration), chest pain, weight increase, anaphylactic reaction/shock, urticaria, arthritis, joint swelling (as a symptom of an acute phase reaction).
Investigations	*Frequent*	Hypophosphataemia, increased blood creatinine, increased blood urea, hypocalcaemia.
	Less frequent	Hypomagnesaemia, hyperkalaemia, hypokalaemia, hypernatraemia.

c. Description of selected adverse reactions

Renal function impairment:

ZOBONE has been associated with reports of renal function impairment. In a pooled analysis of safety data from ZOBONE registration trials for the prevention of skeletal-related events in patients with advanced malignancy involving bone, the frequency of renal function impairment adverse events suspected to be related to ZOBONE (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 ZOBONE 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 ZOBONE (see section 4.4).

Osteonecrosis of the jaw:

Cases of osteonecrosis (primarily of the jaws) have been reported predominantly in cancer patients treated with medicines that inhibit bone resorption, such as ZOBONE (see section 4.4). Many of these patients had signs of local infection, including osteomyelitis. The majority of the reports refer to cancer patients following tooth extractions or other dental surgeries. Osteonecrosis of the jaws has multiple well documented risk factors including a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids) and co-morbid conditions (e.g. anaemia, coagulopathies, infection, pre-existing oral disease). Although causality cannot be determined, it is prudent to avoid dental surgery as recovery may be prolonged (see section 4.4).

Osteonecrosis of other anatomical sites:

Cases of osteonecrosis of other anatomical sites including the hip, femur and external auditory canal have been reported predominantly in adult cancer patients treated with bisphosphonates, including ZOBONE.

Acute phase reaction:

This adverse reaction consists of a constellation of symptoms that includes fever, fatigue, bone pain, chills, myalgia, headache, extremity pain, nausea, vomiting, diarrhoea, arthralgia and arthritis with subsequent joint swelling. The onset time is ≤ 3 days post-ZOBONE infusion, and the reaction is also referred to using the terms “flu-like” or “post-dose” symptoms. These symptoms usually resolve within a few days.

Atypical fractures of the femur:

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

Hypocalcaemia-related adverse drug reactions:

Hypocalcaemia is an important identified risk with ZOBONE in the approved indications. Based on the review of both clinical trial and post-marketing cases, there is sufficient evidence to support an

association between ZOBONE therapy, the reported event of hypocalcaemia, and the secondary development of cardiac dysrhythmia. Furthermore, there is evidence of an association between hypocalcaemia and secondary neurological events reported in these cases including convulsions, hypaesthesia and tetany (see section 4.4).

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of medicine is important. It allows continued monitoring of the benefit/risk balance of medicine. Health care providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Suspected adverse reactions can also be reported directly to the Holder of certificate of registration via email or telephonically: pharmacovigilance.africasme@sunpharma.com or tel:+27(0) 12 643 2000

4.9 Overdose

There is no experience of acute intoxication with ZOBONE. Patients who have received high doses of ZOBONE should be carefully monitored and in the presence of clinically significant hypocalcaemia, hypophosphataemia or hypomagnesaemia, the treatment is generally symptomatic and supportive. The reversal in the event of clinically significant hypocalcaemia may be achieved with an infusion of calcium gluconate. Treatment should be supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 34 Other.

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

ATC code: M05 BA08.

Zoledronic acid, 1-hydroxy-2-imidazol-1-ylethylidene diphosphonic acid, is a bisphosphonate that acts primarily on bone, inhibiting the bone resorption.The antiresorptive action of zoledronic acid on bone is based on its affinity for mineralised bone. The molecular mechanism leading to the inhibition of osteoclastic activity is not fully understood. Zoledronic acid further inhibits the various stimulatory factors released by tumours such as increased osteoclastic activity and

skeletal calcium release. *In vitro*, zoledronic acid inhibits osteoclastic activity and induced osteoclast apoptosis.

5.2 Pharmacokinetic properties

Single and multiple 5- and 15-minute infusions of 2, 4, 8 and 16 mg zoledronic acid in 64 patients with bone metastases yielded the following pharmacokinetic data, which were found to be 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 $t_{½\beta}$ 1,87 hours, followed by a long elimination phase with a terminal elimination half-life of $t_{½\gamma}$ 146 hours. There was no accumulation of zoledronic acid in plasma after multiple doses given every 28 days. 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. 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 seen with other bisphosphonates. No pharmacokinetic data for zoledronic acid are available in patients with hypercalcaemia or in patients with hepatic insufficiency. Zoledronic acid does not inhibit human P450 enzymes *in vitro*, shows 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 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 the 64 cancer patients studied. Population analysis showed 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). In an *in vitro* study, zoledronic acid showed low affinity for the cellular components of human blood, with a mean blood to plasma concentration ratio of 0,59 in a concentration range of 30 ng/Ml to 5000 ng/Ml. The plasma protein binding is low, with the unbound fraction ranging from 60 % at 2 ng/ml to 77 % at 2000 ng/Ml of zoledronic acid.

Special populations

Paediatric patients

Limited pharmacokinetic data in children with severe osteogenesis imperfecta suggest that zoledronic acid pharmacokinetics in children aged 3 to 17 years are similar to those in adults at a similar mg/kg dose level. Age, body weight, gender and creatinine clearance appear to have no effect on zoledronic acid systemic exposure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (parenteral grade)

Sodium citrate dihydrate (buffering agent)

Water for injection.

6.2 Incompatibilities

Glass bottles, as well as several types of infusion bags and infusion lines made from polyvinylchloride, polyethylene and polypropylene (pre-filled with 0,9 % sodium chloride solution or 5 % glucose solution), showed no incompatibility with zoledronic acid. To avoid potential

incompatibilities, ZOBONE is to be diluted with 0,9 % sodium chloride solution or 5 % glucose solution.

ZOBONE reconstituted solution must not be mixed with calcium-containing solutions such as Lactated Ringer's solution.ZOBONE should be administered as a single intravenous solution

in a separate line from all other medicines.

6.3 Shelf life

Unopened vials:

24 months.

After first opening:

The reconstituted product may be stored for 24 hours at 25 °C or refrigerated between 2 °C and 8 °C, and must be visually inspected for particulate matter and discolouration.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the vial in the outer carton until required for use.

For storage conditions after first opening of ZOBONE, see section 6.3

6.6 Special precautions for disposal and other handling

The powder must first be reconstituted in the vial using 5 Ml water for injection from the ampoule supplied and must be completely dissolved before the solution is withdrawn. The reconstituted solution should be visually inspected for the absence of particulate matter and discolouration. The reconstituted solution of ZOBONE must then be further diluted with 100 Ml of sterile 0,9 % sodium chloride solution or sterile 5 % glucose solution. These solutions must be calcium-free. If refrigerated between 2 °C and 8 °C, the solution must be allowed to reach room temperature before administration.

In the case of retreatment with an 8 mg dose, two vials of 4 mg should each be reconstituted with 5 Ml water for injection as described above and the resulting 10 Ml reconstituted solution further diluted with 100 Ml sterile 0,9 % sodium chloride solution or sterile 5 % glucose solution.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

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8. REGISTRATION NUMBER

42/34/0664

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04 March 2011

10. DATE OF REVISION OF THE TEXT

06 March 2026

Namibia: NS2 13/34/0190