Professional Information for ZOBONE

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.

Treatment of:

- Osteolytic lesions of multiple myeloma, in conjunction with standard antineoplastic therapy.
- Breast carcinoma with metastatic bone lesions in combination with appropriate anticancer therapy.
- Prostate carcinoma in patients with bone metastases who have increased prostate specific antigen (PSA) levels despite hormonal therapy.

4.2 Posology and method of administration

Posology

For the treatment of:

- Osteolytic lesions of multiple myeloma, in conjunction with standard antineoplastic therapy.
- Breast carcinoma with metastatic bone lesions in combination with appropriate anticancer therapy.
- Prostate carcinoma in patients with bone metastases who have increased prostate specific antigen (PSA) levels despite hormonal therapy.

Adults and elderly patients:

The dose of 4 mg zoledronic acid is recommended in the treatment of the above. The 4 mg dose of ZOBONE powder for solution for infusion is reconstituted and further diluted (reconstituted with

5 mL sterile water for injection and diluted with 100 mL 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.

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

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 which is reconstituted and further diluted (diluted with 100 L 0,9 % sodium chloride or 5 % glucose solution), given as a single 15 minute intravenous infusion.

Patients must be maintained well hydrated prior to and following administration of ZOBONE.

Retreatment of tumour-induced hypercalcaemia:

If serum calcium does not return to normal or does not remain normal after initial treatment in patients who showed complete or partial response, retreatment with ZOBONE may be instituted. The retreatment can only commence at least one week (7 days) after the initial treatment to allow for a full response to the initial dose. The solution for this infusion is prepared by reconstituting two vials of ZOBONE 4 mg, combining them and then further diluting with 100 mL 0,9 % *w/v* sodium chloride or 5 % *w/v* glucose solution (see section 6.6). Serum creatinine must be evaluated prior to each dose.

The median time to relapse is 30 days with a dose of 4 mg and 40 days with a dose of 8 mg ZOBONE.

Special populations

Renal impairment:

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.

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.

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 only be resumed when the creatinine level returns to within 10 % of the baseline value (see section 4.2).

The risk/benefit should be considered in patients with serum creatinine more than 400 µmol/L or more than 4,5 mg/dL. In patients with severe renal impairment and a 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.

Osteonecrosis of the jaw (ONJ):

Osteonecrosis of the jaw 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). 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.

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.

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 has an additive effect, resulting in a lower serum calcium level for prolonged periods. 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

Pregnancy:

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

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

Women of childbearing potential should be advised to avoid becoming pregnant and advised of the potential hazard to the fetus while receiving ZOBONE. There may be a risk of fetal harm (e.g. skeletal and other abnormalities) if a woman becomes pregnant 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.

Breastfeeding:

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

ZOBONE should not be used during breastfeeding.

4.7 Effects on ability to drive and use machines

No studies with ZOBONE on the effects on the ability to drive and use machines have been performed. Care should be exercised when feeling dizzy, tired or drowsy while receiving ZOBONE.

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 “Description of selected adverse reactions” below).

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.

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.

Vascular disorders

Less frequent: 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.

Renal and urinary disorders

Frequent: Renal impairment.

Less frequent: Acute renal failure, haematuria, proteinuria, acquired Fanconi syndrome.

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 bisphosphonates, such as ZOBONE. 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 ZOBONE is important. It allows continued monitoring of the benefit/risk balance of ZODONE. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

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.

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, z*oledronic acid inhibits osteoclastic activity and induced osteoclast apoptosis.

5.2 Pharmacokinetic properties

The accumulation of zoledronic acid measured over three cycles was low. The plasma protein binding is low with values reported as 22 % and 56 % and independent of the concentration.

Zoledronic acid is not metabolised and about 23 % to 56 % of the dose is excreted unchanged via the kidney. The remainder of the medicine is bound to bone and is slowly released back into the systemic circulation, giving rise to a 146 hour terminal half-life. Renal clearance is slower in patients with renal impairment leading to increases in the AUC of 15 % and 43 %, respectively, in patients with mild and moderate renal impairment. The risk of renal deterioration appears to increase with AUC, which is doubled at creatine clearance of 10 mL/min.

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*.

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.

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.

6.5 Nature and contents of container

ZOBONE is packed in a 5 mL clear colourless USP type I tubular glass vial, with a 20 mm grey bromobutyl Igloo RFS (ready for sterilisation) rubber stopper and 20 mm flip off seal with golden brown colour.

Pack size:

1 vial.

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

14 Lautre Road

Stormill, Ext. 1, Roodepoort

Johannesburg 1724

8. REGISTRATION NUMBER

42/34/0664

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

4 March 2011

10. DATE OF REVISION OF THE TEXT

22 April 2022

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