NOVARTIS

**ZOMETA** ® (zoledronic acid)

4 mg concentrate for solution for infusion

Professional Information

Document status: Final

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**SCHEDULING STATUS:** S4

## 1. NAME OF THE MEDICINE

ZOMETA® 4 mg concentrate for solution for infusion.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial with 5 ml concentrate contains 4 mg zoledronic acid (anhydrous), corresponding to 4,264 mg zoledronic acid monohydrate.

## 3. PHARMACEUTICAL FORM

ZOMETA® Concentrate for solution for infusion is a clear, colourless solution.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

Treatment of tumour-induced hypercalcaemia (TIH).

ZOMETA® 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

**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. The concentrate 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 of no less than 15 minutes. Patients must be maintained well-hydrated prior to and following administration of ZOMETA®.

**Skeletal conditions in patients with advanced malignancies involving bone:**

*Adults and elderly:*

The recommended dose is 4 mg. The concentrate must be further diluted with 100 ml sterile 0,9 % w/v sodium chloride or 5 % w/v glucose solution), and given as an intravenous infusion lasting no less than 15-minutes 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 patients with renal impairment:**

*Patients with HCM:*

ZOMETA® 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 ZOMETA® 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. ZOMETA® 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 ZOMETA®, 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 ZOMETA® dose is recommended (see also section 4.4).

**Table 1:**

| ***Baseline Creatinine Clearance (ml/min)*** | ***ZOMETA 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 ZOMETA® 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.

In the clinical studies, ZOMETA® treatment was resumed only when the creatinine level returned to within 10 % of the baseline value (see section 4.4). ZOMETA® should be resumed at the same dose as that prior to treatment interruption.

*Paediatric population*

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

**Instructions on preparing reduced doses of ZOMETA®:**

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 ZOMETA®, 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.

**Instructions for use and handling:**

ZOMETA 4 mg/5 ml concentrate for solution for infusion is for intravenous use only. 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 or 5 % w/v glucose solution).If refrigerated, the solution must be allowed to reach room temperature before administration (see section 4.2).

**Incompatibilities:**

Studies with 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 ZOMETA®

To avoid potential incompatibilities, ZOMETA® concentrate is to be diluted with 0,9 % sodium chloride solution or 5 % glucose solution. ZOMETA® concentrate must not be mixed with calcium containing solutions such as Ringer's solution.

ZOMETA® should be administered as a single intravenous solution in a line separate from all other medicines.

## 4.3. Contraindications

Hypersensitivity to zoledronic acid, other bisphosphonates or any of the excipients in the formulation of ZOMETA® 4 mg Concentrate for solution for infusion.

Pregnancy, and breast-feeding women (see section 4.6).

Severe impairment of renal function.

## 4.4. Special warnings and precautions for use

Patients must be assessed prior to administration of ZOMETA® to ensure that they are adequately hydrated.

Overhydration should be avoided in patients at risk of cardiac failure.

ZOMETA® should not be given together with other bisphosphonates since the combined effects of these medicines are unknown.

Standard hypercalcaemia-related metabolic parameters, such as serum levels of calcium, phosphate, magnesium as well as serum creatinine should be carefully monitored after initiating ZOMETA® therapy. If hypocalcaemia, hypophosphataemia, or hypomagnesaemia occur, short-term supplemental therapy may be necessary. 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 ZOMETA® 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 ZOMETA®, 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 ZOMETA® or other bisphosphonates as well as use of nephrotoxic drugs, or using a shorter infusion time than currently recommended. While the risk is reduced with a dose of ZOMETA® 4 mg administered over no less than 15 minutes, deterioration in renal function may still occur. Increases in serum creatinine also occur in some patients with chronic administration of ZOMETA® 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 ZOMETA®.

Patients should have their serum creatinine levels assessed prior to each dose of ZOMETA®. Upon initiation of treatment in patients with bone metastases with mild to moderate renal impairment, lower doses of ZOMETA® are recommended.

In patients who show evidence of renal deterioration during treatment, ZOMETA® should only be resumed when the creatinine level returns to within 10 % of the baseline value (see section 4.2).

In view of the potential impact of bisphosphonates, including ZOMETA® on renal function, the lack of extensive clinical safety data in patients with severe renal impairment (in clinical trials defined as serum creatinine ≥ 400 micromol/l or ≥ 4,5 mg/dl for patients with HCM and ≥ 265 micromol/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 < 30 ml/min), the use of ZOMETA® is not recommended in patients with severe renal impairment (see section 4.3).

*Hepatic insufficiency:*

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

*Osteonecrosis of the jaw (ONJ):*

Osteonecrosis of the jaw has been reported predominantly in patients with cancer receiving treatment regimens including bisphosphonates such as ZOMETA®. 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 (e.g. ZOMETA®) therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate (e.g. ZOMETA®) treatment reduces the risk of osteonecrosis of the jaw. Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

**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 ZOMETA®-treated patients, who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of ZOMETA® 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 ZOMETA® 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 ZOMETA®. 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 re-challenged with the same drug or another bisphosphonate.

**Hypocalcaemia:**

Hypocalcaemia has been reported in patients treated with ZOMETA®. Cardiac dysrhythmias and neurologic 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 ZOMETA® 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 ZOMETA® therapy. Patients should be adequately supplemented with calcium and vitamin D*.*

While not observed with ZOMETA®, administration of bisphosphonates as a class has been associated with bronchoconstriction in acetylsalicylic acid-sensitive asthmatic patients.

**Paediatric use**

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

Use in the elderly

Clinical studies of Zometa 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 Zometa as compared to younger adult patients. Because decreased renal function occurs with bisphosphonates including Zometa more commonly in the elderly, special care should be taken to monitor renal function.

## 4.5 Interaction with other medicines and other forms of interaction

Caution is advised when ZOMETA® 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.

Caution is indicated when ZOMETA® is used with other potentially nephrotoxic medicines. Attention should also be paid to the possibility of hypomagnesaemia developing during treatment.

Caution is advised when Zometa is administered with anti-angiogenic drugs as an increase in incidence of ONJ has been observed in patients treated concomitantly with these drugs.

In multiple myeloma patients, the risk of renal dysfunction may be increased when intravenous bisphosphonates, such as ZOMETA®, are used in combination with thalidomide.

**Observed interactions to be considered:**

Caution is advised when Zometa is administered with anti-angiogenic medicines as an increase in incidence of ONJ have been observed in patients treated concomitantly with these medicines.

**Absence of interactions:**

In clinical studies, ZOMETA® has been administered concomitantly with commonly used anticancer medicines, diuretics, antibiotics and analgesics without clinically apparent interactions occurring. ZOMETA® 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 ZOMETA® 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 ZOMETA® (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 safety of ZOMETA® in pregnant and lactating women has not been established.

Women of child-bearing potential should be advised to avoid becoming pregnant and advised of the potential hazard to the foetus while receiving ZOMETA®. There may be a risk of foetal harm (e.g. skeletal and other abnormalities) if a woman becomes pregnant (see section 4.3) while receiving bisphosphonate therapy.

It is not known whether ZOMETA is excreted into human milk (see section 4.3).
Women receiving Zometa should not breastfeed their infants.

In animal reproduction studies zoledronic acid was administered subcutaneously to rats and rabbits. It was found to be teratogenic at doses ≥ 0,2 mg/kg bodyweight in rats. In rabbits, there was no teratogenicity or foetotoxicity but maternotoxicity was found. In the absence of adequate available experience in human pregnancy, ZOMETA® should not be used during pregnancy (see section 4.3).
The fertility was decreased in rats dosed SC with 0.1 mg/kg/day zoledronic acid (0.1 times the maximum human exposure of 8 mg, based on BSA), and pre-implantation loss was increased at 0.01 mg/kg/day. Reversible testicular atrophy occurred in rats at 0.003 mg/kg/day SC for 12 months (0.004 times the maximum human exposure of 8 mg, based on BSA). In dogs, testicular and prostatic atrophy and oligospermia were observed at 0.2

mg/kg/day IV for 3 months (0.6 times the maximum human exposure of 8 mg, based on BSA), and testicular atrophy and/or mineralisation at 0.03 mg/kg IV dosed every 2-3 days for 6 months (0.1 times the maximum human exposure of 8 mg, based on BSA). Female dogs had decreased weights of ovaries and uterus, correlated with anoestrus and, in some animals, with vaginal epithelial degeneration at 0.01 mg/kg/day IV (0.03 times the maximum human exposure of 8 mg, based on BSA).

### 4.7 Effects on ability to drive and use machines

Cases of dizziness, blurred vision and somnolence have been reported with the use of zoledronic acid. 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 ZOMETA® 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 ZOMETA® affects them.

Within three days after ZOMETA® 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 (see description of selected adverse reactions).

The following are the important identified risks with ZOMETA® in the approved indications: Renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, atrial fibrillation, anaphylaxis, interstitial lung disease. The frequencies for each of these identified risks are shown in Table 2.

Tabulated list of adverse reactions

The following adverse drug reactions, listed in *Table 2*, have been accumulated from clinical studies and post-marketing reports following predominantly chronic treatment with ZOMETA®.

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: Very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1000, < 1/100), rare (≥ 1/10000, < 1/1000), very rare (< 1/10000), including isolated reports.

**Table 2:**

| | |
|---|---|
| ***Blood and lymphatic system disorders*** | |
| Common | Anaemia |
| Uncommon: | Thrombocytopenia, leukopenia |
| Rare: | Pancytopenia |
| ***Nervous system disorders*** | |
| Common: | Headache |
| Uncommon: | Dizziness, paraesthesia, dysgeusia, hypoaesthesia, hyperaesthasia, tremor, somnolence |
| Very rare: | Convulsion, hypoaesthesia and tetany (secondary to hypocalcaemia) |
| ***Psychiatric disorders*** | |
| Uncommon: | Anxiety, sleep disturbance |

| | |
|---|---|
| Rare: | Confusion |
| ***Eye disorders*** | |
| Common: | Conjunctivitis |
| Uncommon: | Blurred vision, scleritis and orbital inflammation |
| Rare: | Uveitis |
| Very rare: | Episcleritis |

| | |
|---|---|
| ***Gastrointestinal disorders*** | |
| Common: | Nausea, vomiting, anorexia, decreased appetite |
| Uncommon: | Diarrhoea, constipation, abdominal pain, dyspepsia, stomatitis, dry mouth |
| ***Respiratory, thoracic and mediastinal disorders:*** | |
| Uncommon: | Dyspnoea, cough, bronchoconstriction |
| Rare: | Interstitial lung disease |
| ***Skin and subcutaneous tissue disorders*** | |
| Common: | Hyperhidrosis |
| Uncommon: | Pruritus, rash (including erythematous and macular rash), increased sweating |
| ***Musculoskeletal and connective tissue disorders*** | |
| Common: | Bone pain, myalgia, arthralgia, generalised pain, joint stiffness |
| Uncommon: | Muscle spasms, osteonecrosis of the jaw |

| | |
|---|---|
| ***Cardiovascular disorders*** | |
| Uncommon: | Hypertension, hypotension, atrial fibrillation, hypotension leading to syncope or circulatory collapse |
| Rare: | Bradycardia, cardiac dysrhythmia (secondary to hypocalcaemia) |
| ***Renal and urinary disorders*** | |
| Common: | Renal impairment |
| Uncommon: | Acute renal failure, haematuria, proteinuria |
| Rare: | Acquired Fanconi syndrome |

| | |
|---|---|
| ***Immune system disorders*** | |
| Uncommon: | Hypersensitivity reaction |
| Rare: | Angioedema |
| ***General disorders and administration site conditions*** | |
| Common: | Fever, flu-like syndrome (including: fatigue, rigors, malaise and flushing) |
| Uncommon: | Asthenia, peripheral oedema, injection site reactions (including pain, irritation, swelling, induration), chest pain, weight increase, anaphylactic reaction/shock, urticaria |
| Rare: | Arthritis and joint swelling as a symptom of an acute phase reaction |

| ***Laboratory abnormalities*** | |
|---|---|
| Very common: | Hypophosphataemia |
| Common: | Blood creatinine and blood urea increased, hypocalcaemia |
| Uncommon: | Hypomagnesaemia, hypokalaemia |
| Rare: | Hyperkalaemia, hypernatraemia |

**Description of selected adverse reactions**

*Renal function impairment:*

ZOMETA® has been associated with reports of renal function impairment. In a pooled analysis of safety data from ZOMETA® 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 ZOMETA® (adverse reactions) was as follows: multiple myeloma (3,2 %), prostate cancer (3,1 %), breast cancer (4,3 %), lung and other solid tumors (3,2 %). Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of ZOMETA® or other bisphosphonates, as well as concomitant use of nephrotoxic medicinal products 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 ZOMETA® (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 ZOMETA®. 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 ZOMETA®.

*Acute phase reaction:*

This adverse drug 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-Zometa 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 ADRs:*

Hypocalcaemia is an important identified risk with ZOMETA® 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 ZOMETA® 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, hypoaesthesia and tetany (see section 4.4).

**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 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 ZOMETA®. 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

**Pharmacological Classification :** A 34 Other

(*ATC code*: M05 BA08)

### 5.1 Pharmacodynamic properties

Zoledronic acid is a bisphosphonate which potently inhibits 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).

In long-term animal studies, zoledronic acid inhibits bone resorption without adversely affecting the formation, mineralisation or mechanical properties of bone.

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 inhibits human endothelial cell proliferation in vitro and is anti-angiogenic in animals. Moreover, the observation that zoledronic acid reduces the invasion of human breast cancer cells through extracellular matrix in vitro indicates that it may have anti-metastatic properties.

### 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 drug increased, achieving their peak at the end of the infusion period, followed by a 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 drug on day 28.

Intravenously administered zoledronic acid is eliminated in two stages: rapid biphasic disappearance from the systemic circulation, with half-lives of 0,24 and 1,87 hours, followed by a long elimination phase with a terminal elimination half-life of $t_{1/2\gamma}$ 146 hours. There was no accumulation of drug in plasma after multiple doses of the drug 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 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.

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 significantly positively 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).

Zoledronic acid shows 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 injections

## 6.2 Incompatibilities

Studies with 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 ZOMETA.

To avoid potential incompatibilities, ZOMETA concentrate is to be diluted with 0,9 % sodium chloride solution or 5 % glucose solution. ZOMETA concentrate must not be mixed with calcium-containing solutions such as Ringer's solution.

## 6.3 Shelf life

3 years

## 6.4 Special precautions for storage

Store at or below 30 °C.

KEEP OUT OF THE REACH OF CHILDREN.

After aseptic dilution, it is preferable to use the diluted product 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 to 8 °C and end of administration must not exceed 24 hours. Do not freeze the reconstituted solution.

Only clear solution free from particles and discoloration should be used.

## 6.5 Nature and contents of container

ZOMETA concentrate for solution for infusion is a clear colourless solution in a colourless plastic vial, grey rubber-stopper and aluminium cap with a flip-off component.

It is supplied as packs containing 1, 4 or 10 vials. Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

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

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd

Magwa Crescent West

Waterfall City, Jukskei View

Johannesburg, 2090

South Africa

## 8. REGISTRATION NUMBER

38/34/0086

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

15 September 2006

## 10. DATE OF REVISION OF THE TEXT

16 August 2021

2016-PSB/GLC-0806-s, 2015-PSB/GLC-0746-s, 2013-PSB/GLC-0659-s, 2013-PSB/GLC-0606-s, 2012-PSB/GLC-0580-s, 2011-PSB/GLC-0468-s, 2011-PSB/GLC-0417-s, 2010-PSB/GLC-0339-s, 2006-PSB/GLC-0041-s