PROFESSIONAL INFORMATION[1]

SCHEDULING STATUS **S4**

1 NAME OF THE MEDICINE

ZOLEDRONIC ACID 4 mg/5 ml FRESENIUS

Concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

One ml concentrate contains zoledronic acid (as monohydrate) corresponding to 0,8 mg zoledronic acid.

Contains mannitol (220 mg per 5 ml vial).

Contains less than 1 mmol (23 mg) sodium per 5 ml vial, that is to say essentially ‘sodium-free’.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion

Clear and colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of tumour-induced hypercalcaemia **(**TIH).

ZOLEDRONIC ACID 4 mg/5 ml slows progression of skeletal conditions

in adult patients when used in conjunction with appropriate antineoplastic therapy in patients with advanced carcinoma of the breast, prostate, lung and myeloma.

4.2 Posology and method of administration

Posology

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 ZOLEDRONIC ACID FRESENIUS.

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:

ZOLEDRONIC ACID FRESENIUS 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.

Data are not available on patients with serum creatinine > 400 micromole/l or > 4,5 mg/dl. No dose adjustment is necessary in HCM patients with serum creatinine < 400 micromole/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 bone pain, fractures, bladder and bowel disturbances, anxiety, depression, and decreased survival.

When initiating treatment with ZOLEDRONIC ACID FRESENIUS 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 Cockcroft-Gault formula. ZOLEDRONIC ACID FRESENIUS 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. Clinical data are not available on patients with serum creatinine > 265 micromole/L or > 3,0 mg/dL.

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 ZOLEDRONIC ACID FRESENIUS dose is recommended (see also section 4.4).

Table 1:

Baseline creatinine clearance (ml/min)	**ZOLEDRONIC ACID FRESENIUS 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 ZOLEDRONIC ACID FRESENIUS and treatment should be withheld if renal function has deteriorated. In the published clinical data, 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.

According to published clinical data, zoledronic acid treatment was resumed only when the creatinine level returned to within 10 % of the baseline value (see section 4.4). ZOLEDRONIC ACID FRESENIUS should be resumed at the same dose as that prior to treatment interruption.

Paediatric population

The safety and efficacy of ZOLEDRONIC ACID FRESENIUS have not been established.

Instructions on preparing reduced doses of ZOLEDRONIC ACID FRESENIUS

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 ZOLEDRONIC ACID FRESENIUS, 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:

ZOLEDRONIC ACID 4 mg/5 ml FRESENIUS 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:

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), are compatible with ZOLEDRONIC ACID FRESENIUS.

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

ZOLEDRONIC ACID FRESENIUS 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 ZOLEDRONIC ACID FRESENIUS listed in section 6.1.

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

4.4 Special warnings and precautions for use

General

Patients must be assessed prior to administration of ZOLEDRONIC ACID FRESENIUS to ensure that they are adequately hydrated.

Over-hydration should be avoided in patients at risk of cardiac failure.

Standard hypercalcaemia-related metabolic parameters, such as serum levels of calcium, phosphate and magnesium, should be carefully monitored after initiating ZOLEDRONIC ACID FRESENIUS therapy. If hypocalcaemia, hypophosphataemia, or hypomagnesaemia occurs, 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 if continued treatment with ZOLEDRONIC ACID FRESENIUS outweighs the possible risk.

The decision to treat patients with bone metastases for the prevention of skeletal related events should consider that the onset of treatment effect is 2–3 months.

ZOLEDRONIC ACID FRESENIUS has 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 ZOLEDRONIC ACID FRESENIUS and other bisphosphonates as well as use of other nephrotoxic medicines. While the risk is reduced with a dose of 4 mg zoledronic acid administered over 15 minutes, deterioration in renal function may still occur. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of 4 mg zoledronic acid. Increases in serum creatinine also occur in some patients with chronic administration of ZOLEDRONIC ACID FRESENIUS at recommended doses for prevention of skeletal related events, although less frequently.

Patients should have their serum creatinine levels assessed prior to each dose of ZOLEDRONIC ACID FRESENIUS. Upon initiation of treatment in patients with bone metastases with mild to moderate renal impairment, lower doses of zoledronic acid are recommended. In patients who show evidence of renal deterioration during treatment, ZOLEDRONIC ACID FRESENIUS should be withheld. ZOLEDRONIC ACID FRESENIUS should only be resumed when serum creatinine returns to within 10 % of baseline. ZOLEDRONIC ACID FRESENIUS treatment should be resumed at the same dose as that given prior to treatment interruption.

In view of the potential impact of zoledronic acid on renal function, the lack of clinical safety data in patients with severe renal impairment the use of ZOLEDRONIC ACID FRESENIUS is not recommended in patients with severe renal impairment (see section 4.3).

Hepatic insufficiency

As only limited clinical data are available in patients with severe hepatic insufficiency, no specific recommendations can be given for this patient population.

Osteonecrosis

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) has been reported uncommonly in clinical trials in patients receiving zoledronic acid, as in ZOLEDRONIC ACID FRESENIUS. Post-marketing experience and the literature suggest a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma). A study showed that ONJ was higher in myeloma patients when compared to other cancers (see section 5.1).

The start of treatment or of a new course of treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth, except in medical emergency situations.

A dental examination with appropriate preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with bisphosphonates in patients with concomitant risk factors.

The following risk factors should be considered when evaluating an individual's risk of developing ONJ:

- Potency of the bisphosphonate (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bisphosphonate.
- Cancer, co-morbid conditions (e.g. anaemia, coagulopathies, infection), smoking.

- Concomitant therapies: chemotherapy, angiogenesis inhibitors (see section 4.5), radiotherapy to neck and head, corticosteroids.
- History of dental disease, poor oral hygiene, periodontal disease, invasive dental procedures (e.g. tooth extractions) and poorly fitting dentures.

All patients should be encouraged to maintain good oral hygiene, undergo routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling, or non-healing of sores or discharge during treatment with ZOLEDRONIC ACID FRESENIUS. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to ZOLEDRONIC ACID FRESENIUS administration. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment as in ZOLEDRONIC ACID FRESENIUS 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 medical practitioner and a dentist or oral surgeon with expertise in ONJ. Temporary interruption of ZOLEDRONIC ACID FRESENIUS treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.

Osteonecrosis of other anatomical sites

- Auditory canal:

Osteonecrosis of the external auditory canal has been reported with bisphosphonates (such as ZOLEDRONIC ACID FRESENIUS), mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving ZOLEDRONIC ACID FRESENIUS who present with ear symptoms including chronic ear infections.

- Other sites:

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 FRESENIUS.

Musculoskeletal pain

In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain have been reported in patients taking ZOLEDRONIC ACID FRESENIUS. 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 ZOLEDRONIC ACID FRESENIUS or another bisphosphonate.

Atypical fractures of the femur

Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy (such as ZOLEDRONIC ACID FRESENIUS), 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 bisphosphates (such as ZOLEDRONIC ACID FRESENIUS) who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of ZOLEDRONIC ACID FRESENIUS 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 ZOLEDRONIC ACID FRESENIUS treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.

Hypocalcaemia

Hypocalcaemia has been reported in patients treated with zoledronic acid, as in ZOLEDRONIC ACID FRESENIUS. Cardiac dysrhythmias and neurologic adverse events (including convulsions, hypoaesthesia and tetany) have been reported secondary to cases of severe

hypocalcaemia. Cases of severe hypocalcaemia requiring hospitalisation have been reported. In some instances, the hypocalcaemia may be life-threatening (see section 4.8). Caution is advised when ZOLEDRONIC ACID FRESENIUS is administered with medicines known to cause hypocalcaemia, as they may have a synergistic effect resulting in severe hypocalcaemia (see section 4.5). Serum calcium should be measured and hypocalcaemia must be corrected before initiating ZOLEDRONIC ACID FRESENIUS therapy. Patients should be adequately supplemented with calcium and vitamin D.

Special patient groups

Paediatric population

The safety and efficacy of ZOLEDRONIC ACID FRESENIUS in paediatric patients have not been established.

Elderly population

Clinical studies of zoledronic acid as contained in ZOLEDRONIC ACID FRESENIUS 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 zoledronic acid as compared to younger adult patients.

Because decreased renal function occurs with bisphosphonates including ZOLEDRONIC ACID FRESENIUS more commonly in the elderly, special care should be taken to monitor renal function.

Excipients

ZOLEDRONIC ACID FRESENIUS contains less than 1 mmol sodium (23 mg) per dosage unit. Patients on low sodium diets can be informed that this medicine is essentially “sodium-free”.

ZOLEDRONIC ACID FRESENIUS may be diluted with sodium-containing solutions (see section 4.2) and this should be considered in relation to the total sodium from all sources that will be administered to the patient.

4.5 Interaction with other medicines and other forms of interaction

Caution is advised when ZOLEDRONIC ACID FRESENIUS is administered with aminoglycosides, calcitonin or loop diuretics, since both medicines may have an additive effect, resulting in a lower serum calcium level for longer periods than required.

Caution is advised when ZOLEDRONIC ACID FRESENIUS is administered with anti-angiogenic medicines, chemotherapy or corticosteroids as an increase in the incidence of osteonecrosis of the jaw (ONJ) has been observed in patients treated concomitantly with these medicines.

Caution is indicated when bisphosphonates, such as ZOLEDRONIC ACID FRESENIUS is used with other potentially nephrotoxic medicines. Attention should also be paid to the possibility of hypomagnesaemia developing during treatment.

In multiple myeloma patients, the risk of renal dysfunction may be increased when intravenous bisphosphonates, like ZOLEDRONIC ACID FRESENIUS are used in combination with thalidomide.

ZOLEDRONIC ACID FRESENIUS can be administered concomitantly with commonly used anticancer medicines, diuretics, antibiotics and analgesics, without apparent interactions occurring.

ZOLEDRONIC ACID FRESENIUS shows no appreciable binding to plasma proteins and does not inhibit human P450 enzymes *in vitro*.

No dose adjustment for ZOLEDRONIC ACID FRESENIUS 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 ZOLEDRONIC ACID FRESENIUS (4 mg given as a 15 minute infusion) did not significantly change the pharmacokinetics of zoledronic acid and the creatinine clearance of patients with multiple myeloma.

4.6 Fertility, pregnancy and lactation

The use of ZOLEDRONIC ACID FRESENIUS during pregnancy and lactation is not recommended as safety and efficacy have 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 ZOLEDRONIC ACID FRESENIUS. 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.

Pregnancy

ZOLEDRONIC ACID FRESENIUS should not be used during pregnancy (see section 4.3).

Lactation

It is not known whether zoledronic acid is excreted into human milk. ZOLEDRONIC ACID FRESENIUS should not be used in women breastfeeding their infants (see section 4.3).

4.7 Effects on ability to drive and use machines

Adverse reactions, such as dizziness, blurred vision and somnolence, may have an influence on the ability to drive or use machines, therefore caution should be exercised with the use of ZOLEDRONIC ACID FRESENIUS along with driving and operating of machinery.

4.8 Undesirable effects

Summary of the safety profile

Within three days after zoledronic acid 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 zoledronic acid risks within 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 summary of adverse reactions

Table 2

Blood and the lymphatic system disorders	
Frequent:	anaemia
Less frequent:	thrombocytopenia, leukopenia, pancytopenia
Immune system disorders	
Less frequent:	hypersensitivity reaction, angioedema, anaphylactic reaction
Psychiatric disorders	
Less frequent:	anxiety, sleep disturbance, confusion
Nervous system disorders	
Frequent:	headache
Less frequent:	dizziness, paraesthesia, dysgeusia, hypoaesthesia, hyperaesthesia, tremor, somnolence, convulsions, hypoaesthesia and tetany (secondary to hypocalcaemia)
Eye disorders	
Frequent:	conjunctivitis
Less frequent:	blurred vision, scleritis, orbital inflammation, uveitis, episcleritis

Cardiac disorders	
Less frequent:	atrial fibrillation, bradycardia, cardiac dysrhythmia (secondary to hypocalcaemia). See section 4.4.
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, decreased appetite
Less frequent:	diarrhoea, constipation, abdominal pain, dyspepsia, stomatitis and dry mouth
Skin and subcutaneous tissue disorders	
Less frequent:	pruritus, rash (including erythematous and macular rash), increased sweating, urticaria
Musculoskeletal, connective tissue and bone disorders	
Frequent:	bone pain, myalgia, arthralgia and generalised pain
Less frequent:	muscle cramps, osteonecrosis of the jaw, osteomyelitis, osteonecrosis of the external auditory canal 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
General disorders and administrative site conditions	
Frequent:	fever, flu-like syndrome (including fatigue, rigors, malaise and flushing)
Less frequent:	asthenia, peripheral oedema, injection site reactions (including pain, irritation, redness, swelling, induration), chest pain, weight increase, arthritis and joint swelling as a symptom of acute phase reaction
Investigations	
Frequent:	hypophosphataemia, increased blood creatinine, increased blood urea and hypocalcaemia
Less frequent:	hypomagnesaemia, hypokalaemia, hyperkalaemia and hypernatraemia

Description of selected adverse reactions

Renal function impairment

Zoledronic acid has been associated with reports of renal dysfunction. In a pooled analysis of safety data from zoledronic acid registration trials for the prevention of skeletal related events in patients with advanced malignancies involving bone, renal impairment adverse events

suspected to be related to zoledronic acid (adverse reactions) were multiple myeloma, prostate cancer, breast cancer, lung and other solid tumours. Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of zoledronic acid or other bisphosphonates, as well as concomitant use of nephrotoxic medicines or using a shorter infusion time than currently recommended. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of 4 mg zoledronic acid (see section 4.4).

Osteonecrosis of the jaw

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

Acute phase reaction

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

Atypical fractures of the femur

During post-marketing experience atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonates class adverse reaction) have been reported.

Hypocalcaemia-related ADRs

Hypocalcaemia is an important identified risk with zoledronic acid 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 zoledronic acid 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. Healthcare 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 ZOLEDRONIC ACID FRESENIUS. Patients who have received doses higher than those recommended should be carefully monitored. In the event of clinically

significant hypocalcaemia, reversal may be achieved with an infusion of calcium gluconate.

Treatment should be supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 34 Others

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

Mechanism of action

Zoledronic acid is a bisphosphonate which primarily acts on the bone by inhibiting osteoclastic bone resorption (process by which osteoclasts break down bone tissues and release the minerals, resulting in a transfer of calcium from bone tissue to the blood).

Long-term animal studies reportedly indicated that 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

Absorption

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 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 on day 28.

Elimination

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 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 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 is 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.

Paediatric population

Not indicated for this population.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Sodium citrate dihydrate

Water for injection

6.2 Incompatibilities

To avoid potential incompatibilities, ZOLEDRONIC ACID FRESENIUS concentrate is to be diluted with 0,9 % m/v sodium chloride solution or 5 % m/v glucose solution.

ZOLEDRONIC ACID FRESENIUS must not be mixed with calcium or other divalent cation-containing infusion solutions such as lactated Ringer's solution and should be administered as a single intravenous solution in a separate infusion line.

6.3 Shelf life

3 years.

After aseptic dilution:

It is preferable to use the diluted product immediately. From a microbiological point of view, the diluted solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2° – 8°C. The refrigerated

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

If refrigerated, the solution must be allowed to reach room temperature before administration.

Do not freeze the diluted solution.

6.4 Special precautions for storage

Store at or below 25 °C.

ZOLEDRONIC ACID FRESENIUS does not require any special storage conditions.

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

6.5 Nature and contents of container

ZOLEDRONIC ACID FRESENIUS is a clear colourless solution in a colourless polypropylene plastic vial with a bromobutyl rubber stopper and an aluminium cap with a plastic flip-off component. It is supplied in packs containing 1, 4 or 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

Prior to administration, 5,0 ml concentrate from one vial or the volume of the concentrate withdrawn as required must be further diluted with 100 ml of calcium-free infusion solution (0,9 % *m/v* sodium chloride solution or 5 % *m/v* glucose solution).

Studies with glass bottles, as well as several containers types made from polyvinylchloride, polyethylene and polypropylene (prefilled with

0,9 % *m/v* sodium chloride solution or 5 % *m/v* glucose solution), showed no incompatibility with ZOLEDRONIC ACID FRESENIUS.

Additional information on handling of ZOLEDRONIC ACID FRESENIUS is provided in section 4.2.

Aseptic techniques must be followed during the preparation of the infusion. For single use only.

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

Healthcare providers are advised not to dispose of unused ZOLEDRONIC ACID FRESENIUS via the domestic sewage system.

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

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Fresenius Kabi South Africa (Pty) Ltd

Stand 7, Growthpoint Business Park

2 Tonetti Street

Halfway House 1685

South Africa

8. REGISTRATION NUMBER

47/34/0262

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 July 2022

10. DATE OF REVISION OF THE TEXT