**NEW ZEALAND DATA SHEET**

# ZOLEDRONIC ACID MYLAN

# 1. Product Name

ZOLEDRONIC ACID MYLAN, 4 mg/ 5 mL, concentrate for infusion.

# 2. Qualitative and Quantitative Composition

Each mL of concentrate for infusion contains 0.8 mg of zoledronic acid (calculated as the anhydrous form, corresponding to 0.8528 mg zoledronic acid monohydrate).

Each 5 mL vial contains 4 mg of zoledronic acid (calculated as the anhydrous form, corresponding to 4.264 mg zoledronic acid monohydrate).

For the full list of excipients, see section 6.1.

# 3. Pharmaceutical Form

ZOLEDRONIC ACID MYLAN concentrate for infusion is a sterile clear and colourless solution.

# 4. Clinical Particulars

## *4.1 Therapeutic indications*

**Adults**

- Prevention of skeletal-related events (pathological fracture, spinal cord compression, radiation to bone or surgery to bone) in patients with advanced malignancies involving bone.
- Treatment of tumour-induced hypercalcaemia.

## *4.2 Dose and method of administration*

ZOLEDRONIC ACID MYLAN concentrate for infusion 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 line separate from all other drugs.

**Prevention of skeletal related events in patients with advanced malignancies involving bone**

In adults and elderly patients the recommended dose in the prevention of skeletal related events in patients with advanced malignancies involving bone is 4 mg zoledronic acid. The concentrate must be further diluted with 100 mL 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.

## Treatment of tumour-induced hypercalcemia (TIH)

In adults and elderly patients the recommended dose in hypercalcemia (albumin-corrected serum calcium ≥12.0 mg/dL or 3.0 mmol/L) is 4 mg zoledronic acid. The concentrate must be further diluted with 100 mL 0.9% w/v sodium chloride or 5% w/v glucose solution, 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 MYLAN.

## Treatment of patients with renal impairment

### *Treatment of patients with tumour-induced hypercalcemia (TIH)*

Zoledronic acid treatment in adult patients with tumour-induced hypercalcemia (TIH) and who have severe renal impairment should be considered only after evaluating the risks and benefit 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 TIH patients with serum creatinine < 400 micromol/L or < 4.5 mg/dL (see section 4.4).

### *Patients with advanced malignancy involving bone and other patients*

When initiating treatment with ZOLEDRONIC ACID MYLAN in adult patients with multiple myeloma or metastatic bone lesions from solid tumours, serum creatinine levels and creatinine clearance (CLcr) should be determined. CLcr is calculated from serum creatinine levels using the Cockcroft-Gault formula. ZOLEDRONIC ACID MYLAN is not recommended for patients presenting with severe renal impairment prior to initiation of therapy, which is defined for this population as CLcr < 30 mL/min. In clinical trials with zoledronic acid, 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 CLcr 30 to 60 mL/min, the following ZOLEDRONIC ACID MYLAN dose is recommended (see also section 4.4):

| **Baseline creatinine clearance (mL/min)** | **ZOLEDRONIC ACID MYLAN Recommended Dose** |
|---|---|
| >60 | 4.0 mg |
| 50 - 60 | 3.5 mg* |
| 40 - 49 | 3.3 mg* |
| 30 - 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 MYLAN 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), an increase of ≥ 0.5 mg/dL;
- For patients with an abnormal baseline creatinine (>1.4 mg/dL), an increase (of ≥ 1.0 mg/dL.

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

## Paediatric Population

The safety and efficacy of zoledronic acid in children aged 1 year to 17 years have not been established.

### Method of administration

ZOLEDRONIC ACID MYLAN must only be administered to patients by healthcare professionals experienced in the administration of intravenous bisphosphonates.

ZOLEDRONIC ACID MYLAN 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 line separate from all other drugs in no less than 15 minutes.

Patients must be maintained in a well hydrated state prior to and following administration of ZOLEDRONIC ACID MYLAN.

#### *Preparation of reduced ZOLEDRONIC ACID MYLAN doses*

In patients with mild to moderate renal impairment, which is defined as CLcr 30 to 60 mL/min, reduced ZOLEDRONIC ACID MYLAN dosages are recommended, except in patients with TIH (see section 4.2).

To prepare reduced doses of ZOLEDRONIC ACID MYLAN concentrate withdraw an appropriate volume of the liquid concentrate needed, as follows:

4.4 mL for 3.5 mg dose

4.1 mL for 3.3 mg dose

3.8 mL for 3.0 mg dose

The withdrawn amount of liquid concentrate must be further diluted in 100 mL of sterile 0.9% w/v sodium chloride solution or 5% w/v glucose solution. The dose must be given as a single intravenous infusion of no less than 15 minutes.

## *4.3 Contraindications*

Zoledronic acid is contraindicated in pregnancy and breast-feeding women.

Hypersensitivity to zoledronic acid or other bisphosphonates or any of the excipients listed in section 6.1.

## *4.4 Special warnings and precautions for use*

### General

All patients, including paediatric patients and patients with mild to moderate renal impairment, must be assessed prior to administration of ZOLEDRONIC ACID MYLAN to assure that they are adequately hydrated.

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

Standard hypercalcemia-related metabolic parameters, such as albumin-corrected serum levels of calcium, phosphate and magnesium as well as serum creatinine should be carefully monitored after initiating zoledronic acid therapy. If hypocalcemia, hypophosphatemia, or hypomagnesemia occur, short-term supplemental therapy may be necessary. Untreated hypercalcemia patients generally have some degree of renal function impairment, therefore careful renal function monitoring should be considered.

ZOLEDRONIC ACID MYLAN contains the same active ingredient as in Aclasta (zoledronic acid). Patients being treated with ZOLEDRONIC ACID MYLAN should not be treated with Aclasta concomitantly. ZOLEDRONIC ACID MYLAN should also not be given together with other bisphosphonates since the combined effects of these agents are unknown.

While not observed in clinical trials with zoledronic acid, there have been reports of bronchoconstriction in acetylsalicylic acid sensitive asthmatic patients receiving bisphosphonates.

## Paediatric population

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

## Renal impairment

Adult patients with TIH and evidence of deterioration in renal function should be appropriately evaluated with consideration given as to whether the potential benefit of continued treatment with zoledronic acid outweighs the possible risk (see section 4.2).

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 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 zoledronic acid 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 zoledronic acid 4 mg administered over no less than 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 zoledronic acid. Increases in serum creatinine also occur in some patients with chronic administration of zoledronic acid at recommended doses for prevention of skeletal related events, although less frequently.

Serum creatinine levels should be measured before each zoledronic acid dose. In patients with bone metastases with mild to moderate renal impairment at initiation of zoledronic acid treatment, lower doses are recommended in all patients except patients with TIH. In patients who show evidence of renal deterioration during treatment, zoledronic acid should only be resumed when creatinine level returns to within 10% of baseline value (see section 4.2).

The use of zoledronic acid is not recommended in patients with severe renal impairment because there are limited clinical safety and pharmacokinetic data in this population, and there is a risk of renal function deterioration in patients treated with bisphosphonates, including zoledronic acid. In clinical trials, patients with severe renal impairment were defined as those with baseline serum creatinine ≥ 400 micromol/L or ≥ 4.5 mg/dL for patients with TIH and ≥ 265 micromol/L or ≥ 3.0 mg/dL for patients with cancer and bone metastases respectively. In pharmacokinetic studies, patients with severe renal impairment were defined as those with baseline creatinine clearance < 30 mL/min (see sections 5.2 and 4.2).

The safety of zoledronic acid in paediatric patients with renal impairment has not been established.

## 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 predominantly in adult cancer patients treated with bisphosphonates, including zoledronic acid. Many of these patients were also receiving chemotherapy and corticosteroids. 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 a dental examination with preventive dentistry prior to treatment with bisphosphonates.

While on treatment with bisphosphonates, patients should avoid invasive dental procedures if possible. 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 reduces the risk of osteonecrosis of the jaw. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

***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 zoledronic acid.

### Atypical fractures of the femur

Atypical subtrochanteric and diaphyseal femoral fractures have been reported in patients receiving 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 zoledronic acid-treated patients, who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of zoledronic acid 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. Reports of atypical femoral fracture have been received in patients treated with zoledronic acid; however causality with zoledronic acid therapy has not been established.

During ZOLEDRONIC ACID MYLAN 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 zoledronic acid (see section 4.8). 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.

### Hypocalcemia

Hypocalcemia has been reported in patients treated with zoledronic acid. Cardiac arrhythmias and neurologic adverse events (seizures, tetany, and numbness) have been reported secondary to cases of severe hypocalcemia. In some instances, the hypocalcemia may be life-threatening. Caution is advised when zoledronic acid is administered with other hypocalcemia causing drugs, as they may have synergistic effect resulting in severe hypocalcemia (see section 4.5). Serum calcium should be measured and hypocalcemia must be corrected before initiating zoledronic acid therapy. Patients should be adequately supplemented with calcium and vitamin D*.*

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

### Anticipated interactions to be considered

Caution is advised when bisphosphonates like ZOLEDRONIC ACID MYLAN are administered with aminoglycosides or calcitonin or loop diuretics, since these agents may have an additive effect, resulting in a lower serum calcium level for longer periods than required (see section 4.4).

Caution is indicated when ZOLEDRONIC ACID MYLAN is used with other potentially nephrotoxic drugs.

### Observed interactions to be considered

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

### Absence of interactions

In clinical studies, zoledronic acid has been administered concomitantly with commonly used anticancer agents, diuretics (except for loop diuretics, see Anticipated interactions to be considered), antibiotics and analgesics without clinically apparent interactions occurring.

No dose adjustment for ZOLEDRONIC ACID MYLAN 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 mg once daily) with zoledronic acid (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*

### Women of child-bearing potential

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 MYLAN. There may be a risk of foetal harm (e.g. skeletal and other abnormalities) if a woman becomes pregnant while receiving bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration on this risk has not been established.

### Pregnancy

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 foeto-toxicity but maternotoxicity was found. Zoledronic acid should not be used during pregnancy (see section 4.3).

### Breast-feeding

It is not known whether zoledronic acid is excreted into human milk. Zoledronic acid should not be used by breast-feeding women (see section 4.3).

### Fertility

See section 5.3.

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

No studies on the effects of zoledronic acid on the ability to drive and use machines have been performed.

## *4.8 Undesirable effects*

### Summary of the safety profile

The most serious adverse drug reactions reported in patients receiving zoledronic acid in the approved indications are: anaphylactic reaction, ocular adverse events, osteonecrosis of the jaw, atypical femoral fracture, atrial fibrillation, renal function impairment, acute phase reaction, and hypocalcemia. The frequencies of these adverse reactions are shown in Table 1 or shown as adverse reactions from 'Spontaneous reports and literature cases' with "not known" frequency.

Frequencies of adverse reactions for zoledronic acid are mainly based on data collected from chronic treatment. Adverse reactions to zoledronic acid are usually mild and transient and similar to those reported for other bisphosphonates. Those reactions can be expected to occur in approximately one third of patients treated with zoledronic acid. Intravenous administration has been most commonly associated with a flu-like illness including bone pain, arthritis with subsequent joint swelling, fever, fatigue and rigors. Cases of arthralgia and myalgia have commonly been reported.

Very commonly, the reduction in renal calcium excretion is accompanied by a fall in serum phosphate levels, which is asymptomatic not requiring treatment. Commonly, the serum calcium may fall to asymptomatic hypocalcemic levels.

Gastrointestinal reactions, such as nausea and vomiting have been reported following intravenous infusion of zoledronic acid. Uncommonly local reactions at the infusion site such as redness or swelling and/or pain were also observed.

Anorexia was commonly reported in patients treated with zoledronic acid.

Rash or pruritus has been uncommonly observed.

As with other bisphosphonates, cases of conjunctivitis have been commonly reported.

Reports of impaired renal function in clinical trials in postmenopausal women with early breast cancer treated with aromatase inhibitors were 0.2%. Based on pooled analysis of placebo-controlled studies, severe anaemia (Hb < 8.0 g/dL) was reported in 5.2% of patients receiving zoledronic acid versus 4.2% on placebo.

Based on pooled analysis of placebo-controlled studies, severe anaemia (Hb < 8.0 g/dL) was commonly reported in patients receiving zoledronic acid 4mg.

Adverse drug reactions from clinical studies (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked under headings of frequency, the most frequent first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS):

*Very common (≥ 1/10),*
*Common (≥ 1/100, < 1/10)*
*Uncommon (≥ 1/1,000, < 1/100),*
*Rare (≥ 1/10,000, < 1/1,000),*
*Very rare (< 1/10,000)*.

## Table 1: Adverse drug reactions

***Blood and lymphatic system disorders***

| | |
|---|---|
| Common | Anaemia |
| Uncommon | Thrombocytopenia, leukopenia |
| Rare | Pancytopenia |

***Nervous system disorders***

| | |
|---|---|
| Common | Headache, parathesia |
| Uncommon | Dizziness, dysgeusia, hypoesthesia, hyperesthesia, tremor |
| Rare | Convulsion, hypoesthesia and tetany (secondary to hypocalcemia) |

***Psychiatric disorders***

| | |
|---|---|
| Common | Sleep disorders |
| Uncommon | Anxiety |
| Rare | Confusional state |

***Eye disorders***

| | |
|---|---|
| Common | Conjunctivitis |
| Uncommon | Blurred vision |
| Rare | Uveitis, episcleritis |

***Gastrointestinal disorders***

| | |
|---|---|
| Common | Nausea, vomiting, decreased appetite, constipation |
| Uncommon | Diarrhoea, abdominal pain, dyspepsia, stomatitis, dry mouth |

***Respiratory, thoracic and mediastinal disorders***

| | |
|---|---|
| Uncommon | Dyspnoea, cough |
| Rare | Interstitial lung disease (ILD) |

***Skin and subcutaneous tissue disorders***

| | |
|---|---|
| Common | Hyperhidrosis |
| Uncommon | Pruritis, rash (including erythematous and macular rash) |

***Musculoskeletal, connective tissue and bone disorders***

| | |
|---|---|
| Common | Bone pain, myalgia, arthralgia, generalised pain, joint stiffness |
| Uncommon | Osteonecrosis of jaw (ONJ), muscle spasms |

***Cardiac disorders***

| | |
|---|---|
| Rare | Bradycardia, cardiac arrhythmia (secondary to hypocalcemia) |

***Vascular disorders***

| | |
|---|---|
| Common | Hypertension |
| Uncommon | Hypotension |

***Renal and urinary disorders***

| | |
|---|---|
| Common | Renal impairment |
| Uncommon | Acute renal failure, haematuria, proteinuria |
| Rare | Acquired Fanconi syndrome |

***Immune System disorders***

| | |
|---|---|
| Uncommon | Hypersensitivity reaction |
| Rare | Angiodema |

***General disorders and administration site conditions***

| | |
|---|---|
| Common | Acute phase reaction, fever, flu-like syndrome (including fatigue, rigors, malaise and flushing), peripheral oedema, asthenia |
| Uncommon | Injection site reactions (including pain, irritation, swelling, induration, redness), chest pain, weight increased |
| Rare | Arthritis and joint swelling as a symptom of Acute phase reaction |

***Investigations***

| | |
|---|---|
| Very common | Hypophosphatemia |
| Common | Blood creatinine and blood urea increased, hypocalcemia |
| Uncommon | Hypomagnesemia, hypokalemia |
| Rare | Hyperkalemia, hypernatremia |

## Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse reactions have been reported during post-marketing experience with zoledronic acid via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency (which is therefore categorized as not known) or establish a causal relationship to drug exposure.

***Immune system disorders:*** anaphylactic reaction/shock

***Nervous system disorders:*** somnolence

***Eye disorders***: episcleritis, scleritis and orbital inflammation

***Cardiac disorders***: atrial fibrillation

***Vascular disorders:*** hypotension leading to syncope or circulatory collapse, primarily in patients with underlying risk factors

***Respiratory, thoracic and mediastinal disorders:*** bronchospasms

***Skin and subcutaneous tissue disorders:*** urticaria

***Musculoskeletal and connective tissue disorders:*** severe and occasionally incapacitating bone, joint, and/or muscle pain, atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction, including zoledronic acid).

## Description of selected adverse reactions

### *Renal function impairment*

Zoledronic acid has been associated with reports of renal function impairment. In a pooled analysis of safety data from zoledronic acid 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 zoledronic acid (adverse reactions) was as follows: multiple myeloma (3.2%), prostate cancer (3.1%), breast cancer (4.3%), lung and other solid tumours (3.2%). Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of zoledronic acid or other bisphosphonates, as well as concomitant use of nephrotoxic 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 zoledronic acid (see section 4.4).

### *Osteonecrosis*

Cases of osteonecrosis (primarily of the jaw but also of other anatomical sites including hip, femur and external auditory canal) have been reported predominantly in cancer patients treated with bisphosphonates, including zoledronic acid. Many patients with osteonecrosis of the jaw had signs of local infection including osteomyelitis, and 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, anti-angiogenic drugs, radiotherapy, corticosteroids) and co-morbid conditions (e.g. anaemia, coagulopathies, infection, pre-existing oral disease). Although causality has not been determined, it is prudent to avoid dental surgery as recovery may be prolonged (see section 4.4). Data suggests a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma).

***Acute phase reaction***

This adverse drug reaction consists of a constellation of symptoms that includes pyrexia, fatigue, bone pain, chills, influenza-like illness, 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; these symptoms usually resolve within a few days.

***Atrial fibrillation***

In one 3 year, randomised, double-blind controlled trial that evaluated the efficacy and safety of zoledronic acid 5 mg once yearly vs placebo in the treatment of postmenopausal osteoporosis (PMO), the overall incidence of atrial fibrillation was 2.5% (96 out of 3,862) and 1.9% (75 out of 3,852) in patients receiving zoledronic acid 5 mg and placebo, respectively. The rate of atrial fibrillation serious adverse events was 1.3% (51 out of 3,862) and 0.6% (22 out of 3,852) in patients receiving zoledronic acid 5 mg and placebo, respectively. The imbalance observed in this trial has not been observed in other trials with zoledronic acid, including those with zoledronic acid 4 mg every 3 to 4 weeks in oncology patients. The mechanism behind the increased incidence of atrial fibrillation in this single clinical trial is unknown.

**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 professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

## *4.9 Overdose*

Clinical experience with acute overdosage of zoledronic acid is limited. Patients who have received doses higher than those recommended should be carefully monitored, since renal function impairment (including renal failure) and serum electrolyte (including calcium, phosphorus and magnesium) abnormalities have been observed. In the event of hypocalcemia, calcium gluconate infusions should be administered as clinically indicated.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

# 5. Pharmacological Properties

## *5.1 Pharmacodynamic properties*

Pharmacotherapeutic group: Bisphosphonate, ATC code: M05 BA08

**Mechanism of action**

Zoledronic acid is a highly potent drug that belongs to the bisphosphonate class of drugs, which act primarily on bone. It is one of the most potent inhibitors of osteoclastic bone resorption known to date.

The selective action of bisphosphonates on bone is based on their high affinity for mineralised bone, but the precise molecular mechanism leading to the inhibition of osteoclastic activity is

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

In addition to being a very potent inhibitor of bone resorption, zoledronic acid also possesses several anti-tumour properties that could contribute to its overall efficacy in the treatment of metastatic bone disease. The following properties have been demonstrated in preclinical studies:

***In vivo:*** Inhibition of osteoclastic bone resorption, which alters the bone marrow microenvironment making it less conducive to tumour cell growth, anti-angiogenic activity, anti-pain activity.

***In vitro:*** Inhibition of osteoblast proliferation, direct cytostatic and pro-apoptotic activity on tumour cells, synergistic cytostatic effect with other anti-cancer drugs, anti-adhesion/invasion activity.

## Clinical efficacy and safety

***Clinical trial results in the prevention of skeletal related events in patients with advanced malignancies involving bone***

Zoledronic acid was compared to placebo for the prevention of skeletal related events (SREs) in adult prostate cancer patients with 214 men receiving zoledronic acid 4 mg versus 208 receiving placebo. After the initial 15 months of treatment, 186 patients continued for up to an additional 9 months, giving a total duration of double-blind therapy up to 24 months. zoledronic 4 mg demonstrated a significant advantage over placebo for the proportion of patients experiencing at least one skeletal related event (SRE) (38% for zoledronic acid 4 mg versus 49 % for placebo, p=0.028), delayed the median time to first SRE (488 days for zoledronic acid 4 mg versus 321 days for placebo, p=0.009), and reduced the annual incidence of event per patient - skeletal morbidity rate (0.77 for zoledronic acid 4 mg versus 1.47 for placebo, p=0.005). Multiple event analysis showed 36% risk reduction in developing skeletal related events in the zoledronic acid group compared with placebo (p=0.002). Pain was measured at baseline and periodically throughout the trial. Patients receiving zoledronic acid reported less increase in pain than those receiving placebo, and the differences reached significance at months 3, 9, 21 and 24. Fewer zoledronic acid patients suffered pathological fractures. The treatment effects were less pronounced in patients with blastic lesions. Efficacy results are provided in Table 2.

In a second study, zoledronic acid reduced the number of SREs and extended the median time to an SRE by over two months in the population of adult patients who had other solid tumours involving bone, which had a median survival of only six months (134 patients with non-small-cell lung cancer [NSCLC], 123 with other solid tumours treated with zoledronic acid vs 130 patients with NSCLC, 120 with other solid tumours treated with placebo). After initial 9 months of treatment, 101 patients entered the 12 month extension study, and 26 completed the full 21 months. zoledronic acid 4 mg reduced the proportion of patients with SREs (39% for zoledronic acid 4 mg versus 48% for placebo, p=0.039), delayed the median time to first SRE (236 days for zoledronic acid 4 mg versus 155 days for placebo, p=0.009), and reduced the annual incidence of events per patient - skeletal morbidity rate (1.74 for 4 mg versus 2.71 for placebo, p=0.012). Multiple event analysis showed 30.7% risk reduction in developing skeletal related events in the zoledronic acid group compared with placebo (p=0.003). The treatment effect in non-small cell lung cancer patients appeared to be smaller than in patients with other solid tumours. Efficacy results are provided in Table 3.

Table 2: Efficacy results (prostate cancer patients receiving hormonal therapy)

| | Any SRE (-TIH) | | Fractures * | | Radiation therapy to bone | |
|---|---|---|---|---|---|---|
| | Zoledronic acid 4 mg | Placebo | Zoledronic acid 4 mg | Placebo | Zoledronic acid 4 mg | Placebo |
| Number of patients | 214 | 208 | 214 | 208 | 214 | 208 |
| Proportion of patients with SREs (%) | 38 | 49 | 17 | 25 | 26 | 33 |
| p-value | 0.028 | | 0.052 | | 0.119 | |
| Median time to SRE (days) | 488 | 321 | NR | NR | NR | 640 |
| p-value | 0.009 | | 0.020 | | 0.055 | |
| Skeletal morbidity rate | 0.77 | 1.47 | 0.20 | 0.45 | 0.42 | 0.89 |
| p-value | 0.005 | | 0.023 | | 0.060 | |
| Risk reduction of suffering from multiple events** (%) | 36 | - | NA | NA | NA | NA |
| p-value | 0.002 | | NA | | NA | |

* includes vertebral and non-vertebral fractures
** Accounts for all skeletal events, the total number as well as time to each event during the trial
NR = not reached
NA = not applicable

Table 3: Efficacy results (solid tumours other than breast or prostate cancer)

| | Any SRE (-TIH) | | Fractures * | | Radiation therapy to bone | |
|---|---|---|---|---|---|---|
| | Zoledronic acid 4 mg | Placebo | Zoledronic acid 4 mg | Placebo | Zoledronic acid 4 mg | Placebo |
| Number of patients | 257 | 250 | 257 | 250 | 257 | 250 |
| Proportion of patients with SREs (%) | 39 | 48 | 16 | 22 | 29 | 34 |
| p-value | 0.039 | | 0.064 | | 0.173 | |
| Median time to SRE (days) | 236 | 155 | NR | NR | 424 | 307 |
| p-value | 0.009 | | 0.020 | | 0.079 | |
| Skeletal morbidity rate | 1.74 | 2.71 | 0.39 | 0.63 | 1.24 | 1.89 |
| p-value | 0.012 | | 0.066 | | 0.099 | |
| Risk reduction of suffering from multiple events ** (%) | 30.7 | - | NA | NA | NA | NA |
| p-value | 0.003 | | NA | | NA | |

* includes vertebral and non-vertebral fractures
** Accounts for all skeletal events, the total number as well as time to each event during the trial
NR = not reached
NA = not applicable

In a third phase III randomised, double-blind trial comparing zoledronic acid 4 mg to pamidronate 90 mg, 1,122 adult patients (564 zoledronic acid 4 mg, 558 pamidronate 90 mg) with multiple myeloma or breast cancer with at least one bone lesion were treated with 4 mg zoledronic acid or 90 mg pamidronate every 3 to 4 weeks. Eight patients were excluded from the efficacy analysis because of good clinical practice non-compliance. 606 patients entered the 12-month, double-blind extension phase. Total therapy lasted up to 24 months. The results demonstrated that zoledronic acid 4 mg showed comparable efficacy to 90 mg pamidronate in the prevention of skeletal related events. The multiple event analyses revealed a significant risk reduction of 16 % (p=0.030) in patients treated with zoledronic acid 4 mg. Efficacy results are provided in Table 4.

Table 4: Efficacy results (breast cancer and multiple myeloma patients)

| | Any SRE (-TIH) | | Fractures * | | Radiation therapy to bone | |
|---|---|---|---|---|---|---|
| | Zoledronic acid 4 mg | Pam 90 mg | Zoledronic acid 4 mg | Pam 90 mg | Zoledronic acid 4 mg | Pam 90 mg |
| Number of patients | 561 | 555 | 561 | 555 | 561 | 555 |
| Proportion of patients with SREs (%) | 48 | 52 | 37 | 39 | 19 | 24 |
| p-value | 0.198 | | 0.653 | | 0.037 | |
| Median time to SRE (days) | 376 | 356 | NR | 714 | NR | NR |
| p-value | 0.151 | | 0.672 | | 0.026 | |
| Skeletal morbidity rate | 1.04 | 1.39 | 0.53 | 0.60 | 0.47 | 0.71 |
| p-value | 0.084 | | 0.614 | | 0.015 | |
| Risk reduction of suffering from multiple events** (%) | 16 | - | NA | NA | NA | NA |
| p-value | 0.030 | | NA | | NA | |

* includes vertebral and non-vertebral fractures
** Accounts for all skeletal events, the total number as well as time to each event during the trial
NR = not reached
NA = not applicable

In clinical trials performed in adult patients with bone metastases or osteolytic lesions, the overall safety profile amongst all treatment groups (zoledronic acid 4 mg, and pamidronate 90 mg and placebo) was similar in types and severity.

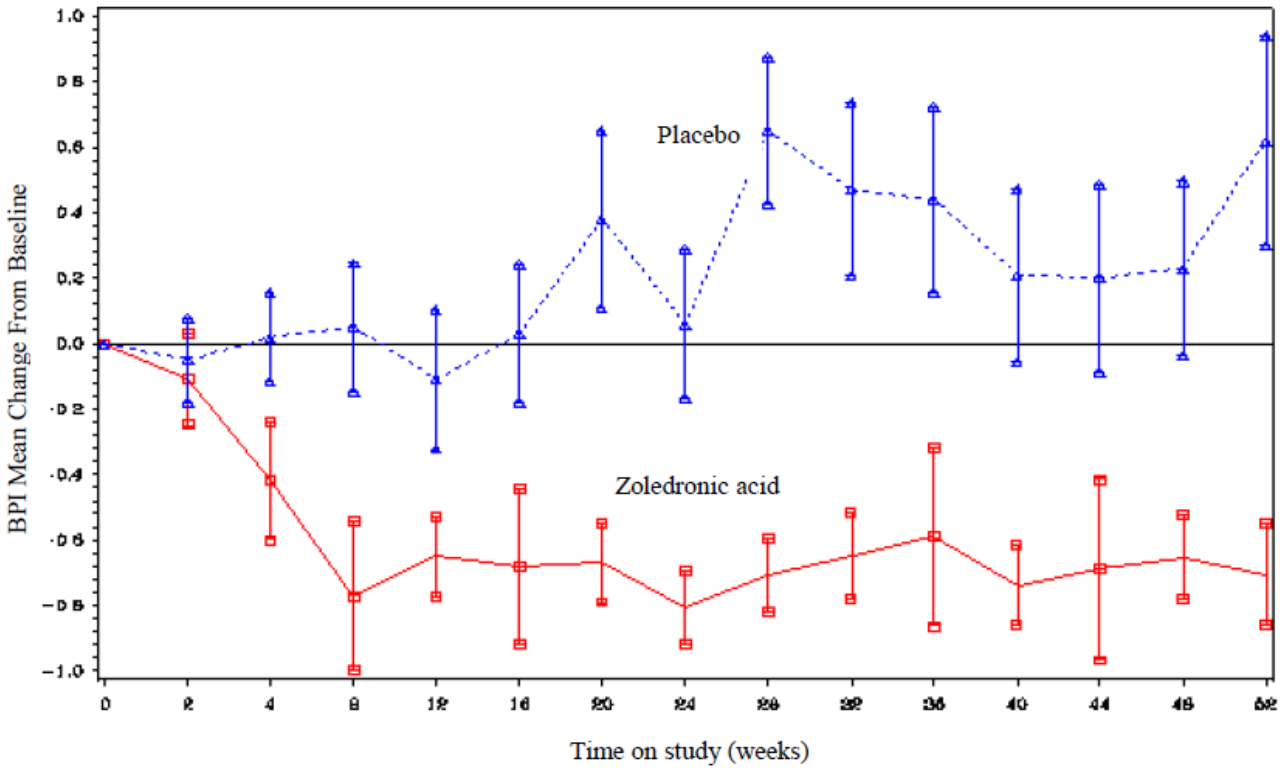
Zoledronic acid was also studied in a double-blind, randomized, placebo-controlled trial in 228 adult patients with documented bone metastases from breast cancer to evaluate the effect of zoledronic acid on the skeletal related event (SRE) rate ratio, calculated as the total number of SRE events (excluding hypercalcemia and adjusted for prior fracture), divided by the total risk period. Patients received either 4 mg zoledronic acid or placebo every four weeks for one year. Patients were evenly distributed between zoledronic acid-treated and placebo groups.

The SRE rate ratio at one year was 0.61, indicating that treatment with zoledronic acid reduced the rate of occurrence of SREs by 39% compared with placebo (p=0.027). The proportion of patients with at least one SRE (excluding hypercalcemia) was 29.8% in the

zoledronic acid-treated group versus 49.6% in the placebo group (p=0.003). Median time to onset of the first SRE was not reached in the zoledronic acid-treated arm at the end of the study and was significantly prolonged compared to placebo (p=0.007). Zoledronic acid reduced the risk of SREs by 41% in a multiple event analysis (risk ratio=0.59, p=0.019) compared with placebo.

In the zoledronic acid-treated group, decreases in pain scores from baseline (using the Brief Pain Inventory, BPI) occurred from 4 weeks onwards and at every subsequent time point during the study, while the pain score in the placebo group remained unchanged or increased from baseline (Figure 1). Zoledronic acid inhibited the worsening of the analgesic score more than placebo. In addition, 71.8% of zoledronic acid-treated patients versus 63.1% of placebo patients showed improvement or no change in the ECOG performance score at the final observation.

**Figure 1:**
Mean change from baseline in Brief Pain Inventory (BPI) pain scores by treatment group and time on study.




## Clinical trial results in the treatment of TIH

Clinical studies in tumour-induced hypercalcemia (TIH) demonstrated that the effect of zoledronic acid is characterised by decreases in serum calcium and urinary calcium excretion. To assess the effects of zoledronic acid versus pamidronate 90 mg, the results of two pivotal multicentre studies in adult patients with TIH were combined in a pre-planned analysis. The results showed that zoledronic acid 4 mg and 8 mg were statistically superior to pamidronate 90 mg for the proportion of complete responders at day 7 and day 10. There was faster normalisation of corrected serum calcium at day 4 for zoledronic acid 8 mg and at day 7 for zoledronic acid 4 mg and 8 mg. The following response rates were observed Table 5:

**Table 5: proportion of complete responders by day in the combined TIH studies**

| | Day 4 | Day 7 | Day 10 |
|---|---|---|---|
| Zoledronic acid 4 mg (N=86) | 45.3% (p=0.104) | 82.6% (p=0.005)* | 88.4% (p=0.002)* |
| Zoledronic acid 8 mg (N=90) | 55.6% (p=0.021)* | 83.3% (p=0.010)* | 86.7% (p=0.015)* |
| Pamidronate 90 mg (N=90) | 33.3% | 63.6% | 69.7% |

*p-values denote statistical superiority over pamidronate

Median time to normocalcaemia was 4 days. By day 10 the response rate was 87 to 88% for the zoledronic acid treatment groups versus 70% for pamidronate 90 mg. Median time to relapse (re-increase of albumin-corrected serum calcium ≥ 2.9 mmol/L) was 30 to 40 days for patients treated with zoledronic acid versus 17 days for those treated with pamidronate 90 mg. The results showed that both zoledronic acid doses were statistically superior to pamidronate 90 mg for time to relapse. There were no statistically significant differences between the two zoledronic acid doses.

In clinical trials performed in adult patients with tumour-induced hypercalcemia (TIH), the overall safety profile amongst all three treatment groups (zoledronic acid 4 and 8 mg and pamidronate 90 mg) was similar in types and severity.

## *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 rapidly increased, achieving their peak at the end of the infusion period, followed by a rapid decline to < 10% of peak after 4 hours and < 1% of peak after 24 hours, with a subsequent prolonged period of very low concentrations not exceeding 0.1% of peak prior to the second infusion of drug on day 28.

Intravenously administered zoledronic acid is eliminated via a triphasic process: rapid biphasic disappearance from the systemic circulation, with half-lives of $t_{½}$alpha 0.24 and $t_{½}$beta 1.87 hours, followed by a long elimination phase with a terminal elimination half-life of $t_{½}$gamma 146 hours. There was no accumulation of 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. 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.

No pharmacokinetic data for zoledronic acid are available in patients with hypercalcemia 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). The use of zoledronic acid is not recommended in patients with severe renal impairment (See section 4.4).

Zoledronic acid shows no affinity for the cellular components of blood and plasma protein binding is low (approximately 56%) and independent of the concentration of zoledronic acid.

The three pharmacokinetic studies conducted in cancer patients with bones metastases reveal no effect by gender, race, age (range 38 to 84 years), and body weight on zoledronic acid total clearance.

## *5.3 Preclinical safety data*

### Acute toxicity

The highest non-lethal single intravenous dose was 10 mg/kg bodyweight in mice and 0.6mg/kg in rats.

### Subchronic and chronic toxicity

Zoledronic acid was well tolerated when administered subcutaneously to rats and intravenously to dogs at doses up to 0.02 mg/kg daily for 4 weeks. Administration of 0.001 mg/kg/day subcutaneously in rats and 0.005 mg/kg/day intravenously in dogs for up to 52 weeks was also well tolerated.

### Reproduction toxicity

Zoledronic acid was teratogenic in the rat at subcutaneous doses ≥ 0.2mg/kg. Although no teratogenicity or foetotoxicity was observed in the rabbit, maternal toxicity was found.

### Mutagenicity and carcinogenic potential

Zoledronic acid was not mutagenic in the mutagenicity tests performed and carcinogenicity testing did not provide any evidence of carcinogenic potential.

### Local tolerance

Local tolerance testing in rabbits showed that intravenous administration was well tolerated.

# 6. Pharmaceutical particulars

## *6.1 List of excipients*

- Sodium citrate
- Water for injections
- Sodium hydroxide (to adjust pH (6.1-6.4))
- Hydrochloric acid (to adjust pH (6.1-6.4))

## *6.2 Incompatibilities*

Studies with glass bottles, as well as several types of infusion bags and infusion lines made from polyvinylchloride, polyethylene and polypropylene (prefilled with 0.9% w/v sodium chloride solution or 5% w/v glucose solution), showed no incompatibility with zoledronic acid.

To avoid potential incompatibilities, ZOLEDRONIC ACID MYLAN solution is to be diluted with 0.9% w/v sodium chloride solution or 5% w/v glucose solution.

ZOLEDRONIC ACID MYLAN 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 line separate from all other drugs.

### *6.3 Shelf life*

3 years.

Chemical and physical in-use stability of the diluted solution has been demonstrated for 24 hours at 2 to 8°C stored in the original vial.

From a microbiological point of view, the medicine 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 to 8°C.

### *6.4 Special precautions for storage*

Unopened vials: Store below 25°C.

Diluted vials: Store between 2-8°C. Do not freeze.

For storage conditions after reconstitution of the medicine, see section 6.3.

### *6.5 Nature and contents of container*

ZOLEDRONIC ACID MYLAN are filled in 15 mL capacity Type I clear glass vials sealed with a bromobutyl rubber stopper.

Available in pack size of 1, 4 or 10 vials.

Not all pack sizes may be marketed.

### *6.6 Special precautions for disposal and other handling*

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

## 7. Medicines Schedule

Prescription Medicine

## 8. Sponsor Details

Mylan New Zealand Ltd
PO Box 11183
Ellerslie
AUCKLAND
Telephone 09-579-2792

## 9. Date of First Approval

31 January 2013

# 10. Date of Revision of the Text

**11 September 2019**

**Summary table of changes**

| Section | Summary of new information |
|---|---|
| All sections | Administrative changes and rewording with content unchanged except when as detailed below. |
| 4.1 | Clarification that indications are for ADULTS only |
| 4.2 | Details on dilution solutions not to be used<br>Median time to relapse removed<br>Baseline creatinine clearance changed to mg/dL<br>Paediatric population details given<br>Monitoring advice moved to 4.4 |
| 4.5 | No dose adjustment for thalidomide required |
| 4.8 | Atrial fibrillation |
| 5.1 | Additional pharmacodynamic information from clinical trials. |
| 5.3 | Summarised pre-clinical data |