NEW ZEALAND DATA SHEET

ZOLEDRONIC ACID VIATRIS

1. Product Name

Zoledronic Acid Viatris, 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 Viatris 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 Viatris 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 medications.

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 Viatris.

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 Viatris in adult patients with multiple myeloma or metastatic bone lesions from solid tumours, serum creatinine levels and creatinine clearance (CL_{cr}) should be determined. CL_{cr} is calculated from serum creatinine levels using the Cockcroft-Gault formula. Zoledronic Acid Viatris is not recommended for patients presenting with severe renal impairment prior to initiation of therapy, which is defined for this population as CL_{cr} < 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 CL_{cr} 30 to 60 mL/min, the following Zoledronic Acid Viatris dose is recommended (see also section 4.4):

Baseline creatinine clearance (mL/min)	**Zoledronic Acid Viatris 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) (CL_{cr}=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 Viatris 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 Viatris 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 Viatris must only be administered to patients by healthcare professionals experienced in the administration of intravenous bisphosphonates.

Zoledronic Acid Viatris 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 medications in no less than 15 minutes.

Patients must be maintained in a well hydrated state prior to and following administration of Zoledronic Acid Viatris.

Preparation of reduced Zoledronic Acid Viatris doses

In patients with mild to moderate renal impairment, which is defined as CL_{cr} 30 to 60 mL/min, reduced Zoledronic Acid Viatris dosages are recommended, except in patients with TIH (see section 4.2).

To prepare reduced doses of Zoledronic Acid Viatris 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

- Hypersensitivity to zoledronic acid or other bisphosphonates or any of the excipients listed in section 6.1.
- Zoledronic acid is contraindicated in pregnancy and breastfeeding women (see section 4.6).

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 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 contains the same active ingredient as in Aclasta (zoledronic acid). Patients being treated with zoledronic acid should not be treated with Aclasta concomitantly. Zoledronic acid 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 medications 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). A study showed that ONJ was higher in myeloma patients when compared to other cancers (see sections 5.1).

The start of treatment or of a new course of treatment should be delayed in patient 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 bisphosphate.
- 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. 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.

The management plan for patients who develop ONJ should be set up in close collaboration between the treating physician and a dentist or oral surgeon with expertise in ONJ. Temporary interruption of zoledronic acid treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.

Osteonecrosis of other anatomical sites

Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal 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 bisphosphonates who present with ear symptoms including chronic ear infections.

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 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). 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 zoledronic acid or another bisphosphonate.

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

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 (see section 4.8). Caution is advised when zoledronic acid is administered with other hypocalcemia causing medications, 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 Viatris 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 Viatris is used with other potentially nephrotoxic medications. Attention should also be paid to the possibility of hypomagnesaemia developing during treatment.

Observed interactions to be considered

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

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. Zoledronic acid 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 zoledronic acid 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. 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

There are no adequate data on use of zoledronic acid in pregnant women. Animal reproduction studies with zoledronic acid have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Zoledronic acid should not be used during pregnancy (see section 4.3).

Breastfeeding

It is not known whether zoledronic acid is excreted into human milk. Zoledronic acid is contraindicated in breastfeeding women (see section 4.3).

Fertility

Zoledronic acid was evaluated in rats for potential adverse effects on fertility of the parental and F1 generation. This resulted in exaggerated pharmacological effects considered to be related to the compound's inhibition of skeletal calcium metabolisation, resulting in perparturient hypocalcaemia, a bisphosphonate class effect, dystocia and early termination of the study. Thus these results precluded determining a definitive effect of zoledronic acid on fertility in humans.

4.7 Effects on ability to drive and use machines

Adverse reactions, such as dizziness and somnolence, may have influence on the ability to drive or use machines, therefore caution should be exercised with the use of zoledronic acid along with driving and operating of machinery.

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. These symptoms occurred within three days after zoledronic acid administration and usually resolved within a few days.

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, somnolence
Rare	Convulsion, hypoesthesia and tetany (secondary to hypocalcemia)
Psychiatric disorders	
Common	Sleep disorders
Uncommon	Anxiety, sleep disturbance
Rare	Confusion
Eye disorders	
Common	Conjunctivitis
Uncommon	Blurred vision, scleritis and orbital inflammation
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, bronchoconstriction
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
Very Rare	Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction) and other anatomical sites including femur and hip
Cardiac disorders	
Uncommon	Atrial fibrillation
Rare	Bradycardia, cardiac arrhythmia (secondary to hypocalcemia)
Vascular disorders	
Common	Hypertension
Uncommon	Hypotension, hypotension leading to syncope or circulatory collapse
Renal and urinary disorders	
Common	Renal impairment
Uncommon	Acute renal failure, haematuria, proteinuria
Rare	Acquired Fanconi syndrome
Immune System disorders	
Uncommon	Hypersensitivity reaction
Rare	Angioneurotic oedema
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, anaphylactic reaction/shock, urticaria
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 medication exposure.

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 4 mg 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 medications, 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, myalgia, headache, extremity pain, nausea, vomiting, diarrhoea, arthralgia, 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.

Atypical fractures of the femur

During post-marketing experience the following reactions have been reported (frequency rare):

- Atypical subtrochanteric
- Diaphyseal femoral fractures (bisphosphonate class adverse reaction)

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 arrhythmia. 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 professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

Clinical experience with acute overdosage of zoledronic acid is limited. The administration of doses up to 48 mg of zoledronic acid in error has been reported. Patients who have received doses higher than those recommended (see section 4.2) 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: M05BA08

Mechanism of action

Zoledronic acid is a highly potent medication that belongs to the bisphosphonate class of medications, 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, mineralisation 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 medications, 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 acid 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

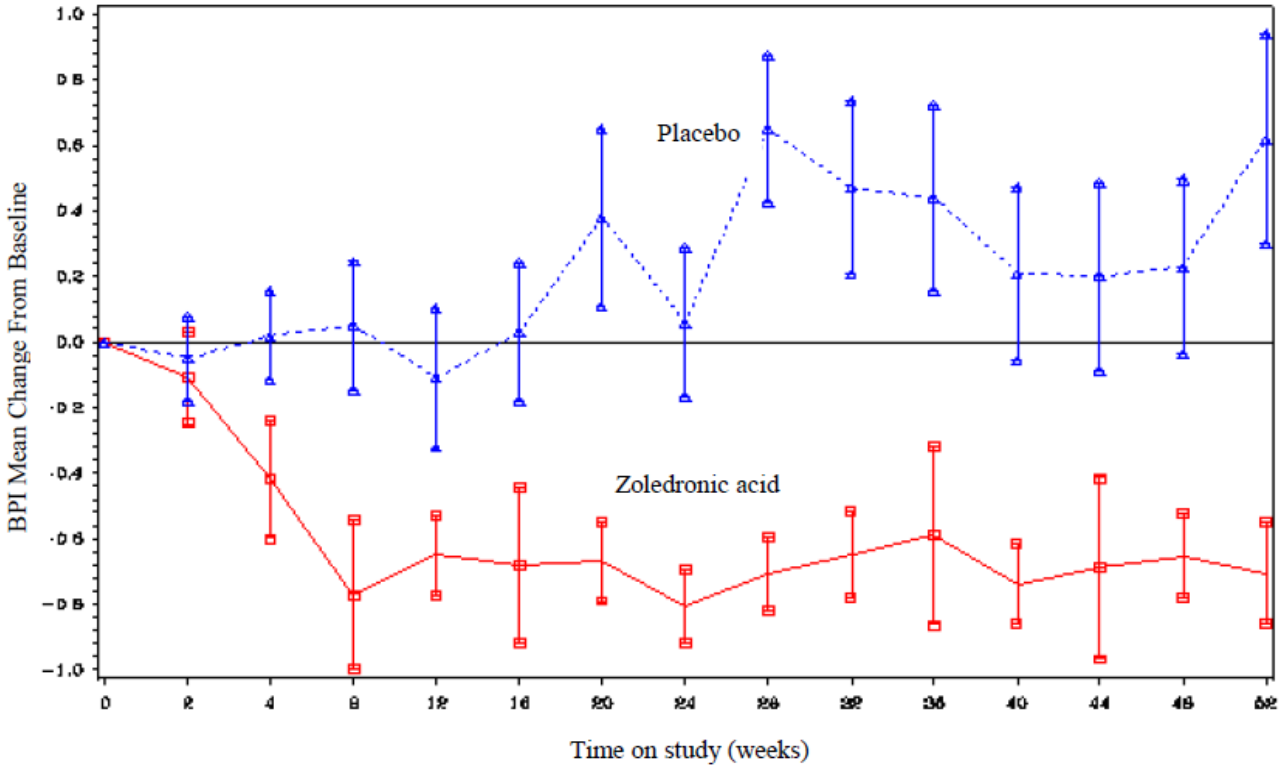
In clinical trials performed in adult patients with bone metastases or osteolytic lesions, the overall safety profile amongst all treatment groups (zoledronic acid 4 mg, and pamidronate 90 mg and placebo) was similar in types and severity.

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

Intravenously administered zoledronic acid is eliminated 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 zoledronic acid in plasma after multiple doses given every 28 days. Zoledronic acid is not metabolised and is excreted unchanged via the kidney. Over the first 24 hours, 39 ± 16% of the administered dose is recovered in the urine, while the remainder is principally bound to bone tissue. From the bone tissue it is released very slowly back into the systemic circulation and eliminated via the kidney. The total body clearance is 5.04 ± 2.5 L/h, independent of dose, and unaffected by gender, age, race, and body weight. Increasing the infusion time from 5 to 15 minutes caused a 30% decrease in zoledronic acid concentration at the end of the infusion, but had no effect on the area under the plasma concentration versus time curve.

The interpatient variability in pharmacokinetic parameters for zoledronic aic dwas high, as seen with other bisphosphates.

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).

In an *in vitro study*, zoledronic acid showed low affinity for the cellular components of human blood, with a mean blood to plasma concentration ratio of 0.59 in a concentration range of 30 ng/ml to 5000 ng/ml. The plasma protein binding is low, with the unbound fraction ranging from 60% at 2 ng/ml to 77% at 2000 ng/ml of zoledronic acid.

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 intravenously once every 2 to 3 days in dogs for up to 52 weeks was also well tolerated.

The most frequent finding in repeat-dose studies consisted of increased primary spongiosa in the metaphyses of long bones in growing animals at nearly all doses, a finding that reflected the compound's pharmacological antiresorptive activity.

The safety margins relative to renal effects were narrow in the long-term repeat-dose parenteral animal studies but the cumulative no adverse event levels (NOAELs) in the single dose (1.6 mg/kg) and multiple dose studies of up to one month (0.06-0.6 mg/kg/day) did not indicate renal effects at doses equivalent to or exceeding the highest intended human therapeutic dose. Longer-term repeat administration at doses bracketing the highest intended human therapeutic dose of zoledronic acid produced toxicological effects in other organs, including the gastrointestinal tract, liver, spleen and lungs, and at intravenous injection sites.

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. Dystocia was observed at the lowest dose (0.01 mg/kg bodyweight) tested in the rat.

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 Viatris solution is to be diluted with 0.9% w/v sodium chloride solution or 5% w/v glucose solution.

Zoledronic Acid Viatris 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 medications.

6.3 Shelf life

2 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 Viatris 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

Viatris Ltd
PO Box 11-183
Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

31 January 2013

10. Date of Revision of the Text

7 November 2024

Summary table of changes

Section	Summary of new information
All	Updated “ZOLEDORNIC ACID VIATRIS” to all lower case Updated “drug(s)” to “medication(s)”
4.3, 4.4, 4.8	Minor editorial changes Minor format changes
4.4	Additional information regarding Osteonecrosis Additional information regarding musculoskeletal pain and hypocalcemia
4.5	Warning of development of hypomagnesaemia Updated absence of interaction section
4.6	Additional warning for use during pregnancy and breastfeeding. Addition of information on fertility
4.7	Updated warning for effects on ability to drive and use machines
4.8	Additional information regarding acute symptoms Rearrangement of table 1 into table format Additional ADR added to table 1 ADR removed from frequency not known section and added to table 1 Addition of “Atypical fractures of the femur” and “Hypocalcaemia-related ADRs section

	Updated ADR reporting website
4.9	Updated overdose information