

SUMMARY OF PRODUCT CHARACTERISTICS

1.NAME OF THE MEDICINAL PRODUCT

Zoledronic Acid Mylan

1.2 Strength

Strength – 0.8 mg/mL [5 mL]

1.3 Pharmaceutical Form and Pack sizes

Form – Liquid Injection

Pack size – 1 vial in a carton.

2.QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains Zoledronic acid monohydrate equivalent to Zoledronic acid anhydrous 0.8mg

3.PHARMACEUTICAL FORM

Liquid injection. Clear and colourless solution.

4.CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

Treatment of adult patients with tumour-induced hypercalcaemia (TIH).

4.2 Posology and method of administration

Zoledronic acid Injection must only be prescribed and administered to patients by healthcare professionals experienced in the administration of intravenous bisphosphonates. Patients treated with Zoledronic acid Injection should be given the package leaflet and the patient reminder card. Posology Prevention of skeletal related events in patients with advanced malignancies involving bone

Adults and older people

The recommended dose in the prevention of skeletal related events in patients with advanced malignancies involving bone is 4 mg zoledronic acid every 3 to 4 weeks.

Patients should also be administered an oral calcium supplement of 500 mg and 400 IU vitamin D daily.

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

Treatment of TIH

Adults and older people

The recommended dose in hypercalcaemia (albumin corrected serum calcium ≥ 12.0 mg/dL or 3.0 mmol/L) is a single dose of 4 mg zoledronic acid.

Renal impairment

TIH:

Zoledronic acid Injection treatment in TIH patients who also have severe renal impairment should be considered only after evaluating the risks and benefits of treatment. In the clinical studies, patients with serum creatinine >400 $\mu\text{mol/L}$ or >4.5 mg/dL were excluded. No dose adjustment is necessary in TIH patients with serum creatinine <400 $\mu\text{mol/L}$ or <4.5 mg/dL (see section 4.4).

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

When initiating treatment with Zoledronic acid Injection in patients with multiple myeloma or metastatic bone lesions from solid tumours, serum creatinine and creatinine clearance (CLcr) should be determined. CLcr is calculated from serum creatinine using the Cockcroft-Gault formula. Zoledronic acid 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 $\mu\text{mol/L}$ 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 30–60 mL/min, the following Zoledronic acid injection dose is recommended (see also section 4.4):

Baseline creatinine clearance (ml/min)	Zoledronic acid recommended dose*
> 60	4.0 mg zoledronic acid
50–60	3.5 mg* zoledronic acid
40–49	3.3 mg* zoledronic acid
30–39	3.0 mg* zoledronic acid

* Doses have been calculated assuming target AUC of 0.66 (mg•hr/L) (CLcr =

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 Injection and treatment should be withheld if renal function has deteriorated. In the clinical trials, renal deterioration was defined as follows:

- For patients with normal baseline serum creatinine (<1.4 mg/dL or < 124 µmol/L), an increase of 0.5 mg/dL or 44 µmol/L;
- For patients with abnormal baseline creatinine (>1.4 mg/dL or > 124 µmol/L), an increase of 1.0 mg/dl or 88 µmol/L.

In the clinical studies, Zoledronic acid Injection treatment was resumed only when the creatinine level returned to within 10% of the baseline value (see section 4.4). Zoledronic acid treatment should be resumed at the same dose as that given 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. Currently available data are described in section and 5.1 but no recommendation on a posology can be made.

Method of administration

Intravenous use.

Zoledronic acid Injection, further diluted in 100 mL (see section 6.6), should be given as a single intravenous infusion in no less than 15 minutes.

In patients with mild to moderate renal impairment, reduced Zoledronic acid Injection doses are recommended (see section “Posology” above and section 4.4).

Instructions for preparing reduced doses of Zoledronic acid injection Withdraw an appropriate volume of the 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

For instructions on the dilution of the medicinal product before administration, see section 6.6. The withdrawn amount of concentrate must be further diluted

in 100 mL of sterile 0.9% w/v sodium chloride solution or 5% w/v Dextrose solution. The dose must be given as a single intravenous infusion over no less than 15 minutes.

4.3 Contra-indications

- Hypersensitivity to the active substance, to other bisphosphonates or to any of the excipients listed in section 6.1
- Breastfeeding (see section 4.6)

4.4 Special warnings and precautions for use

General

Patients must be assessed prior to administration of Zoledronic acid to ensure that they are adequately hydrated.

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

Standard hypercalcaemia-related metabolic parameters, such as serum levels of calcium, phosphate and magnesium, should be carefully monitored after initiating Zoledronic acid Injection therapy. If hypocalcaemia, hypophosphataemia, or hypomagnesaemia occurs, short-term supplemental therapy may be necessary. Untreated hypercalcaemia patients generally have some degree of renal function impairment, therefore careful renal function monitoring should be considered.

Patients being treated with Zoledronic acid should not be treated with any other medicines containing zoledronic acid or any other bisphosphonate concomitantly, since the combined effects of these agents are unknown.

Renal insufficiency

Patients with TIH and evidence of deterioration in renal function should be appropriately evaluated with consideration given as to whether the potential benefit of treatment with Zoledronic acid injection outweighs the possible risk.

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

Zoledronic acid Injection has been associated with reports of renal dysfunction. Factors that may increase the potential for deterioration in renal function include dehydration, preexisting renal impairment, multiple cycles of Zoledronic acid Injection and other bisphosphonates as well as use of other nephrotoxic medicinal products. While the risk is reduced with a dose of 4 mg zoledronic

acid administered over 15 minutes, deterioration in renal function may still occur. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of 4 mg zoledronic acid. Increases in serum creatinine also occur in some patients with chronic administration of Zoledronic acid Injection at recommended doses for prevention of skeletal related events, although less frequently.

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

In view of the potential impact of zoledronic acid on renal function, the lack of clinical safety data in patients with severe renal impairment (in clinical trials defined as serum creatinine ≥ 400 $\mu\text{mol/L}$ or ≥ 4.5 mg/dL for patients with TIH and ≥ 265 $\mu\text{mol/L}$ or ≥ 3.0 mg/dL for patients with cancer and bone metastases, respectively) at baseline and only limited pharmacokinetic data in patients with severe renal impairment at baseline ($\text{CLcr} < 30$ mL/min), the use of Zoledronic acid Injection is not recommended in patients with severe renal impairment.

Hepatic insufficiency

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

Osteonecrosis

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) has been reported uncommonly in clinical trials and in the post-marketing setting in patients receiving Zoledronic acid injection.

The start of treatment or of a new course of treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth, except in medical emergency situations. A dental examination with appropriate preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with bisphosphonates in patients with concomitant risk factors. The following risk factors should be considered

when evaluating an individual's risk of developing ONJ:

- Potency of the bisphosphonate (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bisphosphonate.
- Cancer, co-morbid conditions (e.g. anaemia, coagulopathies, infection), smoking.
- Concomitant therapies: chemotherapy, angiogenesis inhibitors (see section 4.5), radiotherapy to neck and head, corticosteroids.
- History of dental disease, poor oral hygiene, periodontal disease, invasive dental procedures (e.g. tooth extractions) and poorly fitting dentures.

All patients should be encouraged to maintain good oral hygiene, undergo routine dental checkups, 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 Injection.

While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to zoledronic acid administration. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment 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 the external auditory canal

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.

Musculoskeletal pain

In post-marketing experience, severe and occasionally incapacitating bone,

joint, and/or muscle pain have been reported in patients taking Zoledronic acid Injection. However, such reports have been infrequent. The time to onset of symptoms varied from one day to several months after starting treatment. Most patients had relief of symptoms after stopping treatment. A subset had recurrence of symptoms when rechallenged with Zoledronic acid or another bisphosphonate.

Atypical fractures of the femur

Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment. During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.

Hypocalcaemia

Hypocalcaemia has been reported in patients treated with Zoledronic acid Injection. Cardiac arrhythmias and neurologic adverse events (including convulsions, hypoaesthesia and tetany) have been reported secondary to cases of severe hypocalcaemia. Cases of severe hypocalcaemia requiring hospitalisation have been reported. In some instances, the hypocalcaemia may be life-threatening (see section 4.8). Caution is advised when Zoledronic acid injection is administered with medicinal products known to cause hypocalcaemia, as they may have a synergistic effect resulting in severe hypocalcaemia (see section 4.5). Serum calcium should be measured and hypocalcaemia must be corrected before initiating Zoledronic acid injection therapy. Patients should be adequately supplemented with calcium and vitamin D.

4.5 Interaction with other medicinal products and other forms of interaction

In clinical studies, Zoledronic acid injection has been administered concomitantly with commonly used anticancer agents, diuretics, 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.

Caution is advised when bisphosphonates are administered with aminoglycosides, 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 injection is used with other potentially nephrotoxic medicinal products. Attention should also be paid to the possibility of hypomagnesaemia developing during treatment.

In multiple myeloma patients, the risk of renal dysfunction may be increased when Zoledronic acid injection is used in combination with thalidomide.

Caution is advised when Zoledronic acid injection is administered with antiangiogenic medicinal products, as an increase in the incidence of ONJ has been observed in patients treated concomitantly with these medicinal products.

4.6 Fertility, pregnancy and lactation

Pregnancy:

There are no adequate data on the 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 Injection should not be used during pregnancy. Women of childbearing potential should be advised to avoid becoming pregnant.

Breastfeeding:

It is not known whether zoledronic acid is excreted into human milk. Zoledronic acid injection 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 metabolism, resulting in periparturient 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 injection along with driving and operating of machinery.

4.8 Undesirable effects:

Summary of the safety profile

Within three days after Zoledronic acid injection administration, an acute phase reaction has commonly been reported, with symptoms including bone pain, fever, fatigue, arthralgia, myalgia, rigors and arthritis with subsequent joint swelling; these symptoms usually resolve within a few days (see description of selected adverse reactions).

The following are the important identified risks with Zoledronic acid injection in the approved indications:

Renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, atrial fibrillation, anaphylaxis, interstitial lung disease. The frequencies for each of these identified risks are shown in Table 1.

Tabulated list of adverse reactions

The following adverse reactions, listed in Table 1, have been accumulated from clinical studies and post-marketing reports following predominantly chronic treatment with 4 mg zoledronic acid:

Table 1

Adverse reactions are ranked under headings of frequency, the most frequent

first, using the following convention: Very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

<i>Blood and lymphatic system disorders</i>	
Common:	Anaemia

Uncommon:	Thrombocytopenia, leukopenia
Rare:	Pancytopenia
<i>Immune system disorders</i>	
Uncommon:	Hypersensitivity reaction
Rare:	Angioneurotic oedema
<i>Psychiatric disorders</i>	
Uncommon:	Anxiety, sleep disturbance
Rare:	Confusion
<i>Nervous system disorders</i>	
Common:	Headache
Uncommon:	Dizziness, paraesthesia, dysgeusia, hypoaesthesia, hyperaesthesia, tremor, somnolence
Very rare:	Convulsions, hypoaesthesia and tetany (secondary to hypocalcaemia)
<i>Eye disorders</i>	
Common:	Conjunctivitis
Uncommon:	Blurred vision, scleritis and orbital inflammation
Rare:	Uveitis
Very rare:	Episcleritis
<i>Cardiac disorders</i>	
Uncommon:	Hypertension, hypotension, atrial fibrillation, hypotension leading to syncope or circulatory collapse
Rare:	Bradycardia, cardiac arrhythmia (secondary to hypocalcaemia)
<i>Respiratory, thoracic and mediastinal disorders</i>	
Uncommon:	Dyspnoea, cough, bronchoconstriction
Rare:	Interstitial lung disease
<i>Gastrointestinal disorders</i>	
Common:	Nausea, vomiting, decreased appetite
Uncommon:	Diarrhoea, constipation, abdominal pain, dyspepsia, stomatitis, dry mouth
<i>Skin and subcutaneous tissue disorders</i>	
Uncommon:	Pruritus, rash (including erythematous and macular rash), increased sweating
<i>Musculoskeletal and connective tissue disorders</i>	
Common:	Bone pain, myalgia, arthralgia, generalised pain
Uncommon:	Muscle spasms, osteonecrosis of the jaw
Very rare:	Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)
<i>Renal and urinary disorders</i>	
Common:	Renal impairment
Uncommon:	Acute renal failure, haematuria, proteinuria
<i>General disorders and administration site conditions</i>	
Common:	Fever, flulike syndrome (including fatigue, rigors, malaise and flushing)

Uncommon:	Asthenia, peripheral oedema, injection site reactions (including pain, irritation, swelling, induration), chest pain, weight increase, anaphylactic reaction/shock, urticaria
Rare:	Arthritis and joint swelling as a symptom of acute phase reaction
<i>Investigations</i>	
Very common:	Hypophosphataemia
Common:	Blood creatinine and blood urea increased, hypocalcaemia
Uncommon:	Hypomagnesaemia, hypokalaemia
Rare:	Hyperkalaemia, hypernatraemia

Description of selected adverse reactions

Renal function impairment

Zoledronic acid Injection has been associated with reports of renal dysfunction. In a pooled analysis of safety data from Zoledronic acid Injection registration trials for the prevention of skeletal-related events in patients with advanced malignancies involving bone, the frequency of renal impairment adverse events suspected to be related to Zoledronic acid Injection (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 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 of the jaw

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

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 Injection 4 mg every 34 weeks in oncology patients. The mechanism behind the increased incidence of atrial fibrillation in this single clinical trial is unknown.

Acute phase reaction

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

Atypical fractures of the femur

During post-marketing experience the following reactions have been reported (frequency rare): Atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction).

Hypocalcaemia-related ADRs

Hypocalcaemia is an important identified risk with 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 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:

Healthcare professionals are requested to report any suspected adverse reactions via the national Pharmacovigilance Electronic Reporting Systems to the respective national regulatory authorities.

4.9 Overdose

Clinical experience with acute overdose of Zoledronic acid Injection 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 hypocalcaemia, calcium gluconate infusions should be administered as clinically indicated

5. Pharmacological properties

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: Drugs for treatment of bone diseases, bisphosphonates,

ATC code: M05BA08

Zoledronic acid belongs to the class of bisphosphonates and acts primarily on bone. It is an inhibitor of osteoclastic bone resorption.

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

In paediatric patients with severe osteogenesis imperfecta, zoledronic acid seems to be associated with more pronounced risks for acute phase reaction, hypocalcaemia and unexplained tachycardia, in comparison to pamidronate, but this difference declined after subsequent infusions.

The European Medicines Agency has waived the obligation to submit the results of studies with zoledronic acid in all subsets of the paediatric population in the treatment of tumour induced Hyper-calcaemia and prevention of skeletal-related events in patients with advanced malignancies involving bone (see

section 4.2 for information on paediatric use).

5.2 Pharmacokinetics 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 zoledronic acid 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 by a triphasic process: rapid biphasic disappearance from the systemic circulation, with half-lives of $t_{1/2\alpha}$ 0.24 and $t_{1/2\beta}$ 1.87 hours, followed by a long elimination phase with a terminal elimination half-life of $t_{1/2\gamma}$ 146 hours. There was no accumulation of zoledronic acid in plasma after multiple doses given every 28 days. Zoledronic acid is not metabolised and is excreted unchanged via the kidney. Over the first 24 hours, $39 \pm 16\%$ 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 acid was high, as seen with other bisphosphonates.

No pharmacokinetic data for zoledronic acid are available in patients with hypercalcaemia or in patients with hepatic insufficiency. Zoledronic acid does not inhibit human P450 enzymes *in vitro*, shows no biotransformation and in animal studies < 3% of the administered dose was recovered in the faeces, suggesting no relevant role of liver function in the pharmacokinetics of zoledronic acid.

The renal clearance of zoledronic acid was correlated with creatinine clearance, renal clearance representing $75 \pm 33\%$ 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).

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.

Special populations

Paediatric patients

Limited pharmacokinetic data in children with severe osteogenesis imperfecta suggest that zoledronic acid pharmacokinetics in children aged 3 to 17 years are similar to those in adults at a similar mg/kg dose level. Age, body weight, gender and creatinine clearance appear to have no effect on zoledronic acid systemic exposure.

5.3 Preclinical safety data:

Acute toxicity

The highest nonlethal single intravenous dose was 10 mg/kg bodyweight in mice and 0.6 mg/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 2–3 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. Long-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 ≥ 0.2 mg/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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Mannitol

Sodium citrate

Water for Injection

6.2 Incompatibilities

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

This medicinal product must not be mixed with calcium or other divalent cation containing infusion solutions such as lactated Ringer's solution, and should be administered as a single intravenous solution in a separate infusion line.

6.3 Shelf-life

24 months from the date of manufacture.

Shelf-life of diluted product: From a microbiological point of view, the diluted solution for infusion should be used immediately. If not used immediately,

in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C when diluted with either 0.9% sodium chloride or 5% dextrose solutions.

6.4 Special precautions for storage

Store below 30°C. This medicinal product does not require any special storage conditions. For storage conditions of the reconstituted solution for infusion, see section 6.3.

6.5 Nature and contents of Container

Injection in a type I tubular, flint glass vial closed with a bromobutyl rubber stopper and flip off maroon red aluminium seal.

1 vial in a carton.

6.6 Instructions for use and disposal and other handling

Prior to administration, 5.0 mL concentrate from one vial or the volume of the concentrate withdrawn as required must be further diluted with 100 mL of calcium free infusion solution (0.9% w/v sodium chloride solution or 5% w/v glucose solution).

If refrigerated, the solution must be allowed to reach room temperature before administration. Any unused product or waste material should be disposed of in accordance with local requirements

7. REGISTRANT/MARKETING AUTHORIZATION HOLDER

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NAME AND ADDRESS OF THE MANUFACTURER

Mylan Laboratories Limited [Specialty Formulation Facility]

No.19A, Plot No.284-B/1,

Bommasandra – Jigani Link

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Anekal Taluk, Bangalore –

560 105.

8. MARKETING AUTHORIZATION NUMBER

H2022/CTD6816/12551

9.DATE OF FIRST AUTHORIZATION /RENEWAL OF THE AUTHORIZATION:

01 December 2022

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