SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zoledronic acid ADVAGEN solution for infusion 5mg/100ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial with 100 ml of solution contains 5 mg zoledronic acid (as monohydrate).

Each ml of the solution contains 0.05 mg zoledronic acid anhydrous (as monohydrate)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion

Clear and colourless solution.

pH: 5.50-7.00

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of osteoporosis

- in post-menopausal women
- in adult men

at increased risk of fracture, including those with a recent low-trauma hip fracture.

To prevent glucocorticoid-induced bone mineral density loss and to increase bone mineral density in post-menopausal women and men on long-term glucocorticoid use, who are at increased risk of fracture

Prevention of osteoporosis in post-menopausal women with increased risk of osteoporosis.

Treatment of Paget’s disease of the bone in adults.

4.2 Posology and method of administration

For the treatment of post-menopausal osteoporosis, osteoporosis in men and the prevention and treatment of osteoporosis associated with long-term systemic glucocorticoid therapy, the recommended dose is a single intravenous infusion of 5 mg Zoledronic Acid administered once a year.

In patients with a recent low-trauma hip fracture, it is recommended to give the Zoledronic Acid infusion two or more weeks after hip fracture repair (see section 5.1).

For the prevention of postmenopausal osteoporosis, the recommended regimen is a single intravenous infusion of 5 mg Zoledronic Acid. An annual assessment of the patient's risk of fracture and clinical response to treatment should guide the decision of when re-treatment should occur.

For the prevention of postmenopausal osteoporosis it is important that patients be adequately supplemented with calcium and vitamin D if dietary intake is inadequate (see section 4.4).

For the treatment of Paget's disease, Zoledronic Acid should be prescribed only by physicians with experience in treatment of Paget's disease of the bone. The recommended dose is a single intravenous infusion of 5 mg Zoledronic Acid. Retreatment of Paget's disease: After the initial treatment with Zoledronic Acid in Paget's disease, an extended remission period of 7.7 years as a mean was observed in responding patients. As Paget's disease of bone is a lifelong disease, re-treatment is likely to be needed. Re-treatment of Paget's disease of bone consists of an additional intravenous infusion of 5 mg Zoledronic Acid after an interval of one year or longer from initial treatment. Periodic assessment of the patient's serum alkaline phosphatase levels, e.g., every 6 to 12 months and clinical responses to treatment should guide the decision of when re-treatment should occur on an individual basis. In the absence of worsening of clinical symptoms (e.g. bone pain or compression symptoms) and/or bone scan consistent with relapse of Paget's disease of bone, a second intravenous infusion of Zoledronic Acid should not be administered earlier than 12 months following the initial treatment. No experience of retreatment more than once is available. (see section 5.1).

Zoledronic Acid (5 mg in 100 ml ready-to-infuse solution) is administered via a vented infusion line and given at a constant infusion rate. The infusion time must not be less than 15 minutes. For information on the infusion of Zoledronic Acid, see section 6.6.

Patients must be appropriately hydrated prior to administration of Zoledronic Acid. This is especially important for the elderly and for patients receiving diuretic therapy.

Adequate calcium and vitamin D intake are recommended in association with Zoledronic Acid administration. In addition, in patients with Paget's disease, it is strongly advised that adequate supplemental calcium corresponding to at least 500 mg elemental calcium twice daily is ensured for at least 10 days following Zoledronic Acid administration (see section 4.4).

In patients with a recent low-trauma hip fracture, a loading dose of 50,000 to 125,000 IU of vitamin D given orally or via the intramuscular route is recommended prior to the first Zoledronic Acid infusion.

The incidence of post-dose symptoms occurring within the first three days after administration of Zoledronic Acid can be reduced with the administration of paracetamol or ibuprofen shortly following Zoledronic Acid administration.

Patients with renal impairment (see section 4.4)

Use of Zoledronic Acid in patients with creatinine clearance < 35 ml/min is contraindicated.

No dose adjustment is necessary in patients with creatinine clearance ⩾ 35 ml/min.

Patients with hepatic impairment

No dose adjustment is required (see section 5.2).

Geriatric patients (65 years or above)

No dose adjustment is necessary since bioavailability, distribution and elimination were similar in elderly patients and younger subjects.

Children and adolescents

Zoledronic Acid is not recommended for use in children and adolescents below 18 years of age due to lack of data on safety and efficacy.

Duration of Treatment

The optimal duration of use of bisphosphonates for the treatment of osteoporosis has not been determined. All patients on Zoledronic Acid should be re-evaluated periodically for an optimal response to therapy and the need for continued treatment for a longer period, based on their response to treatment, fracture risk and comorbidities.

In the treatment of osteoporosis, patients at a low-risk for fracture should be considered for drug discontinuation after initial 3 years of treatment with Zoledronic Acid, while the high risk patients should consider continuing on regular therapy. Patients who discontinue therapy should have their risk for fracture re-evaluated periodically every 2-3 years and restart treatment if necessary.

4.3 Contraindications

- Hypersensitivity to the active substance, to any bisphosphonates or to any of the excipients listed in section 6.1.
- Patients with hypocalcaemia (see section 4.4).
- Severe renal impairment with creatinine clearance < 35 ml/min (see section 4.4)
- Pregnancy and breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Renal function

The use of Zoledronic Acid in patients with severe renal impairment (creatinine clearance < 35 ml/min) is contraindicated due to an increased risk of renal failure in this population.

Renal impairment has been observed following the administration of Zoledronic Acid (see section 4.8), especially in patients with pre-existing renal dysfunction or other risks including advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy (see section 4.5), or dehydration occurring after Zoledronic Acid administration. Renal impairment has been observed in patients after a single administration. Renal failure requiring dialysis or with a fatal outcome has rarely occurred in patients with underlying renal impairment or with any of the risk factors described above.

The following precautions should be taken into account to minimise the risk of renal adverse reactions:

- Creatinine clearance should be calculated based on actual body weight using the Cockcroft-Grault formula before each Zoledronic Acid dose.
- Transient increase in serum creatinine may be greater in patients with underlying impaired renal function.
- Monitoring of serum creatinine should be considered in at-risk patients.
- Zoledronic Acid should be used with caution when concomitantly used with other medicinal products that could impact renal function (see section 4.5).
- Patients, especially elderly patients and those receiving diuretic therapy, should be appropriately hydrated prior to administration of Zoledronic Acid.
- A single dose of Zoledronic Acid should not exceed 5 mg and the duration of infusion should be at least 15 minutes (see section 4.2).

Patients must be appropriately hydrated prior to administration of Zoledronic Acid. This is especially important in the elderly and for patients receiving diuretic therapy. Caution is indicated when Zoledronic Acid is administered in conjunction with medicinal products that can significantly impact renal function (e.g. aminoglycosides or diuretics that may cause dehydration), see section 4.5.

Hypocalcaemia

Pre-existing hypocalcaemia must be treated by adequate intake of calcium and vitamin D before initiating therapy with Zoledronic Acid (see section 4.3). Other disturbances of mineral metabolism must also be effectively treated (e.g. diminished parathyroid reserve, intestinal calcium malabsorption). Physicians should consider clinical monitoring for these patients.

Elevated bone turnover is a characteristic of Paget’s disease of the bone. Due to the rapid onset of effect of zoledronic acid on bone turnover, transient hypocalcaemia, sometimes symptomatic, may develop and is usually maximal within the first 10 days after infusion of Zoledronic Acid (see section 4.8).

Adequate calcium and vitamin D intake are recommended in association with Zoledronic Acid administration. In addition, in patients with Paget's disease, it is strongly advised that adequate supplemental calcium corresponding to at least 500 mg elemental calcium twice daily is ensured for at least 10 days following Zoledronic Acid administration (see section 4.2). Patients should be informed about symptoms of

hypocalcaemia and receive adequate clinical monitoring during the period of risk. Measurement of serum calcium before infusion of Zoledronic Acid is recommended for patients with Paget´s disease.

Severe and occasionally incapacitating bone, joint and/or muscle pain have been infrequently reported in patients taking bisphosphonates, including Zoledronic Acid (see section 4.8).

Osteonecrosis of the jaw (ONJ)

Osteonecrosis of the jaw has been reported predominantly in patients with cancer receiving treatment regimens including bisphosphonates, including zoledronic acid. Many of these patients were also receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in the post-marketing setting in patients receiving Zoledronic Acid for osteoporosis. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection including osteomyelitis. A dental examination with appropriate preventive dentistry and an individual benefit-risk assessment should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, anti-angiogenic drugs, corticosteroids, poor oral hygiene). During the treatment with zoledronic acid, it is prudent to maintain good oral hygiene, undergo routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling, non-healing of sores or discharge. While on treatment, these 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 firm data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. It is unclear whether bisphosphonate therapy should be continued or should be stopped until healing after the dental procedure is complete and hence the treating physician must carefully weigh the benefits and risks when considering drug treatment. The clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Osteonecrosis of other bones

Cases of osteonecrosis of other bones (including femur, hip, knee and humerus) have also been reported; however, causality has not been determined in the population treated with Zoledronic acid

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.

Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

Atypical femur fractures most commonly occur with minimal or no impact to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out a femur fracture. Subjects presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

General

The incidence of post-dose symptoms occurring within the first three days after administration of Zoledronic Acid can be reduced with the administration of paracetamol or ibuprofen shortly following Zoledronic Acid administration.

Other products containing zoledronic acid as an active substance are available for oncology indications. Patients being treated with Zoledronic acid should not be treated with such products or any other bisphosphonate concomitantly, since the combined effects of these agents are unknown.

This medicinal product contains less than 1 mmol sodium (23 mg) per 100 ml vial of Zoledronic acid, i.e. essentially “sodium free”.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies with other medicinal products have been performed. Zoledronic acid is not systemically metabolised and does not affect human cytochrome P450 enzymes *in vitro* (see section 5.2). Zoledronic acid is not highly bound to plasma proteins and interactions resulting from displacement of highly protein-bound drugs are therefore unlikely.

Zoledronic acid is eliminated by renal excretion. Caution is indicated when Zoledronic Acid is administered in conjunction with medicinal products that can significantly impact renal function (e.g. aminoglycosides or diuretics that may cause dehydration) (see section 4.4).

In patients with renal impairment, the systemic exposure to concomitant medicinal products that are primarily excreted via the kidney may increase.

4.6 Pregnancy, lactation, females and males of reproductive potential

Pregnancy

Risk Summary

Zoledronic acid is contraindicated during pregnancy (see section 4.3). Studies in rats with zoledronic acid have shown reproductive toxicological effects including malformations. The potential risk for humans is unknown.

There is a theoretical risk of fetal 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 have not been established (See section 4.3 and section 5.3).

Data

Human Data

There are no data on the use of zoledronic acid in pregnant women.

Animal Data

Teratogenicity studies were performed in two species, both via subcutaneous administration of zoledronic acid. In rats, teratogenicity was observed at doses $\geqslant$0.2 mg/kg/day (2.4 fold, the anticipated human exposure, based on AUC comparison) and was manifested by external, visceral and skeletal malformations. Dystocia was observed at the lowest dose (0.01 mg/kg/day) tested in rats.

In rabbits, no teratogenic or embryo/fetal effects were observed, although maternal toxicity was marked at 0.1 mg/kg/day . Adverse maternal effects were associated with, and may have been caused by, drug-induced hypocalcemia.

Lactation

Risk Summary

Zoledronic acid is contraindicated in breast-feeding women (see section 4.3).

Females and males of reproductive potential

Women of child-bearing potential should be advised to avoid becoming pregnant while receiving Zoledronic acid.

Infertility

The fertility was decreased in rats dosed subcutaneously with 0.1 mg/kg/day of zoledronic acid. There are no data available in humans.

4.7 Effects on ability to drive and use machines

Adverse reactions, such as dizziness, may affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The overall percentage of patients who experienced adverse reactions were 44.7%, 16.7% and 10.2% after the first, second and third infusion, respectively. Incidence of individual adverse reactions following the first infusion was: fever (17.1%), myalgia (7.8%), influenza-like illness (6.7%), arthralgia (4.8%) and headache (5.1%). The incidence of these reactions decreased markedly with subsequent annual doses of Zoledronic Acid. The majority of these reactions occur within the first three days following Zoledronic Acid administration. The majority of these reactions were mild to moderate and resolved within three days of the event onset. The percentage of patients who experienced adverse reactions was lower in a smaller study (19.5%, 10.4%, 10.7% after the first, second and third infusion, respectively), where prophylaxis against adverse reactions was used.

The incidence of post-dose symptoms occurring within the first three days after administration of Zoledronic acid can be reduced with the administration of paracetamol or ibuprofen shortly following Zoledronic acid administration as needed. (see section 4.2).

In the HORIZON – Pivotal Fracture Trial [PFT] (see section 5.1), 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 and placebo, respectively. The rate of atrial fibrillation serious adverse events was increased in patients receiving Zoledronic acid (1.3%) (51 out of 3,862) compared with patients receiving placebo (0.6%) (22 out of 3,852). The mechanism behind the increased incidence of atrial fibrillation is unknown. In the osteoporosis trials (PFT, HORIZON - Recurrent Fracture Trial [RFT]) the pooled atrial fibrillation incidences were comparable between Zoledronic acid (2.6%) and placebo (2.1%). For atrial fibrillation serious adverse events the pooled incidences were 1.3% for Zoledronic acid and 0.8% for placebo.

Tabulated list of adverse reactions

Adverse reactions in Table 1 are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1

Infections and infestations	*Uncommon*	Influenza, nasopharyngitis
Blood and lymphatic system disorders	*Uncommon*	Anaemia
Immune system disorders	*Not known***	Hypersensitivity reactions including rare cases of bronchospasm, urticaria and angioedema, and very rare cases of

		anaphylactic reaction/shock
Metabolism and nutrition disorders	*Common* *Uncommon* *Rare*	Hypocalcaemia* Decreased appetite*** Hypophosphataemia
Psychiatric disorders	*Uncommon*	Insomnia
Nervous system disorders	*Common* *Uncommon*	Headache, dizziness Lethargy***, paraesthesia, somnolence, tremor, syncope, dysgeusia
Eye disorders	*Common* *Uncommon* *Rare* *Not known***	Ocular hyperaemia Conjunctivitis, eye pain Uveitis***, episcleritis, iritis Scleritis and parophthalmia
Ear and labyrinth disorders	*Uncommon*	Vertigo
Cardiac disorders	*Common* *Uncommon*	Atrial fibrillation Palpitations
Vascular disorders	*Uncommon* *Not known***	Hypertension, flushing Hypotension (some of the patients had underlying risk factors)
Respiratory, thoracic and mediastinal disorders	*Uncommon*	Cough, dyspnoea***
Gastrointestinal disorders	*Common* *Uncommon*	Nausea, vomiting, diarrhoea Dyspepsia***, abdominal pain upper, abdominal pain***, gastroesophageal reflux disease, constipation, dry mouth, oesophagitis***, toothache, gastritis[#]
Skin and subcutaneous tissue disorders	*Uncommon*	Rash, hyperhydrosis***, pruritus, erythema
Musculoskeletal and connective tissue disorders	*Common* *Uncommon* *Rare* *Very rare*	Myalgia***, arthralgia***, bone pain, back pain, pain in extremity Neck pain, musculoskeletal stiffness***, joint swelling***, muscle spasms, shoulder pain, musculoskeletal chest pain***, musculoskeletal pain, joint stiffness***, arthritis, muscular weakness Atypical subtrochanteric and diaphyseal femoral fractures[+] (bisphosphonate class adverse reaction) Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction) Osteonecrosis of the jaw (see sections

	*Not known***	4.4 and 4.8 Class effects)
Renal and urinary disorders	*Uncommon* *Not known***	Blood creatinine increased, pollakiuria, proteinuria Renal impairment. Rare cases of renal failure requiring dialysis and rare cases with a fatal outcome have been reported in patients with pre-existing renal dysfunction or other risk factors such as advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy, or dehydration in the post infusion period (see sections 4.4 and 4.8 Class effects)
General disorders and administration site conditions	*Very common* *Common* *Uncommon* *Not known***	Pyrexia Influenza-like illness, chills, fatigue***, asthenia, pain***, malaise, infusion site reaction Peripheral oedema, thirst***, acute phase reaction***, non-cardiac chest pain Dehydration secondary to post-dose symptoms such as pyrexia, vomiting and diarrhoea
Investigations	*Common* *Uncommon*	C-reactive protein increased Blood calcium decreased

#Observed in patients taking concomitant glucocorticosteroids.

*Common in Paget's disease only.

**Based on post-marketing reports. Frequency cannot be estimated from available data.

+Identified in post-marketing experience

*** Adverse reactions reported most frequently in the individual studies are: Very common: myalgia, arthralgia, fatigue, pain Common: lethargy, dyspnoea, dyspepsia, oesphagitis, abdominal pain, hyperhidrosis, musculoskeletal (muscle) stiffness, joint swelling, musculoskeletal chest pain, joint stiffness, decreased appetite, thirst, acute phase reaction Uncommon: uveitis

Table 2. Additional adverse reactions which were reported in the individual studies but with a lower frequency in the Zoledronic Acid group compared with that of the placebo group

Cardiac disorders:	Atrial fibrillation*, palpitations
Eye disorders:	Ocular hyperaemia
Gastrointestinal disorders:	Gastritis, toothache
General disorders and administration site conditions:	Infusion site reaction

Investigations:	C-reactive protein increased
Metabolism and nutrition disorders:	Hypocalcaemia
Nervous system disorders:	Dysgeusia

*see below 'atrial fibrillation' subsection in 'description of selected adverse reactions' section.

Prevention of postmenopausal osteoporosis

The overall safety and tolerability profile of Zoledronic acid in the prevention of osteoporosis was comparable to the adverse reaction profile reported in the Zoledronic acid postmenopausal osteoporosis treatment trial, however there was a higher incidence of post-dose symptoms in the Zoledronic acid treated osteopenic patients that occurred within 3 days after infusion: pain, fever, chills, myalgia, nausea, headache, fatigue, dizziness, and arthralgia. The majority of these symptoms were mild to moderate and resolved within 3 days of the reaction onset. The incidence of these symptoms decreased with a subsequent dose of Zoledronic acid. Adverse drug reactions suspected (investigator assessment) to be associated with Zoledronic acid treatment in prevention of postmenopausal osteoporosis which occurred more than once and which are either not included in Table 1 or reported with a higher frequency in the prevention of postmenopausal osteoporosis trial are summarised in Table 3 using the following convention: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100).

Table 3. Suspected adverse drug reactions to Zoledronic acid (investigator assessment) in prevention of postmenopausal osteoporosis. The adverse reactions listed are either in addition to or reported with a higher frequency than those in Table 1

Metabolism and nutrition disorders	*Common*	Decreased appetite
Psychatric disorders	*Uncommon*	Anxiety
Nervous system disorders	*Very common*	Headache
	Common	Tremor, lethargy
	Uncommon	Hypoaesthesia, dysgeusia
Eye disorders	*Common*	Conjunctivitis, eye pain, iritis
	Uncommon	Vision blurred
Gastrointestinal disorders	*Very common*	Nausea
	Common	Abdominal pain, abdominal pain upper, constipation
Skin and subcutaneous tissue disorders	*Common*	Night sweats
Musculoskeletal and connective tissue disorders	*Very common*	Myalgia
	Common	Musculoskeletal pain, muscle spasms, musculoskeletal chest pain, pain in jaw, neck pain

	Uncommon	Flank pain
General disorders and administration site conditions	*Very common*	Pain, chills
	Common	Peripheral oedema, infusion related reaction, non-cardiac chest pain

Description of selected adverse reactions.

Renal impairment

Zoledronic acid has been associated with renal impairment manifested as deterioration in renal function (i.e. increased serum creatinine) and in rare cases acute renal failure. Renal impairment has been observed following the administration of zoledronic acid, especially in patients with pre-existing renal impairment or additional risk factors (e.g advanced age, oncology patients with chemotherapy, concomitant nephrotoxic medicinal products, concomitant diuretic therapy, severe dehydration), with the majority of them receiving a 4 mg dose every 3–4 weeks, but it has been observed in patients after a single administration.

In the HORIZON-PFT core trial, the change in creatinine clearance (measured annually prior to dosing) and the incidence of renal failure and impairment was comparable for both the Zoledronic acid and placebo treatment groups over three years. There was a transient increase in serum creatinine observed within 10 days in 1.8% of Zoledronic acid-treated patients versus 0.8% of placebo-treated patients.

In the prevention of postmenopausal osteoporosis trial, the change in creatinine clearance (measured annually prior to dosing and at one month after the first dose) and the incidence of renal failure and impairment were comparable in the Zoledronic acid and placebo groups.

In the 3-year HORIZON-PFT extension trial, 2.9% of the patients who continued to receive Zoledronic acid (i.e. 6-years total exposure to Zoledronic acid) vs. 0.65 % of the patients who discontinued (i.e. 3-years Zoledronic acid in the core then 3-years placebo in the extension trial) had transient increases in serum creatinine. However, the mean change from baseline in serum creatinine over time was <0.5 micromol/L for both treatment groups at the end of the trial (i.e. +0.4 and -0.26 micromol/L for both treatments, respectively).

Hypocalcemia

In the HORIZON-PFT core trial, approximately 0.2% of patients had notable declines of serum calcium levels (less than 1.87 mmol/l) following Zoledronic acid administration. No symptomatic cases of hypocalcemia were observed.

In the HORIZON-PFT extension trial, 0.4 % of patients who received placebo during the core trial and Zoledronic acid during the extension trial had confirmed events of hypocalcaemia (see section CLINICAL STUDIES). There were no confirmed hypocalcaemia events in the other treatment groups. All of the cases were asymptomatic, no treatment or intervention was required.

In the Paget's disease trials, symptomatic hypocalcemia was observed in approximately 1% of patients, in all of whom it resolved.

Based on laboratory assessment, transient asymptomatic calcium levels below the normal reference range (less than 2.10 mmol/l) occurred in 2.3% of Zoledronic acid-treated patients in a large clinical trial compared to 21% of Zoledronic acid-treated

patients in the Paget's disease trials. The frequency of hypocalcemia was much lower following subsequent infusions. In the prevention of postmenopausal osteoporosis trial there was one patient who had treatment emergent serum calcium levels below 1.87 mmol/L.

All patients received adequate supplementation with vitamin D and calcium in the post-menopausal osteoporosis trial, the prevention of clinical fractures after hip fracture trial, and the Paget's disease trials (see also section 4.2). In the trial for the prevention of clinical fractures following a recent hip fracture, vitamin D levels were not routinely measured but the majority of patients received a loading dose of vitamin D prior to Zoledronic acid administration (see section 4.2).

Local reactions

In a large clinical trial, local reactions at the infusion site, such as redness, swelling and/or pain, were reported (0.7%) following the administration of zoledronic acid. In the prevention of postmenopausal osteoporosis trial, the event rate was 1.1% in Zoledronic acid treated patients compared to 2.0% in placebo treated patients

Osteonecrosis of the jaw

Uncommonly, cases of osteonecrosis (primarily of the jaw) have been reported, predominantly in cancer patients treated with bisphosphonates, including zoledronic acid. Many of these patients 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 jaw 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. anemia, coagulopathies, infection, pre-existing dental disease). Although causality has not been determined, it is prudent to avoid dental surgery as recovery may be prolonged (see section 4.4). In the HORIZON-PFT core trial in 7,736 intention-to-treat (ITT) patients, osteonecrosis of the jaw has been reported in one patient treated with Zoledronic acid and one patient treated with placebo. Both cases resolved.

In the HORIZON-PFT extension trial in 2,456 ITT patients, there were two confirmed cases of ONJ, one in the group of patients receiving Zoledronic acid during the core and the extension trial (i.e. 6-years total exposure to Zoledronic acid) and one in the group of patients receiving placebo in the core and Zoledronic acid in the extension trial (i.e. 3-years of exposure to Zoledronic acid). Both patients had a history of poor dental hygiene and both made a complete recovery.

Atrial fibrillation

In one 3 year trial in postmenopausal women with osteoporosis (Horizon PFT), the overall incidence of all atrial fibrillation adverse events was 2.5% (96 out of 3,862) in the Zoledronic acid group vs. 1.9% (75 out of 3,852) in the placebo group. The rate of atrial fibrillation serious adverse events was 1.3% (51 out of 3,862) in patients receiving Zoledronic acid compared with 0.6% (22 out of 3,852) in patients receiving placebo. The mechanism behind the increased incidence of atrial fibrillation is unknown. The imbalance observed in this trial has not been observed in other clinical trials with zoledronic acid.

In the HORIZON-PFT extension trial, the incidence of atrial fibrillation adverse events was 3.4% (21 out of 613) in the group of patients who received Zoledronic acid in the core and extension trial (i.e. 6-years of total exposure to Zoledronic acid)

vs. 2.1% (13 out of 616) in patients who received Zoledronic acid in the core (i.e. 3-years exposure) and placebo in the extension trial. The rate of atrial fibrillation serious adverse events was 2% (12 out of 613) in patients who received 6-years Zoledronic acid compared with 1.1% (7 out of 616) in patients who received 3-years of Zoledronic acid followed by 3-years of placebo. These imbalances were not statistically significant.

Adverse drug reactions from post-marketing spontaneous reports

The following adverse drug reactions have been derived from 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, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 4. Adverse drug reactions from spontaneous reports and literature (frequency not known)

Eye disorders:
Scleritis, parophthalmia
Immune system disorders:
Hypersensitivity reactions including anaphylactic reaction, anaphylactic shock, angioedema, bronchospasm, urticaria
Metabolism and nutrition disorders:
Dehydration secondary to post-dose symptoms such as pyrexia, vomiting and diarrhea; hypotension in patients with underlying risk factors, hypophosphataemia
Musculoskeletal and connective tissue disorders:
Osteonecrosis of jaw (see section 4.4)
Renal and urinary disorders:
Renal failure requiring dialysis or with fatal outcome*, renal impairment (see section 4.4)
*especially in patients with pre-existing renal impairment or other risk factors such as advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy, or dehydration in the post infusion period.

4.9 Overdose

Clinical experience with acute overdose is limited. Patients who have received doses higher than those recommended should be carefully monitored. In the event of overdose leading to clinically significant hypocalcaemia, reversal may be achieved with supplemental oral calcium and/or an intravenous infusion of calcium gluconate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Zoledronic acid belongs to the class of nitrogen-containing bisphosphonates and acts primarily on bone. It is an inhibitor of osteoclast-mediated bone resorption.

Pharmacodynamic effects

The selective action of bisphosphonates on bone is based on their high affinity for mineralised bone.

The main molecular target of zoledronic acid in the osteoclast is the enzyme farnesyl pyrophosphate synthase. The long duration of action of zoledronic acid is attributable to its high binding affinity for the active site of farnesyl pyrophosphate (FPP) synthase and its strong binding affinity to bone mineral.

Zoledronic Acid treatment rapidly reduced the rate of bone turnover from elevated post-menopausal levels with the nadir for resorption markers observed at 7 days, and for formation markers at 12 weeks. Thereafter bone markers stabilised within the pre-menopausal range. There was no progressive reduction of bone turnover markers with repeated annual dosing.

Clinical efficacy in the treatment of post-menopausal osteoporosis (PFT)

Core study (HORIZON-PFT): In a randomized, double-blind, placebo-control trial, Zoledronic acid significantly decreased the risk of one or more new/worsening vertebral fractures at 1 year (58%), 2 years (68%) and 3 years (67%) (all $p<0.0001$) and also the risk of at least one new moderate or severe vertebral fracture at 1 year (60%), 2 years (71%) and 3 years (70%) (all $p<0.0001$) .Zoledronic acid treatment also reduced the risk of hip fracture by 40% over 3 years ($p=0.003$). Furthermore, Zoledronic acid treatment had beneficial effects on all clinical fractures, bone mineral density, bone histology, bone turnover markers, height, and disability.

Extension study: In a three year extension study in which subjects initially treated with three infusions of Zoledronic acid were randomized to placebo or Zoledronic acid treatment, three additional annual Zoledronic acid infusions compared to placebo significantly ($p<0.05$) reduced the risk of new morphometric vertebral fracture (3.0% vs. 6.2%) and new/worsening morphometric vertebral fracture (3.4% vs. 7.0%).

Clinical efficacy in the treatment of osteoporosis in patients at increased risk of fracture after a recent hip fracture (RFT)

In male and female patients with a recent low-trauma hip fracture, treatment with Zoledronic acid significantly reduced the incidence of any clinical fracture by 35%; 46% reduction in the risk of a clinical vertebral fracture, 27% reduction in the risk for non-vertebral fractures. The study was not designed to measure significant differences in hip fracture, but a 30% reduced risk for a subsequent hip fracture was seen. Zoledronic acid treatment significantly increased BMD relative to placebo at the hip and femoral neck (12, 24, and 36 month time points).

Clinical efficacy in men

In one randomized active-control study an annual infusion of Zoledronic acid was similar to weekly alendronate for the percentage change in lumbar spine BMD at month 12 and non-inferior at month 24 relative to baseline.

Clinical efficacy in osteoporosis associated with long-term systemic glucocorticoid therapy

In a randomized, active-control trial in patients with glucocorticoid-induced osteoporosis, increases in BMD were significantly greater in the Zoledronic acid treated group (treatment population) at all sites, which included the lumbar spine, femoral neck, total hip, trochanter, and distal radius at 12 months compared to risedronate 5 mg daily (all $p<0.03$).

Clinical efficacy in the treatment of Paget's disease of the bone

In two 6-month randomized comparative, well-controlled clinical trials, in patients with Paget's disease, Zoledronic acid demonstrated a superior and more rapid response in serum alkaline phosphatase compared with risedronate. In addition, more Zoledronic acid-treated patients demonstrated normalization of bone turnover as reflected in biochemical markers of bone formation and resorption compared with risedronate treated patients.

Clinical trial results for the prevention of postmenopausal osteoporosis

In a randomized, double-blind, placebo-control trial in women with postmenopausal osteoporosis, Zoledronic acid significantly increased lumbar spine BMD relative to placebo at Month 24. Zoledronic acid administered annually for two years or as a single dose both significantly increased total hip BMD relative to placebo at Month 24 (all $p <0.0001$).

5.2 Pharmacokinetic properties

Single and multiple 5 and 15-minute infusions of 2, 4, 8 and 16 mg zoledronic acid in 64 patients yielded the following pharmacokinetic data, which were found to be dose independent. Pharmacokinetic data in patients with osteoporosis and Paget's disease of bone are not available.

Distribution

After initiation of the zoledronic acid infusion, plasma concentrations of the active substance increased rapidly, 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 levels.

Elimination

Intravenously administered zoledronic acid is eliminated by 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 the active substance in plasma after multiple doses given every 28 days. The early disposition phases (α and β, with $t_{½}$ values above) presumably represent rapid uptake into bone and excretion via the kidneys.

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. This uptake into bone is common for all bisphosphonates and is presumably a consequence of the structural analogy to pyrophosphate. As with other bisphosphonates, the retention time of zoledronic acid in bones is very long. 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 or body weight. The inter- and intra-subject variation for plasma clearance of zoledronic acid was shown to be 36% and 34%, respectively. 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.

Pharmacokinetic/pharmacodynamics relationships

No interaction studies with other medicinal products have been performed with zoledronic acid. Since zoledronic acid is not metabolised in humans and the substance was found to have little or no capacity as a direct-acting and/or irreversible metabolism-dependent inhibitor of P450 enzymes, zoledronic acid is unlikely to reduce the metabolic clearance of substances which are metabolised via the cytochrome P450 enzyme systems. Zoledronic acid is not highly bound to plasma proteins (approximately 43-55% bound) and binding is concentration independent. Therefore, interactions resulting from displacement of highly protein-bound drugs are unlikely.

Special populations (see section 4.2)

Renal impairment

The renal clearance of zoledronic acid was 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 patients studied. Small observed increases in $AUC_{(0\text{-}24hr)}$, by about 30% to 40% in mild to moderate renal impairment, compared to a patient with normal renal function, and lack of accumulation of drug

with multiple doses irrespective of renal function, suggest that dose adjustments of zoledronic acid in mild (Cl_{cr} = 50–80 ml/min) and moderate renal impairment down to a creatinine clearance of 35 ml/min are not necessary. The use of Zoledronic Acid in patients with severe renal impairment (creatinine clearance < 35 ml/min) is contraindicated due to an increased risk of renal failure in this population.

5.3 Preclinical safety data

Acute toxicity

The highest non-lethal single intravenous dose was 10 mg/kg body weight in mice and 0.6 mg/kg in rats. In the single-dose dog infusion studies, 1.0 mg/kg (6 fold the recommended human therapeutic exposure based on AUC) administered over 15 minutes was well tolerated with no renal effects.

Subchronic and chronic toxicity

In the intravenous infusion studies, renal tolerability of zoledronic acid was established in rats when given 0.6 mg/kg as 15-minute infusions at 3-day intervals, six times in total (for a cumulative dose that corresponded to AUC levels about 6 times the human therapeutic exposure) while five 15-minute infusions of 0.25 mg/kg administered at 2–3-week intervals (a cumulative dose that corresponded to 7 times the human therapeutic exposure) were well tolerated in dogs. In the intravenous bolus studies, the doses that were well-tolerated decreased with increasing study duration: 0.2 and 0.02 mg/kg daily was well tolerated for 4 weeks in rats and dogs, respectively but only 0.01 mg/kg and 0.005 mg/kg in rats and dogs, respectively, when given for 52 weeks.

Longer-term repeat administration at cumulative exposures sufficiently exceeding the maximum intended human exposure produced toxicological effects in other organs, including the gastrointestinal tract and liver, and at the site of intravenous administration. The clinical relevance of these findings is unknown. The most frequent finding in the 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.

Reproduction toxicity

Teratology studies were performed in two species, both via subcutaneous administration. Teratogenicity was observed in rats at doses ≥ 0.2 mg/kg and was manifested by external, visceral and skeletal malformations. Dystocia was observed at the lowest dose (0.01 mg/kg body weight) tested in rats. No teratological or embryo/foetal effects were observed in rabbits, although maternal toxicity was marked at 0.1 mg/kg due to decreased serum calcium levels.

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 injections

6.2 Incompatibilities

This medicinal product must not be allowed to come into contact with any calcium-containing solutions. Zoledronic Acid must not be mixed or given intravenously with any other medicinal products.

6.3 Shelf life

Unopened vials: 3 years

After opening:

Chemical and physical stability has been demonstrated for 24 hours at 2°C - 8°C and at 30°C.

From a microbiological point of view, the 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°C - 8°C. The refrigerated solution should then be equilibrated to room temperature prior to administration.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

100 ml solution is packed in clear glass vials with Type I rubber stoppers and sealed with aluminum polypropylene flip off seals.

Zoledronic Acid 5mg/100ml solution for infusions is supplied in:

1 vial

4 vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only.

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

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

If refrigerated, allow the refrigerated solution to reach room temperature before administration.

Aseptic techniques must be followed during the preparation of the infusion.

7 PRODUCT OWNER

ADVAGEN Pte Ltd

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Ubi Techpark

Singapore 408564

8 DATE OF REVISION OF THE TEXT

12/01/2023