

Aclasta®

Bisphosphonate

DESCRIPTION AND COMPOSITION**Pharmaceutical form**

Solution for infusion.

The solution is sterile, clear and colourless.

Active substance

One bottle with 100 mL solution contains 5 mg zoledronic acid (anhydrous), corresponding to 5.330 mg zoledronic acid monohydrate.

Active moiety

Zoledronic acid (anhydrous).

Excipients

Mannitol, sodium citrate, water for injection.

Pharmaceutical formulations may vary between countries.

INDICATIONS

- ❖ Treatment of osteoporosis:
 - in postmenopausal women to reduce the incidence of hip, vertebral and non-vertebral fractures,
 - in men
at increased risk of fracture, including those with a recent low-trauma hip fracture.
- ❖ Treatment and prevention of osteoporosis associated with long-term systemic glucocorticoid therapy in post-menopausal women and in men at increased risk of fracture.
- ❖ Prevention of osteoporosis in post-menopausal women at increased risk of fracture.
- ❖ Treatment of Paget's disease of bone.

DOSAGE AND ADMINISTRATION

For the treatment of postmenopausal osteoporosis and osteoporosis in men, the recommended dose is a single intravenous infusion of 5 mg infusion of Aclasta administered once a year.

For the treatment and prevention of glucocorticoid-induced osteoporosis in women and men, the recommended dose is a single intravenous infusion of 5 mg infusion of Aclasta administered once a year.

In patients with a recent low-trauma hip fracture, it is recommended to give Aclasta infusion two or more weeks after hip fracture repair. 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 Aclasta infusion.

For the prevention of osteoporosis in postmenopausal women, the recommended dose is a single intravenous infusion of 5mg Aclasta administered once every 2 years.

For the treatment of Paget's disease the recommended dose is a single intravenous infusion of 5 mg Aclasta.

Retreatment of Paget's disease: Specific retreatment data are not available. After a single treatment with Aclasta in Paget's disease, an extended remission period is observed in responding patients.

Aclasta (5 mg in 100 mL ready to infuse solution) is administered intravenously via a vented infusion line, given at a constant infusion rate. The infusion time must not be less than 15 minutes.

Patients must be appropriately hydrated prior to administration of Aclasta. This is especially important for patients receiving diuretic therapy.

Adequate calcium and vitamin D intake is important in patients with osteoporosis if dietary intake is inadequate.

Elevated bone turnover is a characteristic of Paget's disease of bone. It is strongly advised that patients with Paget's disease receive the recommended daily allowance of supplemental calcium and vitamin D and this should be ensured during the initial 10 days following Aclasta administration.

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

Special populations

Patients with renal impairment

The use of Aclasta in patients with creatinine clearance <35 mL/min is contraindicated (see section CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS). No dose adjustment is necessary in patients with creatinine clearance ≥35 mL/min.

Patients with hepatic impairment

No dose adjustment is required (see section Pharmacokinetics).

Geriatric patients (≥65 years or above)

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

Pediatric patients

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

For information on the instructions for use and handling of Aclasta, see section INSTRUCTIONS FOR USE AND HANDLING.

CONTRAINDICATIONS

- Hypocalcaemia (see section WARNINGS AND PRECAUTIONS).
- Severe renal impairment with creatinine clearance <35 mL/min (see section WARNINGS AND PRECAUTIONS).
- Pregnancy and breast-feeding women (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL).
- Hypersensitivity to the active substance or to any of the excipients or to any bisphosphonates.

WARNINGS AND PRECAUTIONS

General

The dose of 5 mg zoledronic acid must be administered over at least 15 minutes.

Aclasta contains the same active ingredient found in Zometa (zoledronic acid), used for oncology indications, and a patient being treated with Zometa should not be treated with Aclasta.

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

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

Renal impairment

The use of Aclasta 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 Aclasta (see section ADVERSE DRUG REACTIONS, post marketing spontaneous reports), especially in patients with pre-existing renal impairment or other risk factors including advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy (see section INTERACTIONS), or dehydration occurring after Aclasta 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 minimize the risk of renal adverse reactions:

- Creatinine clearance should be calculated (e.g. Cockcroft-Gault formula) before each Aclasta dose. Transient increase in serum creatinine may be greater in patients with

underlying impaired renal function; interim monitoring of serum creatinine should be considered in at-risk patients.

- Aclasta should be used with caution when concomitantly used with other medicinal products that could impact renal function (see section INTERACTIONS).
- Patients, especially elderly patients and those receiving diuretic therapy, should be appropriately hydrated prior to administration of Aclasta.
- A single dose of Aclasta should not exceed 5 mg and the duration of infusion should not be less than 15 minutes (see section DOSAGE AND ADMINISTRATION).

Calcium and Vitamin D Supplementation

Treatment and prevention of Osteoporosis

Adequate supplemental calcium and vitamin D intake is important in men and women with osteoporosis or treated to prevent postmenopausal osteoporosis if dietary intake is inadequate.

Prevention of Clinical Fractures after a Hip Fracture

Supplemental calcium and vitamin D intake is recommended for patients treated to prevent clinical fractures after a hip fracture.

Treatment of Paget's disease of bone

Elevated bone turnover is a characteristic of Paget's disease of 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 Aclasta (see section ADVERSE DRUG REACTIONS). Adequate vitamin D intake is recommended in association with Aclasta administration. In addition, it is strongly advised that adequate supplemental calcium corresponding to at least 500 mg elemental calcium twice daily is ensured in patients with Paget's disease for at least 10 days following Aclasta administration. Patients should be informed about symptoms of hypocalcaemia. Physicians should consider clinical monitoring for patients at risk.

Musculoskeletal pain

Severe and occasionally incapacitating bone, joint, and/or muscle pain have been infrequently reported in patients taking bisphosphonates, including Aclasta.

Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ): Osteonecrosis of the jaw has been reported predominantly in cancer patients treated with bisphosphonates, including zoledronic acid. Many of these patients were also receiving chemotherapy and corticosteroids. 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 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 treatment with zoledronic acid, it is prudent to maintain good oral hygiene, undergo routine dental check-ups, and immediately report any oral symptoms. 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 data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. 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 Aclasta.

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 fractures of the femur

Atypical subtrochanteric and diaphyseal femoral fractures have been reported in association 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 weeks to months before 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 an individual benefit risk assessment. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

During bisphosphonate treatment, including Aclasta, patients should be advised to report any thigh, hip or groin pain and any patient with such symptoms should be evaluated for possible femur fracture.

ADVERSE DRUG REACTIONS

Summary of the safety profile

The presented adverse reactions in this section have been derived from different studies in the clinical program (see section CLINICAL STUDIES).

Aclasta was studied in:

- Postmenopausal osteoporosis - in the pivotal fracture trial, a randomized, double-blind, placebo-controlled, multinational study (HORIZON-PFT) including 7,736 women and its extension study including 2,456 women:

- Paget's disease - in two double blind, randomized safety and efficacy trials involving 357 patients;
- Prevention of clinical fractures in patients who suffered from a recent low-trauma hip fracture was demonstrated in a randomized, double-blind, placebo-controlled, multinational endpoint study (HORIZON-RFT) of 2,127 men and women.
- Treatment and prevention of glucocorticoid-induced osteoporosis in a randomized, multicentre, double-blind, stratified, active-controlled study of 833 men and women.
- Men with osteoporosis or significant osteoporosis secondary to hypogonadism in a randomized, multicentre, double-blind, active-controlled study of 302 men.
- Prevention of bone loss in postmenopausal women with osteopenia in a 2-year randomized, multi-center, double-blind, placebo-controlled study of 581 postmenopausal women.

Treatment of postmenopausal osteoporosis, osteoporosis in men, prevention of clinical fractures after low trauma hip fracture, treatment and prevention of glucocorticoid-induced osteoporosis and Paget's disease of the bone

In the studies to support the indications treatment of osteoporosis in men and postmenopausal women, prevention of clinical fractures after low trauma hip fracture, treatment and prevention of glucocorticoid-induced osteoporosis and Paget's disease of the bone, there were no significant differences in the overall incidence of serious adverse events compared to placebo or comparator and most adverse events were mild to moderate. Aclasta was administered once a year in all aforementioned studies.

Consistent with the intravenous administration of bisphosphonates, Aclasta has been most commonly associated with the following post-dose symptoms (frequencies derived from the study in treatment of postmenopausal osteoporosis: fever (18.1%), myalgia (9.4%), flu-like symptoms (7.8%), arthralgia (6.8%) and headache (6.5%), the majority of which occur within the first 3 days following Aclasta administration. The majority of these symptoms were mild to moderate in nature and resolved within 3 days of the event onset. The incidence of these symptoms decreased markedly with subsequent annual doses of Aclasta.

The incidence of post-dose symptoms occurring within the first 3 days after administration of Aclasta, can be reduced by approximately 50% with the administration of paracetamol or ibuprofen shortly following Aclasta administration as needed.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 1) are listed according to system organ classes in MedDRA. These are suspected adverse reactions to Aclasta (investigator assessment) in the pooled studies supporting the indications: treatment of osteoporosis in men and postmenopausal women, prevention of clinical fractures after low trauma hip fracture, treatment and prevention of glucocorticoid-induced osteoporosis and Paget's disease of the bone. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency using the following convention (CIOMS III) is also provided for each adverse drug reaction: very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1,000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1,000$), very rare ($< 1/10,000$), including isolated reports.

Table 1 Suspected adverse reactions to Aclasta (investigator assessment) in clinical trials

Infections and infestations	
Uncommon:	Influenza, nasopharyngitis
Blood and lymphatic system disorders	
Uncommon:	Anaemia
Metabolism and nutrition disorders	
Uncommon:	Decreased appetite*
Psychiatric disorders	
Uncommon:	Insomnia
Nervous system disorders	
Common:	Headache, dizziness
Uncommon:	Lethargy*, paraesthesia, somnolence, tremor, syncope
Eye disorders	
Uncommon:	Conjunctivitis, eye pain
Rare:	Uveitis*, episcleritis, iritis
Ear and labyrinth disorders	
Uncommon:	Vertigo
Vascular disorders	
Uncommon:	Hypertension, flushing
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Cough, dyspnoea*
Gastrointestinal disorders	
Common:	Nausea, vomiting, diarrhoea
Uncommon:	Dyspepsia*, abdominal pain upper, abdominal pain*, gastroesophageal reflux disease, constipation, dry mouth, oesophagitis*
Skin and subcutaneous tissue disorders	
Uncommon:	Rash, hyperhidrosis*, pruritus, erythema
Musculoskeletal and connective tissue disorders	
Common:	Myalgia*, arthralgia*, bone pain, back pain, pain in extremity
Uncommon:	Neck pain, musculoskeletal stiffness*, joint swelling*, muscle spasms, musculoskeletal chest pain*, musculoskeletal pain, joint stiffness*, arthritis, muscular weakness
Very rare:	Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction).
Renal and urinary disorders	
Uncommon:	Blood creatinine increased, pollakiuria, proteinuria
General disorders and administration site conditions	
Very common:	Pyrexia
Common:	Influenza-like illness, chills, fatigue*, asthenia, pain*, malaise
Uncommon:	Peripheral oedema, thirst*, acute phase reaction*, non-cardiac chest pain

* Adverse reactions reported most frequently in the individual studies are: *Very common*: myalgia, arthralgia, fatigue, pain *Common*: lethargy, dyspnoea, dyspepsia, esophagitis, 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 Aclasta 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 Aclasta in the prevention of osteoporosis was comparable to the adverse reaction profile reported in the Aclasta postmenopausal osteoporosis treatment trial, however there was a higher incidence of post-dose symptoms in the Aclasta 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 Aclasta. Suspected adverse reactions to Aclasta (investigator assessment) 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 summarized in Table 3 using the following convention: very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1,000$, $< 1/100$).

Table 3 Suspected adverse reactions to Aclasta (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
Psychiatric 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

Treatment with intravenous bisphosphonates, including 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 to 4 weeks), but it has also 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 Aclasta and placebo treatment groups over 3 years. There was a transient increase in serum creatinine observed within 10 days in 1.8% of Aclasta-treated patients versus 0.8% of placebo-treated patients.

In the 3-year HORIZON-PFT extension trial, 2.9% of the patients who continued to receive Aclasta (i.e. 6-years total exposure to Aclasta) vs. 0.65 % of the patients who discontinued (i.e. 3-years Aclasta 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).

In the studies to support the indications prevention of clinical fractures after hip fracture in men and women, treatment of osteoporosis in men, treatment and prevention of glucocorticoid-induced osteoporosis, the change in creatinine clearance (measured annually prior to dosing), and the incidence of renal failure and impairment was comparable for both the Aclasta and placebo or comparator treatment groups.

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 Aclasta and placebo groups.

Hypocalcaemia

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 Aclasta administration. No symptomatic cases of hypocalcaemia were observed.

In the HORIZON-PFT extension trial, 0.4% of patients who received placebo during the core trial and Aclasta 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 HORIZON-RFT, treatment of male osteoporosis and treatment and prevention of glucocorticoid-induced osteoporosis trials, there were no patients who had treatment emergent serum calcium levels below 1.87 mmol/L.

In the prevention of postmenopausal osteoporosis trial there was one patient who had treatment emergent serum calcium levels below 1.87 mmol/L.

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

Local reactions

In the HORIZON-PFT 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 HORIZON-RFT trial, the event rate was comparable for both the Aclasta and placebo treatment groups.

In the treatment of male osteoporosis trial, the event rate was 2.6% in the zoledronic acid treatment group and 1.4% in the alendronate treatment group.

In the treatment and prevention of glucocorticoid-induced osteoporosis trial, no local reactions were reported.

In the prevention of postmenopausal osteoporosis trial, the event rate was 1.1% in Aclasta treated patients compared to 2.0% in placebo treated patients.

Osteonecrosis of the jaw

Cases of osteonecrosis (primarily of the jaw) have been reported predominantly in cancer patients treated with bisphosphonates, including zoledronic acid (uncommon). 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 (ONJ) 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 WARNINGS AND PRECAUTIONS).

In the HORIZON-PFT core trial in 7,736 intention-to-treat (ITT) patients, ONJ has been reported in one patient treated with Aclasta 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 Aclasta during the core and the extension trial (i.e. 6-years total exposure to Aclasta) and one in the group of patients receiving placebo in the core and Aclasta in the extension trial (i.e. 3-years of exposure to Aclasta). Both patients had a history of poor dental hygiene and both made a complete recovery.

In the HORIZON-RFT, treatment of male osteoporosis, treatment and prevention of glucocorticoid-induced osteoporosis and prevention of postmenopausal osteoporosis trials there were no cases of osteonecrosis of the jaw.

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 Aclasta 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 Aclasta 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 Aclasta in the core and extension trial (i.e. 6-years of total exposure to Aclasta) vs. 2.1% (13 out of 616) in patients who received Aclasta 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 Aclasta compared with 1.1% (7 out of 616) in patients who received 3-years of Aclasta 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 Aclasta 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 WARNINGS & PRECAUTIONS)
Renal and urinary disorders: Renal failure requiring dialysis or with fatal outcome*, renal impairment (see section WARNINGS & PRECAUTIONS)

*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.

INTERACTIONS

Specific drug-drug interaction studies have not been conducted with zoledronic acid. Zoledronic acid is not systemically metabolised and does not affect human cytochrome P450 enzymes *in vitro* (see section CLINICAL PHARMACOLOGY; sub section Pharmacokinetics). Zoledronic acid is not highly bound to plasma proteins (approximately 23 to 40% bound) and interactions resulting from displacement of highly protein-bound drugs are therefore unlikely. Zoledronic acid is eliminated by renal excretion.

Drugs that could Impact Renal Function

Caution is indicated when Aclasta is administered in conjunction with medicinal products that can significantly impact renal function (e.g. aminoglycosides or diuretics that may cause dehydration).

Drugs Primarily Excreted by the Kidney

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

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk Summary

Aclasta is contraindicated during pregnancy (see section CONTRAINDICATIONS). Studies in rats have shown reproductive toxicological effects. The potential risk in 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 CONTRAINDICATIONS and section NON-CLINICAL SAFETY DATA).

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 ≥ 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

Aclasta is contraindicated in breast-feeding women (see section CONTRAINDICATIONS).

Females and males of reproductive potential

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

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.

OVERDOSAGE

Clinical experience with acute overdosage 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 infusion of calcium gluconate.

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

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

The selective action of bisphosphonates on bone is based on their high affinity for mineralized bone. Intravenously administered zoledronic acid is rapidly distributed to bone and, like other bisphosphonates, localizes preferentially at sites of high bone turnover. The main molecular target of zoledronic acid in the osteoclast is the enzyme farnesyl pyrophosphate synthase, but this does not exclude other mechanisms. The relatively 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.

Pharmacodynamics (PD)

Osteoporosis

Aclasta treatment rapidly reduced the rate of bone turnover from elevated postmenopausal levels with the nadir for resorption markers observed at 7 days, and for formation markers at

12 weeks. Thereafter bone markers stabilized within the premenopausal range. There was no progressive reduction of bone turnover markers with repeated annual dosing.

In long-term animal studies, zoledronic acid inhibits bone resorption without adversely affecting bone formation, mineralization or the mechanical properties of bone. Histomorphometric data from long-term rat and monkey experiments showed the typical response of bone to an anti-resorptive agent with a dose-dependent reduction in osteoclastic activity and activation frequency of new remodeling sites in both trabecular and Haversian bone. Continuing bone remodeling was observed in bone samples from all animals treated with clinically relevant doses of zoledronic acid. There was no evidence of a mineralising defect, no aberrant accumulation of osteoid, and no woven bone in treated animals.

Pharmacokinetics (PK)

Single and multiple 5 and 15-minute infusions of 2, 4, 8 and 16 mg zoledronic acid in 64 cancer patients with bone metastases 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.

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.

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 the active substance in plasma after multiple doses given every 28 days. The early disposition phases (alpha and beta, with $t_{1/2}$ 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, $39 \pm 16\%$ 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 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.

Drug-drug interactions

No specific drug-drug interaction studies have been conducted 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 23 to 40% bound) and binding is concentration independent. Therefore, interactions resulting from displacement of highly protein-bound drugs are unlikely.

Special populations (see section DOSAGE AND ADMINISTRATION)

Renal impairment

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 patients studied. Small observed increases in $AUC_{(0-24hr)}$, 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 ($Cl_{cr} = 50$ to 80 mL/min) and moderate ($Cl_{cr} = 30$ to 50 mL/min) renal impairment are not necessary. The use of Aclasta in patients with creatinine clearance <35 mL/min is not recommended due to limited clinical safety data in such patients (see section WARNINGS AND PRECAUTIONS). No dose adjustment is necessary in patients with creatinine clearance ≥ 35 mL/min.

CLINICAL STUDIES

Clinical trial results for the treatment of postmenopausal osteoporosis

Core study (HORIZON-PFT): In a randomized, double-blind, placebo-control trial, Aclasta 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 $p < 0.0001$). Aclasta treatment also reduced the risk of hip fracture by 40% over 3 years ($p = 0.003$). Furthermore, Aclasta 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 Aclasta were randomized to placebo or Aclasta treatment, three additional annual Aclasta 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 trial results in the prevention of clinical fractures after hip fracture

In male and female patients with a recent low-trauma hip fracture, treatment with Aclasta 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 and also 30% reduced risk for a subsequent hip fracture. Aclasta treatment significantly increased BMD relative to placebo at the hip and femoral neck (12, 24, and 36 month time points).

Clinical trial results for the treatment of male osteoporosis (MO)

In one randomized active-control study an annual infusion of Aclasta 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 trial results in the treatment and prevention of glucocorticoid-induced osteoporosis

In a randomized, active-control trial in patients with glucocorticoid-induced osteoporosis, increases in BMD were significantly greater in the Aclasta treated group 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 trial results for the prevention of postmenopausal osteoporosis

The efficacy and safety of Aclasta in postmenopausal women with osteopenia (low bone mass) was assessed in a 2-year randomized, multi-center, double-blind, placebo-controlled study of 581 postmenopausal women aged greater than or equal to 45 years, who were stratified by years since menopause: Stratum I women less than 5 years from menopause ($n=224$); Stratum II women greater than or equal to 5 years from menopause ($n=357$). Patients within Stratum I and II were randomized to one of three treatment groups: (1) Aclasta given at randomization and at Month 12 ($n=77$) in Stratum I and ($n=121$) in Stratum II; (2) Aclasta given at randomization and placebo at Month 12 ($n=70$) in Stratum I and ($n=111$) in Stratum II; and (3) Placebo given at randomization and Month 12 ($n=202$). Aclasta was administered as a single 5 mg dose in 100 mL solution infused over at least 15 minutes. All women received 500 to 1200 mg elemental calcium plus 400 to 800 international units vitamin D supplementation per day. The primary efficacy variable was the percent change of BMD at 24 Months relative to baseline.

Effect on Bone Mineral Density (BMD)

Aclasta significantly increased lumbar spine BMD relative to placebo at Month 24 across both strata. Aclasta given once at randomization (and placebo given at Month 12) resulted in 4.0% increase in BMD in Stratum I patients and 4.8% increase in Stratum II patients over 24 months. Placebo given at randomization and at Month 12 resulted in 2.2% decrease in BMD in Stratum I patients and 0.7% decrease in BMD in Stratum II patients over 24 months. Therefore, Aclasta given once at randomization (and placebo given at Month 12) resulted in a 6.3% increase in BMD in Stratum I patients and 5.4% increase in Stratum II patients over 24 months as compared to placebo (both $p < 0.0001$).

Aclasta also significantly increased total hip BMD relative to placebo at Month 24 across both strata. Aclasta given once at randomization (and placebo given at Month 12) resulted in 2.6% increase in BMD in Stratum I patients and 2.1% in Stratum II patients over 24 months. Placebo given at randomization and at Month 12 resulted in 2.1% decrease in BMD in Stratum I patients and 1.0% decrease in BMD in Stratum II patients over 24 months. Therefore, Aclasta given once at randomization (and placebo given at Month 12) resulted in a 4.7% increase in BMD in Stratum I patients and 3.2% increase in Stratum II patients over 24 months as compared to placebo (both $p < 0.0001$).

Paget's disease of bone

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

NON-CLINICAL SAFETY DATA

Toxicity studies

In the bolus parenteral studies, zoledronic acid was well tolerated when administered subcutaneously to rats and intravenously to dogs at doses of 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 kidney was identified as a target organ for toxicity in parenteral studies with zoledronic acid.

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.

Reproductive toxicity

For reproductive toxicity see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

Mutagenicity

Zoledronic acid was not mutagenic *in vitro* and *in vivo* in the mutagenicity tests performed.

Carcinogenicity

In oral carcinogenicity studies in rodents, zoledronic acid revealed no carcinogenic potential.

INCOMPATIBILITIES

Aclasta solution for infusion must not be allowed to come into contact with any calcium- or other divalent cation-containing solutions.

Aclasta is compatible with the typical infusion line materials polyvinylchloride (PVC), polyurethane (PUR) and polyethylene (PE).

STORAGE

Unopened bottle: see folding box.

After opening, the solution is chemically and physically stable for at least 24 hours at 2 to 8°C.

From a microbiological point of view, the product 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.

Aclasta should not be used after the date marked “EXP” on the pack.

Aclasta must be kept out of the reach and sight of children.

PACK SIZE

One 100ml plastic vial per box.

INSTRUCTIONS FOR USE AND HANDLING

Aclasta must not be mixed or given intravenously with any other medication and must be given through a separate vented infusion line at a constant infusion rate. If refrigerated, allow the refrigerated solution to reach room temperature before administration. Aseptic techniques must be followed during the preparation of the infusion.

For single use only. Any unused solution should be discarded. Only clear solution free from particles and discoloration should be used.

Product Registration Holder:

Sandoz Products Malaysia Sdn. Bhd.
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Malaysian Package Leaflet

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