1. NAME OF THE MEDICINAL PRODUCT

Aclasta 5 mg solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion

Clear and colourless solution.

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.

Treatment of osteoporosis associated with long-term systemic glucocorticoid therapy
- in post-menopausal women
- in adult men

at increased risk of fracture.

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

4.2 Posology and method of administration

Posology

Patients must be appropriately hydrated prior to administration of Aclasta. This is especially important for the elderly (≥65 years)and for patients receiving diuretic therapy.

Adequate calcium and vitamin D intake are recommended in association with Aclasta administration.

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

The optimal duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of Aclasta on an individual patient basis, particularly after 5 or more years of use.

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

Paget's disease
For the treatment of Paget's disease, Aclasta should be prescribed only by physicians with experience in the treatment of Paget's disease of the bone. The recommended dose is a single intravenous infusion of 5 mg Aclasta. 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 Aclasta administration (see section 4.4).

Re-treatment of Paget's disease: After initial treatment with Aclasta in Paget's disease, an extended remission period is observed in responding patients. Re-treatment consists of an additional intravenous infusion of 5 mg Aclasta after an interval of one year or longer from initial treatment in patients who have relapsed. Limited data on re-treatment of Paget's disease are available (see section 5.1).

Special populations
Patients with renal impairment
Aclasta is contraindicated in patients with creatinine clearance < 35 ml/min (see sections 4.3 and 4.4).

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).

Elderly (≥ 65 years)
No dose adjustment is necessary since bioavailability, distribution and elimination were similar in elderly patients and younger subjects.

Paediatric population
Aclasta should not be used in children and adolescents below 18 years of age. There are no data available for children under 5 years of age. Currently available data for children aged 5 to 17 years are described in section 5.1.

Method of administration

Intravenous use.
Aclasta is administered via a vented infusion line and given slowly at a constant infusion rate. The infusion time must not be less than 15 minutes. For information on the infusion of Aclasta, see section 6.6.

Patients treated with Aclasta should be given the package leaflet and the patient reminder card.

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 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 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 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 minimise the risk of renal adverse reactions:

- Creatinine clearance should be calculated based on actual body weight using the Cockcroft-Gault formula before each Aclasta 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.
- Aclasta 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 Aclasta.
- A single dose of Aclasta should not exceed 5 mg and the duration of infusion should be at least 15 minutes (see section 4.2).

Hypocalcaemia

Pre-existing hypocalcaemia must be treated by adequate intake of calcium and vitamin D before initiating therapy with Aclasta (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 Aclasta (see section 4.8).

Adequate calcium and vitamin D intake are recommended in association with Aclasta 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 Aclasta 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 Aclasta 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)

ONJ has been reported in the post-marketing setting in patients receiving Aclasta (zoledronic acid) for osteoporosis (see section 4.8).

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

The following should be considered when evaluating a patient's risk of developing ONJ:
- Potency of the medicinal product that inhibits bone resorption (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapy.
- Cancer, co-morbid conditions (e.g. anaemia, coagulopathies, infection), smoking.
- Concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck.
- Poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures, e.g. tooth extractions.

All patients should be encouraged to maintain good oral hygiene, undergo routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling, non-healing of sores or discharge during treatment with zoledronic acid. While on treatment, invasive dental procedures should be performed with caution and avoided in close proximity to zoledronic acid treatment.

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

Osteonecrosis of the external auditory canal

Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections.

Atypical fractures of the femur

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

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

Acute phase reactions

Acute phase reactions (APRs) or post-dose symptoms such as fever, myalgia, flu-like symptoms, arthralgia and headache have been observed, the majority of which occurred within three days following Aclasta administration.

APRs may sometimes be serious or prolonged in duration. The incidence of post-dose symptoms can be reduced with the administration of paracetamol or ibuprofen shortly following Aclasta administration. It is also advisable to postpone treatment if the patient is clinically unstable due to an acute medical condition and an APR could be problematic (see section 4.8).

General

Other products containing zoledronic acid as an active substance are available for oncology indications. Patients being treated with Aclasta 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 Aclasta, 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 (approximately 43-55% bound) and interactions resulting from displacement of highly protein-bound medicinal products 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 Fertility, pregnancy and lactation

Women of childbearing potential

Aclasta is not recommended in women of childbearing potential.

Pregnancy

Aclasta is contraindicated during pregnancy (see section 4.3). There are no adequate data on the use of zoledronic acid in pregnant women. Studies in animals with zoledronic acid have shown reproductive toxicological effects including malformations (see section 5.3). The potential risk for humans is unknown.

Breast-feeding

Aclasta is contraindicated during breast-feeding (see section 4.3). It is unknown whether zoledronic acid is excreted into human milk.

Fertility

Zoledronic acid was evaluated in rats for potential adverse effects on fertility of the parental and F1 generation. This resulted in exaggerated pharmacological effects considered related to the compound's inhibition of skeletal calcium mobilisation, resulting in periparturient hypocalcaemia, a bisphosphonate class effect, dystocia and early termination of the study. Thus these results precluded determining a definitive effect of Aclasta on fertility 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: pyrexia (17.1%), myalgia (7.8%), influenza-like illness (6.7%), arthralgia (4.8%) and headache (5.1%), see "acute phase reactions" below.

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, gastro-oesophageal reflux disease, constipation, dry mouth, oesophagitis, toothache, gastritis[#]
Skin and subcutaneous tissue disorders	*Uncommon*	Rash, hyperhidrosis, pruritus, erythema
Musculoskeletal and connective tissue disorders	*Common* *Uncommon* *Rare* *Very rare* *Not known***	Myalgia, arthralgia, bone pain, back pain, pain in extremity Neck pain, musculoskeletal stiffness, joint swelling, muscle spasms, 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 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 acute phase reactions (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.

Description of selected adverse reactions

Atrial fibrillation
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 Aclasta and placebo, respectively. The rate of atrial fibrillation serious adverse events was increased in patients receiving Aclasta (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 Aclasta (2.6%) and placebo (2.1%). For atrial fibrillation serious adverse events the pooled incidences were 1.3% for Aclasta and 0.8% for placebo.

Class effects
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 dysfunction 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 clinical trials in 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 treatment groups over three 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.

Hypocalcaemia
In clinical trials in osteoporosis, 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 Paget's disease trials, symptomatic hypocalcaemia 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 Aclasta-treated patients in a large clinical trial compared to 21% of Aclasta-treated patients in the Paget's disease trials. The frequency of hypocalcaemia was much lower following subsequent infusions.

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 Aclasta 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.

Osteonecrosis of the jaw
Cases of osteonecrosis of the jaw have been reported, predominantly in cancer patients treated with medicinal products that inhibit bone resorption, including zoledronic acid (see section 4.4). In a large clinical trial in 7,736 patients, osteonecrosis of the jaw has been reported in one patient treated with Aclasta and one patient treated with placebo. Cases of ONJ have been reported in the post-marketing setting for Aclasta.

Acute phase reactions
The overall percentage of patients who reported acute phase reactions or post-dose symptoms (including serious cases) after Aclasta administration is as follows (frequencies derived from the study in treatment of post-menopausal osteoporosis): fever (18.1%), myalgia (9.4%), flu-like symptoms (7.8%), arthralgia (6.8%) and headache (6.5%), the majority of which occurred 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 with subsequent annual doses of Aclasta. 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 (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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.

Aclasta 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)

The efficacy and safety of Aclasta 5 mg once a year for 3 consecutive years were demonstrated in post-menopausal women (7,736 women aged 65–89 years) with either: a femoral neck bone mineral density (BMD) with a T-score ≤ –1.5 and at least two mild or one moderate existing vertebral fracture(s); or a femoral neck BMD T-score ≤ –2.5 with or without evidence of existing vertebral fracture(s). 85% of patients were bisphosphonate-naïve. Women who were evaluated for the incidence of vertebral fractures did not receive concomitant osteoporosis therapy, which was allowed for women contributing to the hip and all clinical fracture evaluations. Concomitant osteoporosis therapy included: calcitonin, raloxifene, tamoxifen, hormone replacement therapy, tibolone; but excluded other bisphosphonates. All women received 1,000 to 1,500 mg elemental calcium and 400 to 1,200 IU of vitamin D supplements daily.

Effect on morphometric vertebral fractures
Aclasta significantly decreased the incidence of one or more new vertebral fractures over three years and as early as the one year timepoint (see Table 2).

Table 2 Summary of vertebral fracture efficacy at 12, 24 and 36 months

Outcome	Aclasta (%)	Placebo (%)	Absolute reduction in fracture incidence % (CI)	Relative reduction in fracture incidence % (CI)
At least one new vertebral fracture (0–1 year)	1.5	3.7	2.2 (1.4, 3.1)	60 (43, 72)**
At least one new vertebral fracture (0–2 year)	2.2	7.7	5.5 (4.4, 6.6)	71 (62, 78)**
At least one new vertebral fracture (0–3 year)	3.3	10.9	7.6 (6.3, 9.0)	70 (62, 76)**
** p <0.0001				

Aclasta-treated patients aged 75 years and older exhibited a 60% reduction in the risk of vertebral fractures compared to placebo patients (p<0.0001).

Effect on hip fractures
Aclasta demonstrated a consistent effect over 3 years, resulting in a 41% reduction in the risk of hip fractures (95% CI, 17% to 58%). The hip fracture event rate was 1.44% for Aclasta-treated patients compared to 2.49% for placebo-treated patients. The risk reduction was 51% in bisphosphonate-naïve patients and 42% in patients allowed to take concomitant osteoporosis therapy.

Effect on all clinical fractures
All clinical fractures were verified based on the radiographic and/or clinical evidence. A summary of results is presented in Table 3.

Table 3 Between treatment comparisons of the incidence of key clinical fracture variables over 3 years

Outcome	Aclasta (N=3,875) event rate (%)	Placebo (N=3,861) event rate (%)	Absolute reduction in fracture event rate % (CI)	Relative risk reduction in fracture incidence % (CI)
Any clinical fracture (1)	8.4	12.8	4.4 (3.0, 5.8)	33 (23, 42)**
Clinical vertebral fracture (2)	0.5	2.6	2.1 (1.5, 2.7)	77 (63, 86)**
Non-vertebral fracture (1)	8.0	10.7	2.7 (1.4, 4.0)	25 (13, 36)*
*p-value <0.001, **p-value <0.0001 (1) Excluding finger, toe and facial fractures (2) Including clinical thoracic and clinical lumbar vertebral fractures				

Effect on bone mineral density (BMD)
Aclasta significantly increased BMD at the lumbar spine, hip, and distal radius relative to treatment with placebo at all timepoints (6, 12, 24 and 36 months). Treatment with Aclasta resulted in a 6.7% increase in BMD at the lumbar spine, 6.0% at the total hip, 5.1% at the femoral neck, and 3.2% at the distal radius over 3 years as compared to placebo.

Bone histology
Bone biopsies were obtained from the iliac crest 1 year after the third annual dose in 152 post-menopausal patients with osteoporosis treated with Aclasta (N=82) or placebo (N=70). Histomorphometric analysis showed a 63% reduction in bone turnover. In patients treated with Aclasta, no osteomalacia, marrow fibrosis or woven bone formation was detected. Tetracycline label was detectable in all but one of 82 biopsies obtained from patients on Aclasta. Microcomputed tomography (μCT) analysis demonstrated increased trabecular bone volume and preservation of trabecular bone architecture in patients treated with Aclasta compared to placebo.

Bone turnover markers
Bone specific alkaline phosphatase (BSAP), serum N-terminal propeptide of type I collagen (P1NP) and serum beta-C-telopeptides (b-CTx) were evaluated in subsets ranging from 517 to 1,246 patients at periodic intervals throughout the study. Treatment with a 5 mg annual dose of Aclasta significantly reduced BSAP by 30% relative to baseline at 12 months which was sustained at 28% below baseline levels at 36 months. P1NP was significantly reduced by 61% below baseline levels at 12 months and was sustained at 52% below baseline levels at 36 months. B-CTx was significantly reduced by 61% below baseline levels at 12 months and was sustained at 55% below baseline levels at 36 months. During this entire time period bone turnover markers were within the pre-menopausal range at the end of each year. Repeat dosing did not lead to further reduction of bone turnover markers.

Effect on height
In the three-year osteoporosis study standing height was measured annually using a stadiometer. The Aclasta group revealed approximately 2.5 mm less height loss compared to placebo (95% CI: 1.6 mm, 3.5 mm) [p<0.0001].

Days of disability
Aclasta significantly reduced the mean days of limited activity and the days of bed rest due to back pain by 17.9 days and 11.3 days respectively compared to placebo and significantly reduced the mean days of limited activity and the days of bed rest due to fractures by 2.9 days and 0.5 days respectively compared to placebo (all p<0.01).

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

The incidence of clinical fractures, including vertebral, non-vertebral and hip fractures, was evaluated in 2,127 men and women aged 50-95 years (mean age 74.5 years) with a recent (within 90 days) low-trauma hip fracture who were followed for an average of 2 years on study treatment (Aclasta). Approximately 42% of patients had a femoral neck BMD T-score below -2.5 and approximately 45% of the patients had a femoral neck BMD T-score above -2.5. Aclasta was administered once a year, until at least 211 patients in the study population had confirmed clinical fractures. Vitamin D levels were not routinely measured but a loading dose of vitamin D (50,000 to 125,000 IU orally or by intramuscular route) was given to the majority of patients 2 weeks prior to infusion. All participants received 1,000 to 1,500 mg of elemental calcium plus 800 to 1,200 IU of vitamin D supplementation per day. Ninety-five percent of the patients received their infusion two or more weeks after the hip fracture repair and the median timing of infusion was approximately six weeks after the hip fracture repair. The primary efficacy variable was the incidence of clinical fractures over the duration of the study.

Effect on all clinical fractures
The incidence rates of key clinical fracture variables are presented in Table 4.

Table 4 Between treatment comparisons of the incidence of key clinical fracture variables

Outcome	Aclasta (N=1,065) event rate (%)	Placebo (N=1,062) event rate (%)	Absolute reduction in fracture event rate % (CI)	Relative risk reduction in fracture incidence % (CI)
Any clinical fracture (1)	8.6	13.9	5.3 (2.3, 8.3)	35 (16, 50)**
Clinical vertebral fracture (2)	1.7	3.8	2.1 (0.5, 3.7)	46 (8, 68)*
Non-vertebral fracture (1)	7.6	10.7	3.1 (0.3, 5.9)	27 (2, 45)*
*p-value <0.05, **p-value <0.01 (1) Excluding finger, toe and facial fractures (2) Including clinical thoracic and clinical lumbar vertebral fractures				

The study was not designed to measure significant differences in hip fracture, but a trend was seen towards reduction in new hip fractures.

All cause mortality was 10% (101 patients) in the Aclasta-treated group compared to 13% (141 patients) in the placebo group. This corresponds to a 28% reduction in the risk of all cause mortality (p=0.01).

The incidence of delayed hip fracture healing was comparable between Aclasta (34 [3.2%]) and placebo (29 [2.7%]).

Effect on bone mineral density (BMD)
In the HORIZON-RFT study Aclasta treatment significantly increased BMD at the total hip and femoral neck relative to treatment with placebo at all timepoints. Treatment with Aclasta resulted in an increase in BMD of 5.4% at the total hip and 4.3% at the femoral neck over 24 months as compared to placebo.

Clinical efficacy in men

In the HORIZON-RFT study 508 men were randomised into the study and 185 patients had BMD assessed at 24 months. At 24 months a similar significant increase of 3.6% in total hip BMD was observed for patients treated with Aclasta as compared to the effects observed in post-menopausal women in the HORIZON-PFT study. The study was not powered to show a reduction in clinical fractures in men; the incidence of clinical fractures was 7.5% in men treated with Aclasta versus 8.7% for placebo.

In another study in men (study CZOL446M2308) an annual infusion of Aclasta was non-inferior to weekly alendronate for the percentage change in lumbar spine BMD at month 24 relative to baseline.

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

The efficacy and safety of Aclasta in the treatment and prevention of osteoporosis associated with long-term systemic glucocorticoid therapy were assessed in a randomised, multicentre, double-blind, stratified, active-controlled study of 833 men and women aged 18-85 years (mean age for men 56.4 years; for women 53.5 years) treated with > 7.5 mg/day oral prednisone (or equivalent). Patients were stratified with respect to duration of glucocorticoid use prior to randomisation (≤ 3 months versus > 3 months). The duration of the trial was one year. Patients were randomised to either Aclasta 5 mg single infusion or to oral risedronate 5 mg daily for one year. All participants received 1,000 mg elemental calcium plus 400 to 1,000 IU vitamin D supplementation per day. Efficacy was demonstrated if non-inferiority to risedronate was shown sequentially with respect to the percentage change in lumbar spine BMD at 12 months relative to baseline in the treatment and prevention subpopulations, respectively. The majority of patients continued to receive glucocorticoids for the one year duration of the trial.

Effect on bone mineral density (BMD)
The increases in BMD were significantly greater in the Aclasta-treated group at the lumbar spine and femoral neck at 12 months compared to risedronate (all $p<0.03$). In the subpopulation of patients receiving glucocorticoids for more than 3 months prior to randomisation, Aclasta increased lumbar spine BMD by 4.06% versus 2.71% for risedronate (mean difference: 1.36% ; $p<0.001$). In the subpopulation of patients that had received glucocorticoids for 3 months or less prior to randomisation, Aclasta increased lumbar spine BMD by 2.60% versus 0.64% for risedronate (mean difference: 1.96% ; $p<0.001$). The study was not powered to show a reduction in clinical fractures compared to risedronate. The incidence of fractures was 8 for Aclasta-treated patients versus 7 for risedronate-treated patients ($p=0.8055$).

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

Aclasta was studied in male and female patients aged above 30 years with primarily mild to moderate Paget's disease of the bone (median serum alkaline phosphatase level 2.6–3.0 times the upper limit of the age-specific normal reference range at the time of study entry) confirmed by radiographic evidence.

The efficacy of one infusion of 5 mg zoledronic acid versus daily doses of 30 mg risedronate for 2 months was demonstrated in two 6-month comparative trials. After 6 months, Aclasta showed 96% (169/176) and 89% (156/176) response and serum alkaline phosphatase (SAP) normalisation rates compared to 74% (127/171) and 58% (99/171) for risedronate (all $p<0.001$).

In the pooled results, a similar decrease in pain severity and pain interference scores relative to baseline were observed over 6 months for Aclasta and risedronate.

Patients who were classified as responders at the end of the 6 month core study were eligible to enter an extended follow-up period. Of the 153 Aclasta-treated patients and 115 risedronate-treated patients who entered an extended observation study, after a mean duration of follow-up of 3.8 years from time of dosing, the proportion of patients ending the Extended Observation Period due to the need for re-treatment (clinical judgment) was higher for risedronate (48 patients, or 41.7%) compared with zoledronic acid (11 patients, or 7.2%). The mean time of ending the Extended Observation Period due to the need for Paget's re-treatment from the initial dose was longer for zoledronic acid (7.7 years) than for risedronate (5.1 years).

Six patients who achieved therapeutic response 6 months after treatment with Aclasta and later experienced disease relapse during the extended follow-up period were re-treated with Aclasta after a mean time of 6.5 years from initial treatment to re-treatment. Five of the 6 patients had SAP within the normal range at month 6 (Last Observation Carried Forward, LOCF).

Bone histology was evaluated in 7 patients with Paget's disease 6 months after treatment with 5 mg zoledronic acid. Bone biopsy results showed bone of normal quality with no evidence of impaired bone remodelling and no evidence of mineralisation defects. These results were consistent with biochemical marker evidence of normalisation of bone turnover.

Paediatric population

A randomised, double-blind, placebo-controlled study was conducted in paediatric patients aged 5 to 17 years treated with glucocorticoids who had decreased bone mineral density (lumbar spine BMD Z-score of -0.5 or less) and a low impact/fragility fracture. The patient population randomised in this study (ITT population) included patients with several sub-types of rheumatic conditions, inflammatory bowel disease, or Duchenne muscular dystrophy. The study was planned to include 92 patients, however only 34 patients were enrolled and randomised to receive either a twice-yearly 0.05 mg/kg (max. 5 mg) intravenous zoledronic acid infusion or placebo for one year. All patients were required to receive background therapy of vitamin D and calcium.

Zoledronic acid infusion resulted in an increase in the lumbar spine BMD Z-score least square (LS) mean difference of 0.41 at month 12 relative to baseline compared to placebo (95% CI: 0.02, 0.81; 18 and 16 patients, respectively). No effect on lumbar spine BMD Z-score was evident after 6 months of treatment. At month 12, a statistically significant ($p<0.05$) reduction in three bone turnover markers (P1NP, BSAP, NTX) was observed in the zoledronic acid group as compared to the placebo group. No statistically significant differences in total body bone mineral content were observed between patients treated with zoledronic acid versus placebo at 6 or 12 months. There is no clear evidence establishing a link between BMD changes and fracture prevention in children with growing skeletons.

No new vertebral fractures were observed in the zoledronic acid group as compared to two new fractures in the placebo group.

The most commonly reported adverse reactions after infusion of zoledronic acid were arthralgia (28%), pyrexia (22%), vomiting (22%), headache (22%), nausea (17%), myalgia (17%), pain (17%), diarrhoea (11%) and hypocalcaemia (11%).

More patients reported serious adverse events in the zoledronic acid group than in the placebo group (5 [27.8%] patients versus 1 [6.3%] patient).

In the 12-month open-label extension of the above-mentioned core study, no new clinical fractures were observed. However 2 patients, one in each of the core study treatment groups (zoledronic acid group: 1/9, 11.1% and placebo group: 1/14, 7.1%), had new morphometric vertebral fractures. There were no new safety findings.

Long-term safety data in this population cannot be established from these studies.

The European Medicines Agency has waived the obligation to submit the results of studies with Aclasta in all subsets of the paediatric population in Paget's disease of the bone, osteoporosis in post-menopausal women at an increased risk of fracture, osteoporosis in men at increased risk of fracture and prevention of clinical fractures after a hip fracture in men and women (see section 4.2 for information on paediatric use).

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.

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/pharmacodynamic 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 medicinal products 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 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.

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. Aclasta must not be mixed or given intravenously with any other medicinal products.

6.3 Shelf life

Unopened bottle: 3 years

After opening: 24 hours at 2°C - 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°C - 8°C.

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 in a transparent plastic (cycloolefinic polymer) bottle closed with a fluoro-polymer coated bromobutyl rubber stopper and an aluminium/polypropylene cap with a flip component.

Aclasta is supplied in packs containing one bottle as unit pack, or in multipacks comprising five packs, each containing one bottle.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only.
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.

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

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 April 2005
Date of latest renewal: 19 January 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu