VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Zoledronic acid 5 mg/100mL solution for injection belongs to the class of nitrogen – containing bisphosphonates and acts primarily on bone. It is used to treat post-menopausal women and men with osteoporosis or osteoporosis caused by treatment with steroids, and Paget's disease of the bone in adults.

Osteoporosis
Osteoporosis is a disease that involves the thinning and weakening of the bones and is common in women after the menopause, but can also occur in men. At the menopause, a woman's ovaries stop producing the female hormone oestrogen, which helps keep bones healthy. Following the menopause bone loss occurs, bones become weaker and break more easily. Osteoporosis could also occur in men and women because of the long term use of steroids, which can affect the strength of bones. Decreased circulating levels of sex hormones, mainly oestrogens converted to androgens, also play a role in the more gradual bone loss observed in men. In both women and men, Zoledronic acid infusion strengthens the bone and therefore makes it less likely to break.

Zoledronic acid infusion is also used in patients who have recently broken their hip in a minor trauma such as a fall and therefore are at risk of subsequent bone breaks.

Paget's disease of the bone
It is normal that old bone is removed and is replaced with new bone material. This process is called remodelling. In Paget's disease, bone remodelling is too rapid and new bone is formed in a disordered fashion, which makes it weaker than normal. If the disease is not treated, bones may become deformed and painful, and may break. Zoledronic acid infusion works by returning the bone remodelling process to normal, securing formation of normal bone, thus restoring strength to the bone.

VI.2.2 Summary of treatment benefits

As this is an abridged application for injection, no studies were conducted only data from published sources has been provided.

Osteoporosis is a disease characterized by low bone mineral density and poor bone quality resulting in reduced bone strength and increased risk of fracture. Zoledronic acid reduces the incidence of fractures (hip, vertebral and non-vertebral osteoporosis-related fractures).

Zoledronic acid 5 mg administered as an annual 15-min intravenous infusion has been shown to reduce the risk of vertebral fractures, hip fractures, and other fractures in a placebo-controlled trial in women with postmenopausal osteoporosis. In a randomized, double blind, placebo-controlled trial in women and men with a recent surgical repair of low-trauma hip fracture, it reduced the risk of new clinical fractures and improved survival.

The efficacy and safety of Zoledronic acid in men with osteoporosis or significant osteoporosis secondary to hypogonadism (an abnormal condition involving gonadal incompetence), was assessed in a study of 302 men. An annual infusion of Zoledronic acid was non-inferior to the oral weekly bisphosphonate active control based on the percentage change in lumbar spine bone mineral density (BMD).
Osteoporosis could also occur in men and women because of the long term use of steroids, which can affect the strength of bones. Zoledronic acid improves the BMD.

The efficacy and safety of Zoledronic acid to prevent and treat steroid-induced osteoporosis was assessed in a study of 833 men and women. Zoledronic acid demonstrated a significant mean increase in lumbar spine bone mineral density.

Zoledronic acid was studied in male and female patients with Paget's disease of bone. In both trials Zoledronic acid demonstrated a superior and more rapid therapeutic response compared with risedronate and returned more patients to normal levels of bone turnover, as evidenced by biochemical markers of formation and bone resorption.

VI.2.3 Unknowns relating to treatment benefits

The test product is aqueous intravenous solution for infusion, which is similar to the reference product Aclasta 5mg/100 ml solution for infusion.

VI.2.4 Summary of Safety concerns

Important identified risks		
Risk	**What is Known**	**Preventability**
Kidney function problem (Renal function impairment)	Zoledronic acid is contraindicated in patients with creatinine clearance less than 35 mL/min and in those with evidence of acute renal impairment. Zoledronic acid should be used with caution in patients with chronic renal impairment. Acute renal impairment, including renal failure, has been observed following the administration of zoledronic acid, especially in patients with pre-existing renal compromise, advanced age, concomitant nephrotoxic medications, concomitant diuretic therapy, or severe dehydration occurring before or after Zoledronic acid administration. Acute renal failure (ARF) has been observed in patients after a single administration.	Creatinine clearance should be calculated based on actual body weight before each Zoledronic acid dose. If history or physical signs suggest dehydration, Zoledronic acid therapy should be withheld until normovolemic status has been achieved. Interim monitoring of creatinine clearance should be performed in at-risk patients. Elderly patients and those receiving diuretic therapy should have their fluid status assessed and be appropriately hydrated prior to administration of Zoledronic acid dose. Zoledronic acid dose should be used with caution with other nephrotoxic drugs. Consider monitoring creatinine clearance in patients at-risk for acute renal failure who are taking concomitant

		medications that are primarily excreted by the kidney. A single dose of Zoledronic acid should not exceed 5 mg and the duration of infusion should be at least 15 minutes.
Necrosis of bone of the jaw (Osteonecrosis of the jaw)	Osteonecrosis of the jaw (ONJ) has been reported in patients treated with bisphosphonates, including zoledronic acid. Most cases have been in cancer patients treated with intravenous bisphosphonates undergoing dental procedures. Some cases have occurred in patients with postmenopausal osteoporosis treated with either oral or intravenous bisphosphonates. For patients who develop ONJ while on bisphosphonate therapy, dental surgery may worsen the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ.	A routine oral examination should be performed by the prescriber prior to initiation of bisphosphonate treatment. A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with a history of concomitant risk factors (e.g., cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene, pre-existing dental disease or infection, anemia, coagulopathy). While on treatment, patients with concomitant risk factors should avoid invasive dental procedures if possible.
Post dose symptoms	zoledronic acid was associated with signs and symptoms of an acute phase reaction myalgia, fever, fatigue, arthralgia, pain, chills, headache, influenza-like illness, malaise, and back pain. The onset time is ≤ 3days post zoledronic acid infusion and the reaction is also referred to using the terms “flu-like” or “post-dose” symptoms	Considering individual benefit risk assessment therapy needs to be initiated.
Deficiency of calcium in the blood (Hypocalcaemia)	Pre-existing hypocalcaemia must be treated by adequate intake of calcium and vitamin D before initiating therapy with Zoledronic acid. Elevated bone turnover is a	Standard hypercalcaemia-related metabolic parameters, such as serum levels of calcium, phosphate and magnesium, should be

	characteristic of Paget's disease of the bone. Due to the rapid onset of effect of zoledronic acid on bone turnover, transient hypocalcaemia, sometimes symptomatic, may develop and is usually maximal within the first 10 days after infusion of Zoledronic acid. In clinical trials in osteoporosis, approximately 0.2% of patients had notable declines of serum calcium levels (less than 1.87mmol/l) following Zoledronic acid 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.	carefully monitored after initiating Zoledronic acid therapy. Adequate calcium and vitamin D intake are recommended in association with Zoledronic acid administration. Patients should be informed about symptoms of hypocalcaemia and receive adequate clinical monitoring during the period of risk.
Ocular Adverse Events	Cases of iritis/uveitis/episcleritis/conjunctivitis have been reported in patients treated with bisphosphonates, including zoledronic acid. In the osteoporosis trials, less than 0.1% to 0.2% patients treated with zoledronic acid and 0% to less than 0.1% patient treated with placebo developed iritis/uveitis/episcleritis. Cases of the following events have been reported: conjunctivitis, iritis, iridocyclitis, uveitis, episcleritis, scleritis and orbital inflammation/edema.	Consider monitoring during the treatment.
Allergic reaction (Anaphylaxis)	Allergic reactions with intravenous zoledronic acid including anaphylactic reaction/shock, urticaria, angioedema, and bronchoconstriction have been reported.	Consider monitoring during the treatment.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Atrial fibrillation	In one 3 year, randomized double- blind controlled trial that evaluated the efficacy and safety of Zoledronic acid 5mg once yearly vs placebo in the treatment of postmenopausal osteoporosis the overall incidences of atrial fibrillation was 2.5% (96 out of 3,862) and 1.9% (75 out of 3,852) in patients receiving Zoledronic acid 5mg and placebo respectively. The rate of atrial fibrillation serious adverse events was 1.3% (51 out of 3,862) and 0.6% (22 out of 3,852) in patients receiving Zoledronic acid 5mg and placebo respectively. The mechanism behind the increased incidence of atrial fibrillation in this single clinical trial is unknown.
Atypical fractures of the femur	A typical subtrochanteric and diaphyseal femoral fracture has 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 biphosphate- treated patients who have sustained femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of bisphosphonate therapy in patient 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.
Gastrointestinal adverse reaction	Adverse reaction reported in greater than or equal to 2% of patients with osteopenia and more frequently than in placebo-treated patients. Also in Paget's patients receiving zoledronic acid (single 5 mg intravenous infusion) reported are nausea, diarrhea, vomiting, dyspepsia, abdominal pain, constipation, abdominal discomfort and abdominal distension
Medication error	Clinical experience with acute overdose of zoledronic acid is limited. The administration of doses up to 48mg of zoledronic acid in error has been reported. Patients who have received doses higher than those recommended should be carefully monitored, since renal function impairment (including renal failure) and serum electrolyte (including calcium, phosphorus and magnesium) abnormalities have been observed. In the event of hypocalcaemia, calcium gluconate infusions should be administer as clinically indicated
Interaction with products that can significantly affect renal function including Paracetamol / acetaminophen	As zoledronic acid has nephrotoxic effect, caution is warranted when pamidronate disodium for Injection is used with other potentially nephrotoxic drugs.

Important missing information

Risk	What is known
Use in pregnancy and lactation	zoledronic acid should not be used during pregnancy. zoledronic acid may cause fetal harm when administered to a pregnant woman. It is not known whether zoledronic acid is excreted into human milk. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while on zoledronic acid therapy. zoledronic acid is contraindicated in breast feeding women.
Use in patients with severe kidney problem (Use in patients with severe renal impairment)	zoledronic acid should be used with caution in patients with chronic renal impairment. Rare reports of hospitalization and/or dialysis or fatal outcome occurred in patients with underlying moderate to severe renal impairment. zoledronic acid can cause serious side effects including Severe kidney problems. 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 zoledronic acid infusion period. Interim monitoring of creatinine clearance should be performed in at-risk patients. Zoledronic acid dose should be used with caution with other nephrotoxic drugs. Consider monitoring creatinine clearance in patients at-risk for Acute renal failure who are taking concomitant medications that are primarily excreted by the kidney.

VI.2.5 Summary of risk minimisation measures by safety concern.

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimization measures.

The Summary of Product information and the package leaflet for zoledronic acid 5mg/100ml solution for infusion are included in Annex 2. In addition an educational programme including Physician reminder card and patient guide would be provided as provided in annex 3. These documents would aim to help physicians to prescribe Zoledronic Acid 5 mg/100 ml for patients with osteoporosis and for patients it would aim to help as a guide that contains important safety information that would be required to be aware of before and during treatment with Zoledronic Acid 5 mg/100 ml solution for infusion.

VI.2.6 Planned post authorisation development plan

Not Applicable

VI.2.7 Summary of changes to the Risk Management Plan over time

Not Applicable