VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Hypercalcemia is too much calcium in the blood. Hypercalcemia can sometimes develop in people who have cancer. It occurs more often with some cancers like breast, myeloma, lung, kidney, and head and neck cancers than in others like lymphoma. It also occurs more often when the cancer is at an advanced stage and is most commonly associated with widespread bone metastases.

VI.2.2 Summary of treatment benefits

Patients with advanced malignancy involving bone are at significant risk, such as the occurrence of tumor-induced hypercalcemia (TIH), which is an elevated level of calcium, and the risk for bone morbidity. TIH in the blood can be a life-threatening complication of malignancy. Bone metastases from solid tumors and osteolytic bone disease in multiple myeloma are associated with considerable skeletal (bone) morbidity, including severe pain, pathologic fracture, the requirement for radiation or surgery to bone (to relieve pain, treat or prevent fracture), nerve root and spinal cord compression. These skeletal complications substantially reduce the quality of life for patients with bone metastases.

Zoledronic acid 4 mg / 5 ml, Concentrate for Solution for Infusion has demonstrated efficacy in the treatment of TIH and the prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumor-induced hypercalcemia) in patients with advanced malignancies involving bone.

Efficacy was established in the marketing authorization of the originator product, and was confirmed by by the medical literature since then.

Bisphosphonates have become a standard of care in patients with multiple myeloma and breast cancer, and are recommended in ASCO clinical practice guidelines for these malignancies [Berenson, 2002] [Hilner 2003]. In addition, the clinical benefit of zolendric acid in preventing or delaying skeletal-related events has been shown in placebo-controlled trials for prostate cancer, breast cancer, lung cancer, and other solid tumors metastatic to bone.

VI.2.3 Unknowns relating to treatment benefits

There is no evidence to suggest that results would be different in any specific population.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Damage to the kidney (Renal function impairment)	Damage to the kidney could occur after the first dose of Zoledronic acid. However, the risk is higher after long-term use of Zoledronic acid. Dehydration, pre-existing kidney damage, use of Zoledronic acid (or same	By assessment of the patient's kidney function and possible dose adjustment.

	class drugs) and other drugs toxic to the kidneys may increase the potential for damage to the kidney.	
Dead bone tissue in the jaw bone (Osteonecrosis of the jaw (ONJ))	Bone damage of the jaw has been reported mostly in cancer patients treated with this drug class (including Zoledronic acid). Many of these patients were also receiving cancer treatment and another medicine called corticosteroids. Many had signs of local infection as well.	A dental examination with appropriate preventive dentistry should be considered prior to treatment, especially if you have the following risk factors: e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene. If you have one of these risk factors, you should avoid invasive dental procedures if possible while on treatment. If you are having dental treatment or surgery or know that you need some in the future, tell your dentist that you are being treated with zoledronic acid.
Inflammatory immune response in the whole body (Acute phase reaction)	Inflammatory reaction could include a wide variety of symptoms: fever, muscle pain, headache, extremity pain nausea, vomiting, diarrhea, joint pain and arthritis followed by joint swelling. The occurrence of these symptoms decreases rapidly with each infusion and is not associated with organ damage.	Always take this medicine as prescribed by your doctor and as indicated in the Package Leaflet. This will minimise the risk of developing adverse drug reactions. If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the package leaflet.
Low calcium levels in your blood (Hypocalcaemia)	People with a low vitamin D level, and/or not enough calcium in their diet, or a low level of a thyroid hormone called PTH may be more likely to have low calcium in the blood while taking Zoledronic acid. Hypocalcemia seems to occur more often after the first infusion of Zoledronic acid. Events are usually temporary and mild.	By daily administration of oral calcium supplement and vitamin D and measuring serum calcium and correcting decreased calcium levels, prior to start of Zoledronic acid treatment.

Ocular adverse events		
Severe, potentially life-threatening allergic reactions (Anaphylaxis)	Allergic reactions have been very rarely seen in studies and after the marketing authorization. These reactions require immediate treatment.	Inform your doctor if you have any known allergies. DO NOT take zoledronic acid if you have previously experienced an allergic reaction to the same. Contact your doctor immediatelly if you notice any of the following symptoms: • skin changes (rash, redness) • swollen eyes, lips, hands and/or feet • swelling of the mouth, throat or tongue • abdominal pain, nausea and vomiting
Irregular heartbeat (Atrial fibrillation)	Irregular heartbeat is observed uncommonly under therapy with zoledronic acid.	Unknown
Damage of the lung (Interstitial lung disease)	This risk could impair lung function and the ability of the blood to take up oxygen.	Unknown

Important potential risks

Risk	**What is known** **(Including reason why it is considered a potential risk)**
Abnormal location of bone fractures (Atypical fractures of the femur)	Zoledronic acid is used in cancer patients. So it is difficult to establish an association between the reported fractures and the use of Zoledronic acid in these patients who have many risk and factors and complicated health conditions (such as bone cancer, other medications, radiotherapy at fracture site).
Interaction with products that can significantly affect renal function (Potential interaction with nephrotoxic medicines)	With concomitant use of Zoledronic acid and thalidomide (a medicine used to treat a certain type of blood cancer involving the bone) or any other medicines which may harm your kidneys, the risk of renal dysfunction may be increased.

Missing information

Risk	**What is known**

Pregnancy and bras feeding (Pregnancy and lactation)	Animal studies have shown reproductive toxicity. The effect in human is unknown. Zoledronic acid should not be used during pregnancy. Women of child-bearing potential should avoid becoming pregnant.
Patients with kidney function problems (Patients with severe renal impairment)	Dose adaptation is required for patient with kidney function problem. Patient with severe kidney function were excluded from the studies.
Patients with liver function problems (Patients with hepatic insufficiency)	Few data available, but animal studies suggest that the drug is not going thought the liver.

VI.2.5 Summary of risk minimisation measures by safety concern

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

The additional risk minimisation measures are for the following risks:

Osteonecrosis of the jaw

Patient reminder card
Objective and rationale: to alert patients on risk of Osteonecrosis of the jaw (ONJ)
Key content: The card will remind patients about: □ the risk of osteonecrosis of the jaw during treatment with zoledronic acid; □ measures to be taken before and during treatment with zoledronic acid for prevention □ Risk factors for development of ONJ □ Symptoms of ONJ and informing them to treating physician and dentist

VI.2.6 Planned post authorisation development plan

No post-authorisation studies have been imposed or are planned.

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