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Summary of the risk management plan (RMP) for Zoledronic acid Teva Generics (zoledronic acid)

This is a summary of the risk management plan (RMP) for Zoledronic acid Teva Generics, which details the measures to be taken in order to ensure that Zoledronic acid Teva Generics is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Zoledronic acid Teva Generics, which can be found on Zoledronic acid Teva Generics' EPAR page.

Overview of disease epidemiology

Osteoporosis is a condition where not enough new bone grows to replace the bone that is naturally broken down. Gradually, the bones become thin and fragile, and more likely to fracture.

Osteoporosis can affect both men and women, however women are at a significantly higher risk for osteoporosis than men, with a female-to-male ratio of 4:1. Osteoporosis due to age-related loss of bone from the skeleton is more common in women where it usually occurs after the menopause, due to the loss of the hormone oestrogen which slows down bone breakdown and makes the bones less likely to fracture. Osteoporosis can also develop as a consequence of treatment with medicines known to cause or accelerate bone loss such as glucocorticoids, in which case it is called secondary osteoporosis and which is the main cause of osteoporosis in men.

In Paget's disease the bone breaks down more quickly, and when it grows back, it is weaker than normal. The disease can affect both men and women and is estimated to occur in 1-3% of individuals older than 45-55 years and in up to 10% of people older than 80 years.

Summary of treatment benefits

Zoledronic acid Teva Generics is available as a solution for infusion (drip) into a vein (5 mg) and is a 'generic medicine'. This means that Zoledronic acid Teva Generics is similar to a 'reference medicine' already authorised in the European Union (EU) called Aclasta.

Because Zoledronic acid Teva Generics is a generic medicine, its benefits and risks are taken as being the same as the reference medicine's. No additional studies were needed as Zoledronic acid Teva Generics is a generic medicine that is given by infusion and contains the same active substance as the reference medicine, Aclasta.

Unknowns relating to treatment benefits

Not applicable.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Osteonecrosis (death of bone tissue) of the jaw (ONJ)	Osteonecrosis of the jaw has been reported predominantly in patients with cancer receiving treatment regimens including bisphosphonates (class of medicines to which zoledronic acid belongs). Additional risk factors include concomitant chemotherapy, corticosteroid use, dental procedures and poor oral hygiene.	A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors. While on treatment, these patients should avoid invasive dental procedures if possible.
Hypocalcaemia (low calcium levels in the blood)	In clinical trials hypocalcaemia was noted following zoledronic acid administration.	Adequate calcium and vitamin D intake are recommended in association with zoledronic acid administration. Pre-existing hypocalcaemia must be treated by adequate intake of calcium and vitamin D before starting therapy with zoledronic acid. Patients should be informed about symptoms of hypocalcaemia (such as loss of sensation in finger tips, muscle cramps) and receive adequate clinical monitoring during the period of risk.
Renal dysfunction (kidney impairment or kidney failure)	Kidney impairment has been observed following the administration of zoledronic acid especially in patients with pre-existing kidney dysfunction or other risks including advanced age, concomitant nephrotoxic medicines (medicines that adversely affect the normal functioning of the kidneys), concomitant diuretic therapy (treatment with diuretics such as furosemide), or dehydration occurring after zoledronic acid administration. Kidney failure requiring dialysis or with a fatal outcome has rarely occurred in	Creatinine clearance (a blood test used to measure how well the kidneys are working) should be measured before each zoledronic acid dose and monitoring of serum creatinine should be considered in at-risk patients. A single dose of zoledronic acid should not exceed 5 mg and the duration of infusion should be at least 15 minutes. Zoledronic acid should be used with caution when used concomitantly with other medicines that could impact kidney function. Patients, especially elderly patients and

Risk	What is known	Preventability
	patients with underlying kidney impairment or with any of the risk factors described above.	those receiving diuretic therapy, should be appropriately hydrated prior to administration.
Hypersensitivity reactions (anaphylaxis)	Hypersensitivity (allergic) reactions including rare cases of bronchoconstriction (constriction of airways in the lungs leading to difficulty breathing), urticaria (itchy rash) and angioedema (rapid swelling of tissues beneath the skin which can obstruct airways), and very rare cases of anaphylactic reaction/shock (severe allergic reaction) have been reported in the post-marketing period.	The risk of hypersensitivity associated with the use of medicines can be managed by monitoring of symptoms and signs patients and usual precautions related to hypersensitivity.
Ocular adverse events (affecting the eye)	Ocular effects have been associated with bisphosphonate class. Ocular hyperaemia (redness of the eye), eye pain, and inflammation of different parts of the eye such as conjunctivitis, uveitis, episcleritis, iritis scleritis and orbital inflammation have been reported with zolendronic acid use.	Treating physician and patient should monitor for early symptoms of ocular adverse events (such as pain, swelling, itching and redness of the eye).
Post-dose symptoms	The majority of these symptoms, such as fever and chills, pain in the muscles or joints, and headache, occur within the first three days following the dose of zoledronic acid. The symptoms are usually mild to moderate and go away within three days.	The incidence of post-dose symptoms occurring within the first three days after administration of zoledronic acid can be reduced with the administration of paracetamol or ibuprofen shortly after giving zoledronic acid.

Important potential risks

Risk	What is known
Atypical femoral fractures	Atypical (subtrochanteric and diaphyseal) femoral fractures have been reported with bisphosphonates, primarily in patients receiving long-term treatment for osteoporosis. These fractures occur after minimal or no trauma. The

Risk	What is known
	mechanism(s) for the development of atypical fractures in patients taking bisphosphonates is not known, however it is thought that the suppression of bone turnover leading indirectly to ageing bone and the delay or prevention of repair of naturally occurring stress fractures is the mechanism that is thought to be involved.
Atrial fibrillation (heart condition that causes an irregular and often abnormally fast heart rate)	An increased incidence of atrial fibrillation was found in some clinical trials.
Cerebrovascular adverse effects (side effects affecting the brain and the circulatory system)	Conflicting results on the increase of cerebrovascular adverse effects associated with bisphosphonate use have been reported in different studies.
Osteonecrosis outside the jaw: avascular necrosis (AVN, disease where bone components die due to interruption of blood supply) and non-union or delayed-union fractures	Conflicting results on the risk of AVN and non-union or delayed union fractures associated with bisphosphonate use have been reported in different studies.
Gastrointestinal adverse effects (side effects affecting the gut)	Gastrointestinal adverse effects are known to occur with bisphosphonates given by mouth due to their direct toxic effects on the lining of the gut. This is not a risk with zoledronic acid as it is given intravenously and therefore bypasses the gut. For that reason gastrointestinal adverse effects are only considered a potential risk.
Potential interaction with nephrotoxic medicines (medicines that impact kidney function)	There are no studies investigating the potential interaction of zoledronic acid with other medicines. Zoledronic acid is not broken down in the body and is eliminated via the kidneys. Caution is needed when zoledronic acid is given together with medicines that can significantly impact kidney function (e.g. aminoglycosides or diuretics that may cause dehydration). In patients with kidney problems, medicines that are eliminated via the kidneys may accumulate and cause side effects.
Medication errors	Due to the availability of various zoledronic acid-containing medicines with similar names, but with different indications, strengths and dosing regimens (Zoledronic Acid Teva 4 mg/5 ml Concentrate for Solution for Infusion vs. Zoledronic acid Teva Pharma 5 mg solution for infusion and Zoledronic acid Teva Generics 5 mg solution for infusion), medication errors are possible.

Risk	What is known
	The potential for medication errors is minimised by the following measures: • Actual sizes of containers (vials or bottles/bags) are clearly different (5 ml for 4 mg/5 ml concentrate vs. 100 ml for 5 mg solution); • Clear difference in appearance (different colours for the different products, visible font sizes/bold letters) of the carton and vial or bottle/bag label for each strength/container; • Visible labelling related to the concentration of the different products (each strength is put in a clearly visible font and bold letters in a coloured box); • For Paget's disease the medicine is prescribed by specialists.

Missing information

Risk	What is known
Use during pregnancy and breastfeeding	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. The potential risk for humans is unknown. It is not known whether zoledronic acid is excreted into human breast milk. Zoledronic acid must not be used during pregnancy and in breast-feeding women.
Patients with severe kidney impairment	The use of zoledronic acid in patients with severe kidney impairment (creatinine clearance < 35 ml/min) is contraindicated due to an increased risk of kidney failure in this population. Kidney impairment has been observed following the administration of zoledronic acid, especially in patients with pre-existing kidney dysfunction or other risks including advanced age, concomitant use of nephrotoxic medicines (that impact kidney function), concomitant diuretic therapy, or dehydration occurring after zoledronic acid administration. Kidney failure requiring dialysis or with a fatal outcome has rarely occurred in patients with underlying kidney impairment or

Risk	What is known
	with any of the risk factors described above.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Zoledronic acid Teva Generics can be found on Zoledronic acid Teva Generics' EPAR page

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published in the EPAR page; how they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimisation measures are for the following risks:

Renal dysfunction (kidney impairment/kidney failure/potential interaction with nephrotoxic medicines)

Risk minimisation measure: Communication and Educational Program (CEP) for healthcare professional (HCP) and patient education
Objective and rationale: considering the potential severity and adverse outcomes of kidney failure, it is considered that physicians and patients should be educated on the risk of kidney failure, including precautions and information on adequate use of the product to minimise the risk.
Description: • Direct HCP communication prior to launch (Physician Information Leaflet). • HCP educational materials to be provided to prescribing physicians including advice on: – Zoledronic acid indications; – Important safety information; – Safety information on reports of renal impairment and renal failure with zoledronic acid. • Patient Information Sheet will inform patients on the important information on use of zoledronic acid; the symptoms of serious side effects, and the important considerations to minimize the risk of renal adverse events. The Communication and Educational Program (CEP) is based on actions included in the risk minimisation plan of the originator product Aclasta.

Planned post-authorisation development plan

Not applicable

Summary of changes to the risk management plan over time

Major changes to the Risk Management Plan over time

Not applicable

This summary was last updated in 02-2014.