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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zoledronic acid Mylan

International non-proprietary name: **zoledronic acid**

Procedure No. **EMEA/H/C/002482**

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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List of abbreviations

AEs	adverse events
ASMF	active substance master file
CLcr	creatinine clearance
CHMP or CPMP	Committee for Medicinal Products for Human Use
EP or Ph. Eur.	European Pharmacopoeia
HPLC	high pressure liquid chromatography
GC	gas chromatography
ICH	International Conference on Harmonisation
ICP	Inductive coupled plasma
IR	infra-red
MAH	Marketing Authorisation Holder
PK	pharmacokinetics
PSUR	periodic safety update report
RH	relative humidity
RMP	Risk Management Plan
SAEs	serious adverse events
SmPC or SPC	Summary of Product Characteristics
TIH	tumour-induced hypercalcaemia
TSE	transmissible spongiform encephalopathy
UV	ultra violet
XRD	X-ray diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mylan S.A.S. submitted on 4 May 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Zoledronic acid Mylan, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 16 December 2010.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication

- Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in patients with advanced malignancies involving bone
- Treatment of tumour-induced hypercalcaemia (TIH)

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information and complete quality data. There is no requirement for bioequivalence testing according to (cf.CPMP/QWP/EWP/1401/98 Rev. 1).

Information on paediatric requirements

Not applicable

The chosen reference product is:

■ Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: ZOMETA 4 mg powder and solvent for solution for infusion and ZOMETA4 mg/5 ml concentrate for solution for infusion.
- Marketing authorisation holder: Novartis Europharm Ltd.
- Date of authorisation: 20/03/2001
- Marketing authorisation granted by:
  - Community
    - Community Marketing authorisation number: EU/1/01/176/001-006

■ Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: ZOMETA 4 mg/5 ml concentrate for solution for infusion.
- Marketing authorisation holder: Novartis Europharm Ltd.
- Date of authorisation: 20/03/2001
- Marketing authorisation granted by:
  - Community
    - Community Marketing authorisation number: EU/1/01/176/004-006

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Not applicable

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturers responsible for batch release

HIKMA FARMACÊUTICA (PORTUGAL) S.A.
Estradra do Rio da Mó, n°8 8-A e 8-B, Fervença
Terrugem SNT, 2705-906
Portugal

MYLAN S.A.S
117 allée des Parcs – 69800 SAINT-PRIEST
France

1.3. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was Milena Stain

- The application was received by the EMA on 4 May 2011.
- The procedure started on 25 May 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 August 2011.
- During the meeting 19-22 September 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 September 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 February 2012.
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 30 March 2012.
- During the CHMP meeting 16-19 April 2012, the CHMP agreed on a List of Outstanding Issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 17 May 2012.

- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 5 June 2012.
- During the meeting on 18-21 June 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Zoledronic acid Mylan on 21 June 2012.

2. Scientific discussion

2.1. Introduction

Zoledronic acid is a bisphosphonate. It stops the action of the osteoclasts, the cells in the body that are involved in breaking down the bone tissue. This leads to less bone loss. The reduction of bone loss helps to make bones less likely to break, which is useful in preventing fractures in cancer patients with bone metastases.

Patients with tumours can have high levels of calcium in their blood, released from the bones. By preventing the breakdown of bones, Zoledronic acid also helps to reduce the amount of calcium released into the blood.

Zoledronic acid Mylan is an application made according to Article 10 (1) generic application of Directive 2001/83/EC. For this application, the reference medicinal product authorised in the Community not less than 6/10 years ago is Zometa 4 mg powder and solvent for solution for infusion and 4mg/5ml concentrate for solution for infusion, by Novartis Europharm Limited. Zometa 4mg powder and solvent for solution for infusion was authorised in the EU on the 20 March 2001 (EU/1/01/176/001-003). Zometa 4mg/5ml concentrate for solution for infusion was authorised on the 24 March 2003 as a line extension to Zometa 4mg powder and solvent for infusion (EU/1/01/176/004-006); this license belongs to the same global marketing authorisation. Zometa 4mg/100ml solution for infusion was also authorised as a line extension (EU/1/01/176/007-009) on the 24 August 2011 under the same global marketing authorisation.

The Zoledronic acid Mylan is designed to be aqueous in nature, contains the same active substance as Zometa and is intended for parenteral administration; in view of this there is no requirement for bioequivalence testing (cf.CPMP/QWP/EWP/1401/98 Rev. 1).

The applicant applied for all the indications of the reference product (Zometa):

- Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in adult patients with advanced malignancies involving bone.
- Treatment of adult patients with tumour-induced hypercalcaemia (TIH).

Zoledronic acid Mylan must only be prescribed and administered to patients by healthcare professionals experienced in the administration of intravenous bisphosphonates.

The recommended dose in the prevention of skeletal related events in patients with advanced malignancies involving bone is 4 mg zoledronic acid every 3 to 4 weeks.

Patients should also be administered an oral calcium supplement of 500 mg and 400 IU vitamin D daily.

The decision to treat patients with bone metastases for the prevention of skeletal related events should consider that the onset of treatment effect is 2-3 months.

The recommended dose in hypercalcaemia is a single dose of 4 mg zoledronic acid.

In patients with renal impairment, the dosing instructions and monitoring of serum creatinine as detailed in SmPC section 4.2 should be followed.

Zoledronic acid Mylan 4 mg/5 ml concentrate for solution for infusion, further diluted in 100 ml should be given as a single intravenous infusion in no less than 15 minutes. Patients must be maintained well hydrated prior to and following administration of Zoledronic acid Mylan.

The safety and efficacy of zoledronic acid in children aged 1 year to 17 years have not been established.

2.2. Quality aspects

2.2.1. Introduction

The product is presented as concentrate for solution for infusion containing 4 mg/5 ml of zoledronic acid as active substance.

Other ingredients are defined in the SPC section 6.1.

The product is packed in clear glass vials with bromobutyl rubber stoppers and aluminium cap with a flip-off component in packs of 1, 4 and 10 vials.

2.2.2. Active substance

The active substance used in Zoledronic acid Mylan is sourced from two suppliers. The information on the active substance is presented in the form of an Active Substance Master File for both of them.

The active substance of Zoledronic acid Mylan is zoledronic acid monohydrate, which has the chemical name: 1-Hydroxy-2-(1*H*-imidazolyl)ethylene-1,1-diphosphoric acid monohydrate. It corresponds to the molecular formula $C_5H_{10}N_2O_7P_2.H_2O$ and relative molecular mass of 290.1.

It appears as a white to almost white crystalline powder, soluble in 0.1N sodium hydroxide solution, slightly soluble in water and practically insoluble in organic solvents. The pH of aqueous suspension is between 2 and 3. It does not exhibit stereo isomerism as it does not contain chiral centre but shows polymorphism. It has been confirmed by data that zoledronic acid manufactured by both active substance suppliers is consistent with regard to the crystalline form.

Manufacture

The information on the active substance is presented in the form of an Active Substance Master File from both suppliers.

Detailed information regarding the control of starting materials, reagents and raw materials as well as the control of critical steps and intermediates is provided in the ASMF.

The synthesis process is sufficiently described in the ASMFs, the choice of the starting materials has been justified, and so have been the process controls, specifications and test methods. Satisfactory information on the validation of production batches, on the manufacturing process development and on the methods used in the control of the starting materials was also provided.

The ASMF holders have adequately discussed the potential carry-over of reagents, solvents and auxiliary material and their presence in the final active substance.

Specification

The specification of the active substance as set up by the drug product manufacturer includes tests and limits for appearance (visual), solubility (Ph.Eur.), clarity and colour index (UV), identification (IR, HPLC, XRD), water content (Ph.Eur.) or loss on drying (Ph.Eur.), heavy metals (Ph.Eur.), assay (HPLC), impurities (HPLC), pH (Ph.Eur.), sulphate and chloride (analytical balance), residual solvents (GC), particle size distribution (laser light diffraction), microbiological quality (Ph.Eur.), bacterial endotoxins (Ph.Eur.), and palladium (ICP).

The specifications are adequate to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety.

Batch analysis data is presented in the ASMFs for three production batches. All the results reported are all within the proposed specifications.

Stability

Stability studies on three production batches of zoledronic acid monohydrate as bulk drug substance packaged in the proposed material were carried out by the first supplier in accordance with current ICH conditions under long term conditions (30°C±2°C/65%±5%RH) and accelerated conditions (40°C±2°C/75%±5%RH).
For stability studies carried out at long term conditions results are available for a time period of 48 months. For the studies performed at accelerated conditions results are presented for a time period of 6 months.

Stability studies on three production batches of zoledronic acid monohydrate as bulk drug substance packaged in the proposed material were carried out by the second supplier in accordance with current ICH conditions under long term conditions (25°C±2°C/60%±5%RH) and accelerated conditions (40°C±2°C/75%±5%RH).
For stability studies carried out at long term conditions results are available for a time period of 36 months. For the studies performed at accelerated conditions results are presented for a time period of 6 months.

Samples were tested for *parameters that are susceptible to change during storage* (description, water content, related substances and assay) using validated analytical methods shown to be stability indicating. At all time points all tested parameters are within the limits of the drug substance specification.

Stress studies (forced degradation studies)

Forced degradation studies were conducted by both suppliers. Under the tested conditions the active substance showed to be stable under acidic and alkalic conditions as well as under light and temperature but susceptible to oxidation.

Based on the stability data provided the proposed re-test period is supported.

2.2.3. Finished medicinal product

Pharmaceutical development

The objective was to develop a generic product similar in formulation, dosage form, concentration and use to the reference drug product Zometa 4 mg/5 ml concentrate for solution for infusion.
Zoledronic acid Mylan 4 mg/5 ml concentrate for solution for infusion is a clear and colourless solution filled in type I glass vial of 15 ml. Each vial contains a quantity of 4.264 mg Zoledronic acid monohydrate equivalent to 4.0 mg of anhydrous Zoledronic acid.
All excipients which are used for the manufacture of the drug product are monographed in Ph. Eur.
Zoledronic acid Mylan was formulated on the basis of the innovator composition with a sodium citrate buffer. No new excipient was introduced in the proposed formulation except sodium hydroxide and hydrochloric acid. These excipients are commonly used for pH adjustment and generally do not generate any compatibility problem. Therefore no specific compatibility studies were warranted.
Different formulae were developed and tested. Appearance and pH are relevant for the biological properties and the stability of the drug product. In order to compare the stability profile of different developed formulae and to highlight conditions which could degrade the drug product a stress study was performed. According to the obtained study results the physicochemical characteristics of the proposed product that can influence the performance and manufacturability of the drug product are considered similar to those of Zometa 4 mg/ 5 ml concentrate for solution for infusion.
Furthermore, the osmolality of the diluted solution was compared between reference product and the proposed medicinal product. It was concluded that the proposed medicinal product when diluted in 0.9 % w/v Sodium chloride solution and 5 % w/v Glucose solution has the same osmolality as the reference product diluted in the same conditions.
Appropriate studies to evaluate the risk of formation of insoluble complexes with divalent cations which are constituents of pharmaceutical glass have been presented. Overall the provided data and the toxicological assessment were considered sufficient and the choice of the proposed glass vials as primary container of Zoledronic acid Mylan can be considered justified.

The manufacturing process is considered as a "standard process" according to CPMP/QWP/848/96 Note for Guidance on Process Validation. The manufacture of this non-heat sensitive solution for infusion filled in glass vials consists of compounding, filtration, filling and terminal sterilisation.
A stress study was performed to define potential manufacturing conditions which could degrade the drug product. Zoledronic acid solutions were exposed to different stress conditions. According to the results of the stress study the optimal parameters with regards to stability and intravenous administration were defined. It was further concluded that the drug product sterilisation method, packaging and proposed storage conditions were suitable.
In the course of the manufacturing process development the optimum introduction of components with regard to active substance dissolution time was established.
Holding times set after relevant steps of the manufacturing process are considered justified. The absence of any adsorption of the actives substance during the filtration steps was checked during process validation.
The method of sterilisation was chosen in compliance with the requirements of the European Pharmacopoeia and the EMEA guideline CPMP/QWP/054/98. Terminal sterilisation was selected due to stability of the formulation.

Since the drug product is intended for parenteral use, the sterility of the solution is of importance. The microbial quality is therefore monitored during the manufacturing process and at release. Furthermore, as the drug substance is administered by injection no visible particle and a limited quantity of sub-visible particles should be present. Visible particles are monitored during the manufacturing process and visible and sub-visible particles are controlled at release.
During manufacture of the drug product an overfilling is performed. The overfilling ensures a minimal extractable volume of 5 ml concentrate which corresponds to a labelled amount of 4 mg anhydrous Zoledronic acid per vial in accordance with the SmPC.

Adventitious agents

No TSE risk materials are used in the manufacture of the finished product.

Manufacture of the product

The manufacturing process is described sufficiently and is controlled by adequate in-process controls.
A list of equipment used during the manufacturing process is provided.
As the manufacturing process is considered as a standard process it is sufficient that process validation data for three pilot batches were provided. The actual commercial batch size has been defined.
The sterilisation methods of the final product (terminal sterilisation) and of the primary packaging materials are according to Ph. Eur.
A survey table on critical steps, tested parameters, acceptance limits and applied test methods is presented. Overall the provided information is considered adequate and sufficient.

Product specification

The finished product release and shelf-life specifications includes tests and limits for appearance (visually), clarity and degree of opalescence (Ph.Eur.), identification of active substance (HPLC, UV), pH (Ph.Eur.), impurities (HPLC), extractable volume (Ph.Eur.), particulate contamination (Ph.Eur.), bacterial endotoxins (Ph.Eur.), sterility (Ph.Eur.) and assay (Ph.Eur.).
Batch analyses data and Certificates of analysis are presented for three validation batches manufactured using active substance from one of the two suppliers.
For all parameters the obtained results from batch analyses are within the limits defined in the release specification.
The applicant committed to validate the manufacturing process for the first finished product batch manufactured with the drug substance supplied by the other supplier according to a presented protocol. In view of this and the fact that the quality of the drug substance from both suppliers was shown to be similar it has been accepted that batch analyses data from batches manufactured with active substance from the other suppliers were not available prior to authorisation.
All results reported indicate that the process is under control, confirming consistency and uniformity of manufacture.

Stability of the product

Stability studies were performed with three validation batches under long term conditions (25°C±2°C/60%RH±5%RH) and under accelerated conditions (40°C±2°C/75%RH±5%RH). The vials were positioned upside and downside. For all three batches results from stability studies over a time

period of 12 months under long term conditions and 6 months under accelerated conditions were presented. All tested parameters (appearance, clarity and degree of opalescence, pH, phosphate and phosphite, impurities, particulate contamination sterility, assay and bacterial endotoxins) remained within the specifications.

In-use stability study

An in-use stability study was carried out with one validation batch stored nine months at 25°C/60%RH after dilution in 0.9%w/v Sodium chloride solution and 5%w/v Glucose solution. The drug product was packaged as for sale. The commercial packaging for the perfusion diluent is a polyolefin bag.
The analytical procedures used are those for the control of the drug product at release and are stability indicating. According to CPMP/QWP/2934/99 the study will be repeated with one batch chosen at the end of its shelf-life when available. According to the obtained results Zoledronic acid Mylan was demonstrated to be stable up to 48 hours after dilution at extreme concentrations in 100 ml 0.9 %w/v Sodium chloride or 5% w/v Glucose solution when stored at 4°C or 25°C.

Photostability study

Photostability testing was carried out with one batch according to the relevant guideline. The drug product was packaged in the proposed packaging. The analytical procedures used are those for the control of the drug product at release. According to the obtained results the primary and secondary packaging provide the necessary protection from light. Although a slight degradation is observed when the product is stored in its primary packaging the product quality remains within the specification. The results are in line with the photostability results of the drug substance from both sources and those obtained for process development on the bulk solution.

In conclusion, stability studies were carried out according to the relevant ICH/CPMP guidelines and included parameters susceptible to change. The obtained results for the tested parameters at all time points are within the limits defined in the shelf-life specification.
An adequate compatibility study for the stability of Zoledronic acid 4 mg/ 5 ml concentrate diluted in 0.9%w/v Sodium chloride solution and 5%w/v Glucose solution was performed.
In the course of the stability studies an additional limit test for two identified impurities was carried out by a suitable and adequately validated method. These two impurities are identified as potential inorganic impurities of zoledronic acid monohydrate. It has been shown they are process related impurities and not degradation products and therefore are not specified as a routine basis in the drug product specifications.
Based on the results of the stability studies, the proposed shelf-life when stored in the original packaging and the storage conditions stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable

2.3. Non- clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

2.3.2. Ecotoxicity/Environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Zoledronic acid Mylan is considered unlikely to result in any significant increase in the combined sales volumes for all zoledronic acid containing products and the exposure of the environment to the active substance. Thus, the environmental risk is expected to be similar and not increased.

2.3.3. Discussion on non-clinical aspects

Not applicable

2.3.4. Conclusion on the non-clinical aspects

Not applicable

2.4. Clinical aspects

2.4.1. Introduction

This is an application for concentrate for solution for infusion containing 4 mg/5 ml zoledronic acid. The Applicant claims essential similarity for their product Zoledronic acid Mylan 4 mg/5 ml concentrate for solution for infusion with the reference product Zometa 4 mg/5 ml concentrate for solution for infusion.

No bioequivalence studies were submitted with this application. Bioequivalence testing with the reference product is not required under the provisions of the "Guideline on the Investigation of

Bioequivalence" (CPMP/QWP/EWP/1401/98 Rev.1): "Bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product".
A bioequivalence study for Zoledronic acid Mylan is not required as the product contains the same active substance as the reference product and is intended for intravenous route use.

The claim of essential similarity can be accepted. There are no objections to the approval of Zoledronic acid Mylan 4 mg/5 ml concentrate for solution for infusion from a clinical point of view.

GCP

Not applicable

Exemption

Not applicable

Clinical studies

Not applicable

2.4.2. Pharmacokinetics

Not applicable

2.4.3. Post marketing experience

No post-marketing data are available for Zoledronic acid Mylan. The medicinal product has not been marketed in any country.

2.4.4. Discussion on clinical aspects

No bioequivalence studies were submitted with this application. Bioequivalence testing with the reference product is not required under the provisions of the "Guideline on the Investigation of Bioequivalence" (CPMP/QWP/EWP/1401/98 Rev.1): "Bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product".
A bioequivalence study for Zoledronic acid Mylan is not required as the product contains the same active substance as the reference product and is intended for intravenous route use.

2.4.5. Conclusion on clinical aspects

A clinical overview has been provided, which is based on scientific literature. The claim of essential similarity can be accepted. The claimed indications are in accordance with those of the reference product.
There are no objections to the approval of Zoledronic acid Mylan 4 mg/5 ml, concentrate for solution for infusion from a clinical point of view.

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk management plan

The applicant submitted a risk management plan.

Table 1. Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important identified risks		
Renal function impairment	1) Close monitoring through routine pharmacovigilance 2) Follow up of reports 3) Cumulative analysis in PSURs	Information is included in labelling (SPC sections 4.2, 4.4, 4.5, and 4.8). Section 4.2 Renal impairment TIH: Zoledronic acid treatment in TIH patients who also have severe renal impairment should be considered only after evaluating the risks and benefits of treatment. In the clinical studies, patients with serum creatinine > 400 µmol/l or > 4.5 mg/dl were excluded. No dose adjustment is necessary in TIH patients with serum creatinine < 400 µmol/l or < 4.5 mg/dl (see section 4.4). Prevention of skeletal related events in patients with advanced malignancies involving bone: When initiating treatment with zoledronic acid in patients with multiple myeloma or metastatic bone lesions from solid tumours, serum creatinine and creatinine clearance (CLcr) should be determined. CLcr is calculated from serum creatinine using the Cockcroft-Gault formula. Zoledronic acid is not recommended for patients presenting with severe renal impairment prior to initiation of therapy, which is defined for this population as CLcr < 30 ml/min. In clinical trials with zoledronic acid, patients with serum creatinine > 265 µmol/l or > 3.0 mg/dl were excluded. In patients with bone metastases presenting with mild to moderate renal impairment prior to initiation of therapy, which is defined for this

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		population as CLcr 30–60 ml/min, the following zoledronic acid dose is recommended (see also section 4.4): Baseline Creatinine Clearance (ml/min) / Zoledronic acid recommended dose* > 60 / 4.0 mg zoledronic acid 50–60 / 3.5 mg* zoledronic acid 40–49 / 3.3 mg* zoledronic acid 30–39 / 3.0 mg* zoledronic acid *Doses have been calculated assuming target AUC of 0.66 (mg•hr/l) (CLcr=75 ml/min). The reduced doses for patients with renal impairment are expected to achieve the same AUC as that seen in patients with creatinine clearance of 75 ml/min. Following initiation of therapy, serum creatinine should be measured prior to each dose of zoledronic acid and treatment should be withheld if renal function has deteriorated. In the clinical trials, renal deterioration was defined as follows: For patients with normal baseline serum creatinine (< 1.4 mg/dl or < 124 µmol/l), an increase of 0.5 mg/dl or 44 µmol/l; For patients with abnormal baseline creatinine (> 1.4 mg/dl or > 124 µmol/l), an increase of 1.0 mg/dl or 88 µmol/l. In the clinical studies, zoledronic acid treatment was resumed only when the creatinine level returned to within 10% of the baseline value (see section 4.4). Zoledronic acid treatment should be resumed at the same dose as that given prior to treatment interruption. Section 4.4 Renal insufficiency Patients with TIH and evidence of deterioration in renal function should be appropriately evaluated with consideration given as to whether the potential benefit of treatment with zoledronic acid outweighs the possible risk. The decision to treat patients with bone metastases for the prevention of skeletal related events should consider that the onset of treatment effect is 2–3 months. Zoledronic acid has been associated with reports of renal dysfunction. Factors that may increase the

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of zoledronic acid and other bisphosphonates as well as use of other nephrotoxic medicinal products. While the risk is reduced with a dose of 4 mg zoledronic acid administered over 15 minutes, deterioration in renal function may still occur. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of 4 mg zoledronic acid. Increases in serum creatinine also occur in some patients with chronic administration of zoledronic acid at recommended doses for prevention of skeletal related events, although less frequently. Patients should have their serum creatinine levels assessed prior to each dose of zoledronic acid. Upon initiation of treatment in patients with bone metastases with mild to moderate renal impairment, lower doses of zoledronic acid are recommended. In patients who show evidence of renal deterioration during treatment, zoledronic acid should be withheld. Zoledronic acid should only be resumed when serum creatinine returns to within 10% of baseline. Zoledronic acid treatment should be resumed at the same dose as that given prior to treatment interruption. In view of the potential impact of zoledronic acid on renal function, the lack of clinical safety data in patients with severe renal impairment (in clinical trials defined as serum creatinine ≥ 400 µmol/l or ≥ 4.5 mg/dl for patients with TIH and ≥ 265 µmol/l or ≥ 3.0 mg/dl for patients with cancer and bone metastases, respectively) at baseline and only limited pharmacokinetic data in patients with severe renal impairment at baseline (creatinine clearance < 30 ml/min), the use of zoledronic acid is not recommended in patients with severe renal impairment. Section 4.5 Caution is indicated when zoledronic acid is used with other potentially nephrotoxic medicinal products. In multiple myeloma patients, the risk of renal dysfunction may be increased when zoledronic acid is used in combination with thalidomide. Section 4.8

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		The following are the important identified risks with zoledronic acid in the approved indications: Renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, ocular adverse events, atrial fibrillation, anaphylaxis. Tabulated list of adverse reactions The following adverse reactions, listed in Table 1, have been accumulated from clinical studies and post-marketing reports following predominantly chronic treatment with 4 mg zoledronic acid: Renal and urinary disorders Common: Renal impairment Uncommon: Acute renal failure, haematuria, proteinuria Description of selected adverse reactions Renal function impairment Zoledronic acid has been associated with reports of renal dysfunction. In a pooled analysis of safety data from zoledronic acid registration trials for the prevention of skeletal-related events in patients with advanced malignancies involving bone, the frequency of renal impairment adverse events suspected to be related to zoledronic acid (adverse reactions) was as follows: multiple myeloma (3.2%), prostate cancer (3.1%), breast cancer (4.3%), lung and other solid tumours (3.2%). Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of zoledronic acid or other bisphosphonates, as well as concomitant use of nephrotoxic medicinal products or using a shorter infusion time than currently recommended. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of 4 mg zoledronic acid (see section 4.4).
Osteonecrosis of the jaw (ONJ)	1) Close monitoring through routine pharmacovigilance 2) Follow up of reports 3) Cumulative analysis in PSURs	Information is included in labelling (SPC sections 4.4, 4.5 and 4.8) Section 4.4 Osteonecrosis of the jaw Osteonecrosis of the jaw (ONJ) has been reported in patients, predominantly those with cancer, receiving treatment with medicinal products that inhibit bone resorption, such as zoledronic acid. Many of these patients were also receiving chemotherapy and corticosteroids. The

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		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, corticosteroids, poor oral hygiene). 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. Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment. Section 4.5 Reports of ONJ have been received in patients treated with zoledronic acid and concomitant anti-angiogenic medicinal products. Section 4.8 The following are the important identified risks with zoledronic acid in the approved indications: Renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, ocular adverse events, atrial fibrillation, anaphylaxis. Tabulated list of adverse reactions The following adverse reactions, listed in Table 1, have been accumulated from clinical studies and post-marketing reports following predominantly chronic treatment with 4 mg zoledronic acid: Musculoskeletal and connective tissue disorders Uncommon: Osteonecrosis of the jaw* * Based on clinical trials with adjudication of possible cases of osteonecrosis of the jaw. Since these reports are subject to confounding factors, it is not possible to reliably establish a causal relationship to exposure to the medicinal product.

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		Description of selected adverse reactions Osteonecrosis of the jaw Cases of osteonecrosis (primarily of the jaws) have been reported, predominantly in cancer patients treated with medicinal products that inhibit bone resorption, such as zoledronic acid. 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 jaws has multiple documented risk factors including a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids) and co-morbid conditions (e.g. anaemia, coagulopathies, infection, pre-existing oral disease). Although causality has not been determined, it is recommended to avoid dental surgery as recovery may be prolonged (see section 4.4).
Acute phase reaction	1) Close monitoring through routine pharmacovigilance 2) Cumulative analysis in PSURs	Information is included in labelling (SPC section 4.8) Section 4.8 Summary of the safety profile Within three days after zoledronic acid administration, an acute phase reaction has commonly been reported, with symptoms including bone pain, fever, fatigue, arthralgia, myalgia and rigors; these symptoms usually resolve within a few days (see description of selected adverse reactions). The following are the important identified risks with zoledronic acid in the approved indications: Renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, ocular adverse events, atrial fibrillation, anaphylaxis. Tabulated list of adverse reactions The following adverse reactions, listed in Table 1, have been accumulated from clinical studies and post-marketing reports following predominantly chronic treatment with 4 mg zoledronic acid: General disorders and administration site conditions Common: Acute phase reaction Description of selected adverse reactions

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		Acute phase reaction This adverse drug reaction consists of a constellation of symptoms that includes fever, myalgia, headache, extremity pain, nausea, vomiting, diarrhoea and arthralgia. The onset time is ≤ 3 days post-zoledronic acid infusion, and the reaction is also referred to using the terms "flu-like" or "post-dose"
Hypocalcemia	1) Close monitoring through routine pharmacovigilance 2) Cumulative analysis in PSURs	Information is included in labelling (SPC sections 4.2, 4.4, 4.5 and 4.8) Section 4.2 Prevention of skeletal related events in patients with advanced malignancies involving bone Adults and elderly The recommended dose in the prevention of skeletal related events in patients with advanced malignancies involving bone is 4 mg zoledronic acid every 3 to 4 weeks. Patients should also be administered an oral calcium supplement of 500 mg and 400 IU vitamin D daily. Section 4.4 Standard hypercalcaemia-related metabolic parameters, such as serum levels of calcium, phosphate and magnesium, should be carefully monitored after initiating zoledronic acid therapy. If hypocalcaemia, hypophosphataemia, or hypomagnesaemia occurs, short-term supplemental therapy may be necessary. Untreated hypercalcaemia patients generally have some degree of renal function impairment, therefore careful renal function monitoring should be considered. Section 4.5 Caution is advised when bisphosphonates are administered with aminoglycosides, since both agents may have an additive effect, resulting in a lower serum calcium level for longer periods than required. Section 4.8 The following are the important identified risks with zoledronic acid in the approved indications: Renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, ocular adverse events, atrial fibrillation, anaphylaxis.

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		Tabulated list of adverse reactions The following adverse reactions, listed in Table 1, have been accumulated from clinical studies and post-marketing reports following predominantly chronic treatment with 4 mg zoledronic acid: Investigations Common: Hypocalcaemia
Ocular adverse events	1) Close monitoring through routine pharmacovigilance 2) Cumulative analysis in PSURs	Information is included in labelling (SPC section 4.8) Section 4.8 The following are the important identified risks with zoledronic acid in the approved indications: Renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, ocular adverse events, atrial fibrillation, anaphylaxis. Tabulated list of adverse reactions The following adverse reactions, listed in Table 1, have been accumulated from clinical studies and post-marketing reports following predominantly chronic treatment with 4 mg zoledronic acid: Eye disorders Common: Conjunctivitis Uncommon: Blurred vision, scleritis and orbital inflammation Very rare: Uveitis, episcleritis
Atrial fibrillation	1) Close monitoring through routine pharmacovigilance 2) Follow up of reports 3) Cumulative analysis in PSURs	Information is included in labelling (SPC section 4.8) Section 4.8 The following are the important identified risks with zoledronic acid in the approved indications: Renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, ocular adverse events, atrial fibrillation, anaphylaxis. Tabulated list of adverse reactions The following adverse reactions, listed in Table 1, have been accumulated from clinical studies and post-marketing reports following predominantly chronic treatment with 4 mg zoledronic acid: Cardiac disorders Uncommon: Atrial fibrillation Description of selected adverse reactions

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		Atrial fibrillation In one 3-year, randomised, double-blind controlled trial that evaluated the efficacy and safety of zoledronic acid 5 mg once yearly vs. placebo in the treatment of postmenopausal osteoporosis (PMO), 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 zoledronic acid 5 mg 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 5 mg and placebo, respectively. The imbalance observed in this trial has not been observed in other trials with zoledronic acid, including those with zoledronic acid 4 mg every 3-4 weeks in oncology patients. The mechanism behind the increased incidence of atrial fibrillation in this single clinical trial is unknown.
GI disorders in paediatric osteogenesis imperfecta patients	1) Close monitoring through routine pharmacovigilance 2) Cumulative analysis in PSURs	This item is appropriately communicated through current labeling. Not applicable for EU.
Anaphylaxis	1) Close monitoring through routine pharmacovigilance 2) Cumulative analysis in PSURs	Information is included in labelling (SPC section 4.8) Section 4.8 The following are the important identified risks with zoledronic acid in the approved indications: Renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, ocular adverse events, atrial fibrillation, anaphylaxis. Tabulated list of adverse reactions The following adverse reactions, listed in Table 1, have been accumulated from clinical studies and post-marketing reports following predominantly chronic treatment with 4 mg zoledronic acid: Immune system disorders Uncommon: Hypersensitivity reaction Rare: Angioneurotic oedema General disorders and administration site conditions Uncommon: Anaphylactic reaction/shock, urticaria
Important potential risks		

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Cardiac arrhythmias	1) Close monitoring through routine pharmacovigilance 2) Follow up of reports 3) Cumulative analysis in PSURs	Atrial fibrillation and bradycardia are included in labelling (SPC section 4.8) Section 4.8 Tabulated list of adverse reactions The following adverse reactions, listed in Table 1, have been accumulated from clinical studies and post-marketing reports following predominantly chronic treatment with 4 mg zoledronic acid: Cardiac disorders Uncommon: Atrial fibrillation Rare: Bradycardia
Cerebrovascular AEs	1) Close monitoring through routine pharmacovigilance 2) Follow up of reports 3) Cumulative analysis in PSURs	Currently available data do not support the need for risk minimization
Focal Segmental Glomerulosclerosis	1) Close monitoring through routine pharmacovigilance 2) Cumulative analysis in PSURs	Currently available data do not support the need for risk minimization
Fracture healing impairment	1) Close monitoring through routine pharmacovigilance 2) Cumulative analysis in PSURs	Information is included in labelling (SPC sections 4.4) Section 4.4 Atypical fractures of the femur […] 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.
Interstitial lung disease	1) Close monitoring through routine pharmacovigilance 2) Follow up of reports 3) Cumulative analysis in PSURs	Currently available data do not support the need for risk minimization
Atypical femoral fractures	1) Close monitoring through routine pharmacovigilance 2) Follow up of reports 3) Review in PSURs	Atypical femoral fracture is included in labelling (SPC section 4.4 and 4.8) Warning in section 4.4 on the risk of atypical fractures of the femur and listed as a class adverse reaction in 4.8. For bisphosphonates indicated for osteoporosis: section 4.2 includes information about the need to periodically evaluate the need for continuing bisphosphonate treatment, particularly after 5 years of treatment, on an individual patient basis. Section 4.4

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		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. Section 4.8 Atypical fractures of the femur During post-marketing experience the following reactions have been reported (frequency rare): Atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction).
Bone growth impairment in paediatric osteogenesis imperfecta patients	1) Close monitoring through routine pharmacovigilance 2) Cumulative analysis in PSURs	Currently available data do not support the need for risk minimization
Progressive hearing loss in paediatric osteogenesis imperfecta patients	1) Close monitoring through routine pharmacovigilance 2) Cumulative analysis in PSURs	Currently available data do not support the need for risk minimization

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Increased risk of fractures in paediatric type I osteogenesis imperfecta patients	1) Close monitoring through routine pharmacovigilance 2) Cumulative analysis in PSURs	Currently available data do not support the need for risk minimization
Medication errors	1) Close monitoring through routine pharmacovigilance 2) Follow up of reports 3) Cumulative analysis in PSURs	Appropriate labelling
Potential interactions		
Products that can significantly affect renal function	1) Close monitoring through routine pharmacovigilance 2) Cumulative analysis in PSURs	Information is included in labelling (SPC sections 4.4 and 4.5) Section 4.4 Renal insufficiency Patients with TIH and evidence of deterioration in renal function should be appropriately evaluated with consideration given as to whether the potential benefit of treatment with zoledronic acid outweighs the possible risk. The decision to treat patients with bone metastases for the prevention of skeletal related events should consider that the onset of treatment effect is 2–3 months. Zoledronic acid has been associated with reports of renal dysfunction. Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of zoledronic acid and other bisphosphonates as well as use of other nephrotoxic medicinal products. While the risk is reduced with a dose of 4 mg zoledronic acid administered over 15 minutes, deterioration in renal function may still occur. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of 4 mg zoledronic acid. Increases in serum creatinine also occur in some patients with chronic administration of zoledronic acid at recommended doses for prevention of skeletal related events, although less frequently. Patients should have their serum creatinine levels assessed prior to each dose of zoledronic acid. Upon initiation of treatment in patients with bone metastases with mild to moderate renal impairment, lower doses of zoledronic acid are recommended. In patients who show

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		evidence of renal deterioration during treatment, zoledronic acid should be withheld. Zoledronic acid should only be resumed when serum creatinine returns to within 10% of baseline. Zoledronic acid treatment should be resumed at the same dose as that given prior to treatment interruption. In view of the potential impact of zoledronic acid on renal function, the lack of clinical safety data in patients with severe renal impairment (in clinical trials defined as serum creatinine ≥ 400 µmol/l or ≥ 4.5 mg/dl for patients with TIH and ≥ 265 µmol/l or ≥ 3.0 mg/dl for patients with cancer and bone metastases, respectively) at baseline and only limited pharmacokinetic data in patients with severe renal impairment at baseline (creatinine clearance < 30 ml/min), the use of zoledronic acid is not recommended in patients with severe renal impairment. Section 4.5 Caution is indicated when zoledronic acid is used with other potentially nephrotoxic medicinal products. Attention should also be paid to the possibility of hypomagnesaemia developing during treatment. In multiple myeloma patients, the risk of renal dysfunction may be increased when zoledronic acid is used in combination with thalidomide.
Important missing information		
Races other than Caucasian	1) Close monitoring through routine pharmacovigilance	Currently available data do not support the need for risk minimization
Fertility, Pregnancy and Lactation	1) Close monitoring through routine pharmacovigilance	Information is included in labelling (SPC section 4.3, 4.6 and 5.3) Section 4.3 Breast-feeding (see section 4.6) Section 4.6 Pregnancy There are no adequate data on the use of zoledronic acid in pregnant women. Animal reproduction studies with zoledronic acid have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Zoledronic acid should not be used during pregnancy. Breast-feeding

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		It is not known whether zoledronic acid is excreted into human milk. Zoledronic acid is contraindicated in breast-feeding women (see section 4.3). 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 to be related to the compound's inhibition of skeletal calcium metabolisation, resulting in periparturient hypocalcaemia, a bisphosphonate class effect, dystocia and early termination of the study. Thus these results precluded determining a definitive effect of zoledronic acid on fertility in humans. Section 5.3 Reproduction toxicity Zoledronic acid was teratogenic in the rat at subcutaneous doses ≥ 0.2 mg/kg. Although no teratogenicity or foetotoxicity was observed in the rabbit, maternal toxicity was found. Dystocia was observed at the lowest dose (0.01 mg/kg bodyweight) tested in the rat.
Patients with severe renal impairment	1) Close monitoring through routine pharmacovigilance	Information is included in labelling (SPC sections 4.2, 4.4, 4.5 and 4.8) Section 4.2 Renal impairment TIH: Zoledronic acid treatment in TIH patients who also have severe renal impairment should be considered only after evaluating the risks and benefits of treatment. In the clinical studies, patients with serum creatinine > 400 µmol/l or > 4.5 mg/dl were excluded. No dose adjustment is necessary in TIH patients with serum creatinine < 400 µmol/l or < 4.5 mg/dl (see section 4.4). Prevention of skeletal related events in patients with advanced malignancies involving bone: When initiating treatment with zoledronic acid in patients with multiple myeloma or metastatic bone lesions from solid tumours, serum creatinine and creatinine clearance (CLcr) should be determined. CLcr is calculated from serum creatinine using the Cockcroft-Gault formula. Zoledronic acid is not recommended for patients presenting with severe renal impairment prior to initiation of

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		therapy, which is defined for this population as CLcr < 30 ml/min. In clinical trials with zoledronic acid, patients with serum creatinine > 265 µmol/l or > 3.0 mg/dl were excluded. In patients with bone metastases presenting with mild to moderate renal impairment prior to initiation of therapy, which is defined for this population as CLcr 30–60 ml/min, the following zoledronic acid dose is recommended (see also section 4.4): Baseline Creatinine Clearance (ml/min) / Zoledronic acid recommended dose* > 60 / 4.0 mg zoledronic acid 50–60 / 3.5 mg* zoledronic acid 40–49 / 3.3 mg* zoledronic acid 30–39 / 3.0 mg* zoledronic acid *Doses have been calculated assuming target AUC of 0.66 (mg•hr/l) (CLcr=75 ml/min). The reduced doses for patients with renal impairment are expected to achieve the same AUC as that seen in patients with creatinine clearance of 75 ml/min. Following initiation of therapy, serum creatinine should be measured prior to each dose of zoledronic acid and treatment should be withheld if renal function has deteriorated. In the clinical trials, renal deterioration was defined as follows: For patients with normal baseline serum creatinine (< 1.4 mg/dl or < 124 µmol/l), an increase of 0.5 mg/dl or 44 µmol/l; For patients with abnormal baseline creatinine (> 1.4 mg/dl or > 124 µmol/l), an increase of 1.0 mg/dl or 88 µmol/l. In the clinical studies, zoledronic acid treatment was resumed only when the creatinine level returned to within 10% of the baseline value (see section 4.4). Zoledronic acid treatment should be resumed at the same dose as that given prior to treatment interruption. Section 4.4 Renal insufficiency Patients with TIH and evidence of deterioration in renal function should be appropriately evaluated with consideration given as to whether the potential benefit of treatment with zoledronic acid outweighs the possible risk.

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		The decision to treat patients with bone metastases for the prevention of skeletal related events should consider that the onset of treatment effect is 2–3 months. Zoledronic acid has been associated with reports of renal dysfunction. Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of zoledronic acid and other bisphosphonates as well as use of other nephrotoxic medicinal products. While the risk is reduced with a dose of 4 mg zoledronic acid administered over 15 minutes, deterioration in renal function may still occur. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of 4 mg zoledronic acid. Increases in serum creatinine also occur in some patients with chronic administration of zoledronic acid at recommended doses for prevention of skeletal related events, although less frequently. Patients should have their serum creatinine levels assessed prior to each dose of zoledronic acid. Upon initiation of treatment in patients with bone metastases with mild to moderate renal impairment, lower doses of zoledronic acid are recommended. In patients who show evidence of renal deterioration during treatment, zoledronic acid should be withheld. Zoledronic acid should only be resumed when serum creatinine returns to within 10% of baseline. Zoledronic acid treatment should be resumed at the same dose as that given prior to treatment interruption. In view of the potential impact of zoledronic acid on renal function, the lack of clinical safety data in patients with severe renal impairment (in clinical trials defined as serum creatinine ≥ 400 µmol/l or ≥ 4.5 mg/dl for patients with TIH and ≥ 265 µmol/l or ≥ 3.0 mg/dl for patients with cancer and bone metastases, respectively) at baseline and only limited pharmacokinetic data in patients with severe renal impairment at baseline (creatinine clearance < 30 ml/min), the use of zoledronic acid is not recommended in patients with severe renal impairment. Section 4.5 Caution is indicated when zoledronic

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		acid is used with other potentially nephrotoxic medicinal products. Section 4.8 The following are the important identified risks with zoledronic acid in the approved indications: Renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, ocular adverse events, atrial fibrillation, anaphylaxis. Tabulated list of adverse reactions The following adverse reactions, listed in Table 1, have been accumulated from clinical studies and post-marketing reports following predominantly chronic treatment with 4 mg zoledronic acid: Renal and urinary disorders Common: Renal impairment Uncommon: Acute renal failure, haematuria, proteinuria Description of selected adverse reactions Renal function impairment Zoledronic acid has been associated with reports of renal dysfunction. In a pooled analysis of safety data from zoledronic acid registration trials for the prevention of skeletal-related events in patients with advanced malignancies involving bone, the frequency of renal impairment adverse events suspected to be related to zoledronic acid (adverse reactions) was as follows: multiple myeloma (3.2%), prostate cancer (3.1%), breast cancer (4.3%), lung and other solid tumours (3.2%). Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of zoledronic acid or other bisphosphonates, as well as concomitant use of nephrotoxic medicinal products or using a shorter infusion time than currently recommended. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of 4 mg zoledronic acid (see section 4.4).
Patients with hepatic insufficiency	1) Close monitoring through routine pharmacovigilance	Information is included in labelling (SPC sections 4.4 and 5.2) Section 4.4 Hepatic insufficiency As only limited clinical data are available in patients with severe hepatic insufficiency, no specific

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		recommendations can be given for this patient population. Section 5.2 No pharmacokinetic data for zoledronic acid are available in patients with hypercalcaemia or in patients with hepatic insufficiency. Zoledronic acid does not inhibit human P450 enzymes in vitro, shows no biotransformation and in animal studies < 3% of the administered dose was recovered in the faeces, suggesting no relevant role of liver function in the pharmacokinetics of zoledronic acid.
Paediatric osteogenesis imperfecta patients <1 year	1) Close monitoring through routine pharmacovigilance	This item is appropriately communicated through current labeling. Not applicable for EU.
Paediatric patients with renal impairment	1) Close monitoring through routine pharmacovigilance	This item is appropriately communicated through current labeling. Not applicable for EU.

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

PSUR submission

The PSUR submission schedule should follow the PSUR schedule for the reference product, which currently is on a 1-yearly cycle until otherwise decided by the CHMP. The next data lock point for the reference medicinal product is 31 August 2012.

User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to another Mylan's product. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of zoledronic acid concentrate for solution for infusion (4mg/ 5 ml). The reference product Zometa is indicated for the prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced

hypercalcaemia) in patients with advanced malignancies involving bone, and for treatment of tumour-induced hypercalcaemia (TIH).

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

There are no bioequivalence studies submitted with this application, and this is not required under the provisions of the "Guideline on the Investigation of Bioequivalence" (CPMP/QWP/EWP/1401/98 Rev.1), as the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Zoledronic acid Mylan in the:

"Prevention of skeletal related events (pathological fractures, spinal compression, radiation or

surgery to bone, or tumour-induced hypercalcaemia) in adult patients with advanced

malignancies involving bone.

Treatment of adult patients with tumour-induced hypercalcaemia (TIH)"

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

Pharmacovigilance System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

Risk management system

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA.

PSUR cycle

The PSUR cycle for the product will follow PSURs submission schedule for the reference medicinal product.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable