Public Assessment Report

Decentralised Procedure

Zoledronic acid 5 mg solution for infusion

(Zoledronic acid)

Procedure No: UK/H/6144/001/DC

UK Licence No: PL 42117/0005

Emcure Pharma UK Ltd.
LAY SUMMARY

Zoledronic acid 5 mg solution for infusion

(Zoledronic acid, solution for infusion, 5 mg/100ml)

This is a summary of the Public Assessment Report (PAR) for Zoledronic acid 5 mg solution for infusion (PL 42117/0005; UK/H/6144/001/DC). It explains how Zoledronic acid 5 mg solution for infusion was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Zoledronic acid 5 mg solution for infusion.

For practical information about using Zoledronic acid 5 mg solution for infusion patients should read the package leaflet or contact their doctor or pharmacist.

The product will be referred to as Zoledronic Acid throughout the remainder of this public assessment report.

What is Zoledronic Acid and what is it used for?
Zoledronic Acid is a ‘generic medicine’. This means that Zoledronic Acid is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Aclasta 5 mg solution for infusion (Novartis Europharm Limited, UK).

Zoledronic Acid contains the active substance zoledronic acid. It belongs to a group of medicines called bisphosphonates and is used to treat post-menopausal women and adult men with osteoporosis or osteoporosis caused by treatment with steroids, and Paget's disease of the bone in adults.

How does Zoledronic Acid work?
In 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. Many patients with osteoporosis have no symptoms but they are still at risk of breaking bones because osteoporosis has made their bones weaker. Decreased circulating levels of sex hormones, mainly oestrogens converted from androgens, also play a role in the more gradual bone loss observed in men. In both women and men, Zoledronic Acid strengthens the bone and therefore makes it less likely to break. Zoledronic Acid 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.

In 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 works by returning the bone remodelling process to normal, securing formation of normal bone, thus restoring strength to the bone.

How is Zoledronic Acid used?
The pharmaceutical form of this medicine is a solution for infusion. The route of administration of this medicine is by infusion into the patient’s vein (intravenously).
**Dose and administration:**
The patient should carefully follow all instructions given to them by their doctor or nurse. The patient must check with their doctor or nurse if they are not sure.

**Osteoporosis**
The usual dose is 5mg given as one infusion per year into a vein by the patient’s doctor or nurse. The infusion will take at least 15 minutes.

If a patient has recently broken their hip, it is recommended that Zoledronic Acid is administered two or more weeks after their hip repair surgery.

It is important to take calcium and vitamin D supplements (for example tablets) as directed by the patient’s doctor.

For osteoporosis, Zoledronic Acid works for one year. The patient’s doctor will let them know when to return for their next dose.

**Paget’s disease**
For the treatment of Paget’s disease, Zoledronic Acid should be prescribed only by physicians with experience in the treatment of Paget’s disease of the bone.

The usual dose is 5mg, given to the patient as one initial infusion into a vein by their doctor or nurse. The infusion will take at least 15 minutes. Zoledronic Acid may work for longer than one year, and the patient’s doctor will let them know if they need to be treated again.

The patient’s doctor may advise them to take calcium and vitamin D supplements (e.g. tablets) for at least the first 10 days after being given Zoledronic Acid. It is important that the patient follows this advice carefully so that the level of calcium in their blood does not become too low in the period after infusion. The patient’s doctor will inform them regarding the symptoms associated with hypocalcaemia.

**Zoledronic Acid with food and drink**
The patient must make sure they drink enough fluids (at least one or two glasses) before and after the treatment with Zoledronic Acid, as directed by their doctor. This will help to prevent dehydration. The patient may eat normally on the day they are treated with Zoledronic Acid. This is especially important in patients who take diuretics (“water pills”) and in elderly patients (age 65 years or over).

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

**What benefits of Zoledronic Acid have been shown in studies?**
No additional studies were needed as Zoledronic Acid is a generic medicine that is given intravenously and contains the same active substance as the reference medicine, Aclasta 5 mg solution for infusion (Novartis Europharm Limited, UK).

**What are the possible side effects of Zoledronic Acid?**
Because Zoledronic Acid is a generic medicine, its benefits and possible side effects are taken as being the same as the reference medicine.
For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Zoledronic Acid, see section 4 of the package leaflet available on the MHRA website.

Why was Zoledronic Acid approved?
It was concluded that, in accordance with EU requirements, Zoledronic Acid has been shown to have comparable quality and to be comparable to Aclasta 5 mg solution for infusion (Novartis Europharm Limited, UK). Therefore, the MHRA decided that, as for Aclasta 5 mg solution for infusion (Novartis Europharm Limited, UK), the benefits are greater than its risk and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Zoledronic Acid?
A risk management plan (RMP) has been developed to ensure that Zoledronic Acid is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Zoledronic Acid including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Zoledronic Acid
Austria, Germany, Spain, Italy and the UK agreed to grant a Marketing Authorisation for Zoledronic Acid on 26 July 2016. A Marketing Authorisation was granted in the UK on 23 August 2016.

The full PAR for Zoledronic Acid follows this summary.

For more information about treatment with Zoledronic Acid, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in October 2016.
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I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Zoledronic Acid (PL 42117/0005; UK/H/6144/001/DC) could be approved. The product is a prescription-only medicine (POM) and is indicated for:

Treatment of osteoporosis:
- in post-menopausal women
- in adult men

at increased risk of fracture, including those with a recent low-trauma hip fracture.

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

at increased risk of fracture.

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

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Austria, Germany, Spain and Italy as Concerned Member States (CMS). The application was submitted under Article 10.1 of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for this application is Aclasta 5 mg solution for infusion which was first authorised to Novartis Europharm Limited, UK on 15 April 2005 via the centralised procedure.

Zoledronic acid belongs to the class of nitrogen-containing bisphosphonates and acts primarily on bone. It is an inhibitor of osteoclast-mediated bone resorption.

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

No new clinical data have been submitted and none are required for applications of this type. A bioequivalence study was not necessary to support this application as both test and reference products are aqueous intravenous solutions at the time of administration.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the application could be approved at the end of procedure on 26 July 2016. After a subsequent national phase, a licence was granted in the UK on 23 August 2016.
II QUALITY ASPECTS

II.1 Introduction
Each vial with 100 ml of solution contains 5 mg Zoledronic acid (as monohydrate).

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

Other ingredients consist of the pharmaceutical excipients mannitol, sodium citrate and Water for injections. The finished product is packed into 100ml clear treated type I glass vials closed with a grey bromobutyl rubber stopper sealed with a flip off aluminium seal.

Zoledronic Acid is supplied in packs containing one vial as unit pack, or in multipacks comprising five packs, each containing one vial. Not all pack sizes may be marketed. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2. Drug Substance
INN: Zoledronic acid
Chemical name: [1-Hydroxy-2-(1H-imidazol-1-yl)-ethyldene]-bisphosphonic acid
Structural formula:

\[
\text{N} \quad \text{P} \quad \text{OH} \quad \text{OH} \quad \text{OH} \quad \text{OH} \quad \text{H}_2\text{O}
\]

Molecular formula: C₅H₁₀N₂O₇P₂·H₂O
Molecular mass: 290.09
Appearance: White to off-white powder.
Solubility: Slightly soluble in water, practically insoluble in ethanol (96%), methanol, dimethyl formamide, ethyl acetate, dimethyl sulphoxide, chloroform and acetone.

Zoledronic acid was not the subject of a European Pharmacopoeia monograph at the time of assessment.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided that comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.
II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate a safe, efficacious, solution for infusion containing 0.05 mg zoledronic acid anhydrous (as monohydrate) per one ml of solution (5 mg/100ml) that was comparable to the originator product Aclasta 5 mg solution for infusion (Novartis Europharm Limited, UK). A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale batch size and has shown satisfactory results.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for the unopened vial with no special storage conditions.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.

III. NON-CLINICAL ASPECTS
III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of zoledronic acid are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The Applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.
III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Zoledronic Acid is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS
IV.1 Introduction
The Applicant has provided a justification for not submitting new clinical data. The proposed product is an aqueous intravenous solution containing the same active substance in the same concentration as the reference product. In addition, the qualitative composition of excipients is the same. Therefore, the submission of a bioequivalence study is not required according to the current CHMP Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**). The justification for not conducting a bioequivalence study is acceptable.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of zoledronic acid.

Based on the data provided, Zoledronic Acid can be considered a generic of Aclasta 5 mg solution for infusion (Novartis Europharm Limited, UK).

IV.2 Pharmacokinetics
In line with the guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), the test product is to be administered as an aqueous intravenous solution containing the same qualitative and quantitative composition in terms of active substance and excipients and is of the same pharmaceutical form as the currently approved product. No bioequivalence study has been submitted with this application and none is required.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for an application of this type.

IV.5 Clinical safety
No new safety data were submitted and none were required for this application.

IV.6 Risk Management Plan (RMP)
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating Zoledronic Acid.
A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary table of safety concerns:

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
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</table>
| **Important identified risks** | • Anaphylaxis  
• Hypocalcaemia  
• Renal impairment  
• Osteonecrosis of the jaw  
• Post dose symptoms/ acute phase reaction  
• Ocular adverse events  
• Atrial fibrillation/ cardiac arrhythmias |
| **Important potential risks** | • Cerebrovascular adverse reactions  
• Gastrointestinal adverse reactions  
• Atypical fractures of the femur  
• Osteonecrosis outside of the jaw - including external auditory canal, avascular necrosis (AVN), fracture non-union and/or delayed union  
• Musculoskeletal pain  
• Potential interaction with products that can significantly affect renal function  
• Potential interaction with paracetamol/ acetaminophen  
• Medication error  
• Off-label use |
| **Missing information** | • Use during pregnancy and breast-feeding  
• Use in patients with renal impairment |
Summary table of risk minimisation measures:

<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Routine Risk Minimisation Measures</th>
<th>Additional Risk Minimisation Measures</th>
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</thead>
<tbody>
<tr>
<td><strong>Important Identified Risks</strong></td>
<td></td>
<td></td>
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<tr>
<td>Anaphylaxis</td>
<td>The risk of anaphylaxis associated with use of the drug product is described in the SPC sections 4.3, 4.8 and PIL sections 2, 4 and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
</tr>
<tr>
<td>Hypocalcaemia</td>
<td>The risk (1) of hypocalcaemia associated with use of the drug product, (2) associated with concomitant use with aminoglycosides, calcitonin or loop diuretics and (3) associated with use of the drug product in patients with hypocalcaemia is described in the SPC sections 4.2, 4.3, 4.4, 4.5, 4.8, 4.9 and PIL sections 2, 4 and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>The risk (1) of renal impairment associated with use of the drug product and, (2) associated with use of the drug product in patients with impaired renal function is described in the SPC sections 4.2, 4.3, 4.4, 4.8 and PIL sections 2, 4 and appropriate advice is provided to the prescriber to minimise this risk. To educate the physicians and patients to understand the risk associated with zoledronic acid 5 mg solution for infusion including precautions and the procedures related to the appropriate management of this risk. Educational material for the</td>
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<tr>
<td>Safety Concern</td>
<td>Routine Risk Minimisation Measures</td>
<td>Additional Risk Minimisation Measures</td>
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<td></td>
<td>advice is provided to the prescriber to minimise this risk.</td>
<td>treatment of osteoporosis is provided in the form of:</td>
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<td>- Physician reminder card</td>
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<td></td>
<td></td>
<td>- Patient guide</td>
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<td>Osteonecrosis of the jaw</td>
<td>The risk of osteonecrosis of the jaw associated with (i) use of the drug product and (ii) coadministration with antiangiogenic medicinal products is described in the SPC sections 4.4, 4.5, 4.8 and PIL sections 2, 4 and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>To remind patients about important safety information that they need to be aware of before and during treatment with zoledronic acid. Educational material is provided in the form of:</td>
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<tr>
<td></td>
<td></td>
<td>- Patient reminder card</td>
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<tr>
<td>Post dose symptoms/ acute phase reactions</td>
<td>The risk of post dose symptoms/ acute phase reactions associated with use of the drug product is described in the SPC sections 4.4, 4.8 and PIL sections 2, 4 and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
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<tr>
<td>Ocular adverse events</td>
<td>The risk of ocular adverse events associated with use of the drug product is described in the SPC section 4.8 and PIL section 4 and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
</tr>
<tr>
<td>Atrial fibrillation/ cardiac arrhythmias</td>
<td>The risk of atrial fibrillation/ cardiac arrhythmias associated with use of the drug product is described in the SPC section 4.8 and PIL section 4 and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
</tr>
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</table>

**Important Potential Risks**

<p>| Cerebrovascular adverse reactions | MAH will collect, process and report (to applicable regulatory authority) information on use of zoledronic acid and increased risk of cerebrovascular adverse reaction | None                                                                                      |</p>
<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Routine Risk Minimisation Measures</th>
<th>Additional Risk Minimisation Measures</th>
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<tr>
<td>Gastrointestinal adverse reactions</td>
<td>The risks of gastrointestinal adverse reactions associated with use of the drug product are described in the SPC section 4.8 and PIL section 4 and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Atypical fractures of the femur</td>
<td>The risk of atypical fractures of the femur associated with use of the drug product is described in the SPC sections 4.4, 4.8 and PIL section 4 and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
</tr>
<tr>
<td>Osteonecrosis outside of the jaw - including external auditory canal, AVN, fracture non-union and/or delayed union</td>
<td>The risk of osteonecrosis outside of the jaw - including external auditory canal, AVN, fracture non-union and/or delayed union associated with use of the drug product is described in the SPC sections 4.4, 4.8 and PIL section 4 and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>The risk of musculoskeletal pain associated with use of the drug product are described in the SPC sections 4.4, 4.8 and PIL section 4 and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Potential interaction with products that can significantly affect renal function</td>
<td>The risk of potential interaction of the drug product with products that can significantly affect renal function are described in the SPC sections 4.4, 4.5 and PIL section 2 and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Potential interaction with paracetamol/ acetaminophen</td>
<td>MAH will collect, process and report (to applicable regulatory bodies)</td>
<td>None</td>
</tr>
</tbody>
</table>
IV.7 Discussion on the clinical aspects
The grant of a marketing authorisation is recommended for this application.

V User consultation
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI Overall conclusion, benefit/risk assessment and recommendation
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with zoledronic acid is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Zoledronic Acid is presented below: