Public Assessment Report

Decentralised Procedure

Zoledronic acid 5 mg/100ml Solution for Infusion

Zoledronic acid 4 mg/5 ml Concentrate for Solution for Infusion

Zoledronic acid monohydrate

UK/H/4727/001-2/DC

UK Licence no: PL 29831/0480-1

Applicant: Wockhardt UK Ltd
Zoledronic acid 5 mg/100 ml Solution for Infusion

Zoledronic acid 4 mg/5 ml Concentrate for Solution for Infusion

LAY SUMMARY

On 30th November 2012, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations to Wockhardt UK Ltd for the medicinal products Zoledronic Acid 5 mg/100 ml Solution for Infusion and Zoledronic Acid 4 mg/5 ml Concentrate for Solution for Infusion (PL 29831/0480-1; UK/H/4727/001-2/DC). These medicines are only available on prescription from your doctor.

For Zoledronic Acid 5 mg/100 ml Solution for Infusion

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

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 Infusion strengthens the bone and therefore makes it less likely to break.

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

Paget’s disease of the bone

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

For Zoledronic Acid 4 mg/5 ml Concentrate for Solution for Infusion

The active substance in Zoledronic Acid Concentrate is zoledronic acid, which belongs to a group of substances called bisphosphonates. Zoledronic acid works by attaching itself to the bone and slowing down the rate of bone change.

It is used:
PAR Zoledronic acid 5 mg/100 ml Solution for Infusion and Zoledronic acid 4 mg/5 ml Concentration Solution for Infusion

UK/H/4727/01-2/DC

• To prevent bone complications, e.g. fractures, in adult patients with bone metastases (spread of cancer from primary site to the bone).

• To reduce the amount of calcium in the blood in adult patients where it is too high due to the presence of a tumour. Tumours can accelerate normal bone change in such a way that the release of calcium from bone is increased. This condition is known as tumour-induced hypercalcaemia (TIH).

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Zoledronic Acid 5 mg/100 ml Solution for Infusion and Zoledronic Acid 4 mg/5 ml Concentrate for Solution for Infusion outweigh the risks; hence Marketing Authorisations were granted.
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</tbody>
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## Module 1

| **Product Name** | Zoledronic Acid 5 mg/100 ml Solution for Infusion  
                        Zoledronic Acid 4 mg/5 ml Concentrate for Solution for Infusion |
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Article 10(1), Generic application</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Zoledronic acid monohydrate</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Solution for Infusion and Concentrate for Solution for Infusion</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>5 mg/100 ml and 4 mg/5 ml</td>
</tr>
</tbody>
</table>
| **MA Holder** | Wockhardt UK Ltd  
                       Ash Road North  
                       Wrexham  
                       LL13 9UF; UK |
| **RMS** | UK |
| **CMSs** | UK/H/4727/01/DC: Malta  
                       UK/H/4727/02/DC: Cyprus, Republic of Ireland and Malta |
| **Procedure Number** | UK/H/4727/001-2/DC |
| **Timetable** | Day 195: 20th October 2012 |
Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4

Labelling

Label:

Each 100 ml bottle contains 5 mg of zoledronic acid (as monohydrate)

Other ingredients: mannitol, sodium citrate and water for injections

Contains sodium

Keep out of the sight and reach of children

Dose: As directed by the doctor

Read the package leaflet before use

For single use only. Any unused product or waste material should be disposed of in accordance with local requirements

Marketing Authorisation Holder:
Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK

Zoledronic Acid

50 micrograms/ml

5mg in 100ml

Solution for Infusion

For intravenous use

100ml
Zoledronic acid 5 mg/100 ml Solution for Infusion and Zoledronic acid 4 mg/5 ml Concentration Solution for Infusion

**Carton:**

Each 100 ml bottle contains 5 mg of zoledronic acid (as monohydrate)
Other ingredients: mannitol, sodium citrate and water for injections
Contains sodium
Keep out of the sight and reach of children
Dose: As directed by the doctor
Read the package leaflet before use
For single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

POM PL 29831/0480
MA 154/08201

Marketing Authorisation Holder: Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK
Label:
Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the applications for Zoledronic Acid 5 mg/100 ml Solution for Infusion and Zoledronic Acid 4 mg/5 ml Concentrate for Solution for Infusion (PL 29831/0480-1; UK/H/4727/001-2/DC) for the following indications could be approved:

For Zoledronic Acid 5 mg/100 ml Solution for Infusion
- Treatment of osteoporosis
  - in post-menopausal women
  - in 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 men
  - at increased risk of fracture.
- Treatment of Paget's disease of the bone in adults.

For Zoledronic Acid 4 mg/5 ml Concentrate for Solution for Infusion
- 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).

These applications were submitted according to Article 10(1) of 2001/83/EC, as amended. The reference medicinal products for these applications are Aclasta® 5 mg/100 ml Solution for Infusion, centrally authorised since 15th April 2005 (EU/1/05/308/001-002) and Zometa® 4 mg powder and solvent for solution for infusion, centrally authorised since 20th March 2001 (EU/1/01/176/001-003) by Novartis Europharma Ltd.

With UK as the RMS in these Decentralised Procedures, Wockhardt UK Ltd applied for the Marketing Authorisations for Zoledronic Acid 5 mg/100 ml Solution for Infusion, in Malta and for Zoledronic Acid 4 mg/5 ml Concentrate for Solution for Infusion in Cyprus, Republic of Ireland and Malta.

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 clinical or non-clinical studies were conducted, which is acceptable given that these are generic applications, which refer to originator products that have been licensed for over 10 years. Bioequivalence studies are not necessary to support this application for a parenteral product.

The RMS has been assured that acceptable standards of GMP are in place for these product
types at all sites responsible for the manufacture and assembly of these products. For manufacturing sites within and outside 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.

The RMS considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A Risk Management Plan (RMP) hasn’t been provided on the basis that these are generic products. Following the outcome of the Article 31 referral on bisphosphonates and atypical femoral fracture, it has been agreed by PhVWP and CMD(h) that a risk management plan will be required for all bisphosphonate products. The applicant agreed to submit a letter of commitment, stating that they will adopt the abbreviated core RMP for bisphosphonates and atypical femoral fractures and commits to adhere to the planned pharmacovigilance activities outlined in the abbreviated core RMP.

All member states agreed to grant a licence for the above products at the end of the procedure (Day 195 – 20th October 2012). After a subsequent national phase, the UK granted a licence for these products on 30th November 2012 (PL 29831/0480-1).
II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Zoledronic Acid 5 mg/100 ml Solution for Infusion Zoledronic Acid 4 mg/5 ml Concentrate for Solution for Infusion</th>
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<tbody>
<tr>
<td>Name(s) of the active substance(s) (USAN)</td>
<td>Zoledronic acid monohydrate</td>
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<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Drugs for treatment of bone diseases, bisphosphonates, ATC code: M05BA08</td>
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<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Solution for infusion (5 mg/100 ml) and Concentrate for Solution for Infusion (4 mg/5 ml)</td>
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<td>Reference numbers for the Decentralised Procedure</td>
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<td>Reference Member State</td>
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<tr>
<td>Concerned Member States</td>
<td>UK/H/4727/01/DC: Malta</td>
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<td>UK/H/4727/02/DC: Cyprus, Republic of Ireland and Malta</td>
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<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 29831/0480-1</td>
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<tr>
<td>Name and address of the authorisation holder</td>
<td>Wockhardt UK Ltd</td>
</tr>
<tr>
<td></td>
<td>Ash Road North</td>
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<tr>
<td></td>
<td>Wrexham</td>
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<tr>
<td></td>
<td>LL13 9UF; UK</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Zoledronic acid monohydrate

Chemical Names: (1-Hydroxy-2-imidazol-1-yl-phosphonoethyl) phosphonic acid monohydrate

Structure:

\[
\begin{align*}
\text{Structure:} & \\
\text{Molecular formula: } C_{5}H_{10}N_{2}O_{7}P_{2} \times H_{2}O & \\
\text{Molecular weight: } 290.11 & \\
\text{Physical form: White to off-white, crystalline powder.} & \\
\text{Solubility: Sparingly soluble in phosphate buffer pH 7.0 and soluble in sodium citrate solution.} & \\
\text{The drug substance is the subject of a European Drug Master File (EDMF).} & \\
\text{Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.} & \\
\text{An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.} & \\
\text{Satisfactory Certificates of Analysis have been provided for working standards used by the drug substance manufacturer and finished product manufacturer.} & \\
\text{The active substance is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.} & \\
\text{Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.} & 
\end{align*}
\]
DRUG PRODUCT

Other Ingredients
Other ingredients consist of the pharmaceutical excipients mannitol (E421), sodium citrate and water for injection. A rationale for the inclusion of each excipient is provided.

All excipients comply with the relevant European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for these excipients.

The above excipients do not contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development
The objective of the pharmaceutical development programme was to obtain a stable solution for infusion containing zoledronic acid monohydrate that could be considered generic medicinal products of Aclasta 5 mg/100 ml Solution for Infusion and Zometa® 4 mg powder and Solvent for Solution for Infusion (Novartis EuroPharm Limited).

Suitable pharmaceutical development data have been provided for these applications.

Comparative impurity profiles have been provided for the proposed and originator products.

Manufacture
Satisfactory batch formulae have been provided for the manufacture of these products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial batches have been provided. The results are satisfactory.

Finished Product Specifications
The finished product specification is satisfactory. Test methods have been described and adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container Closure System
Zoledronic acid 5 ml/100 mg Solution for Infusion is supplied in 100 ml clear plastic (cycloolefinic polymer) bottle fitted with a fluorotech coated rubber stopper and aluminium flip-off seal packs containing one bottle.

Zoledronic Acid 4 mg/5 ml Concentrate for Solution for Infusion is supplied in 5-ml plastic vial made of clear cycloolefine copolymer fitted with a 20mm fluorotech rubber stopper and 20mm aluminium flip-off seal packs containing 1 vial.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with relevant guidelines.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, shelf-lives of 2 year for unopened bottle and vial are set. These medicinal products do not require any special storage conditions. For Zoledronic acid 4 mg/5
PAR Zoledronic acid 5 mg/100 ml Solution for Infusion and Zoledronic acid 4 mg/5 ml Concentration Solution for Infusion

UK/H/4727/01-2/DC

ml Concentrate for Solution for Infusion chemical and physical in-use stability has been demonstrated for 24 hours at 2°C – 8°C when diluted with 100 ml of physiological saline or 5% w/v glucose solution.

From a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. The total time between dilution, storage in a refrigerator at 2°C – 8°C and end of administration must not exceed 24 hours.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SPCs, PILs and labelling are pharmaceutically satisfactory.

User testing of the package leaflet has been accepted, based on a bridging report provided by the applicant making reference to the user-testing of the parent PIL for Ropinirole 5 mg film-coated tablets (UK/H/3489/005/DC). A critical analysis demonstrated that the key messages for safe and effective use for all leaflets were similar. The justification of the rationale for bridging is accepted.

Marketing Authorisation Application (MAA) Form
The MAA forms are pharmaceutically satisfactory.

Expert Report/Quality Overall Summary
A quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There are no objections to the approval of these products from a pharmaceutical point of view.

III.2 NON-CLINICAL ASPECTS
PHARMACODYNAMICS, PHARMACOKINETICS, TOXICOLOGY
The pharmacological, pharmacokinetic and toxicological properties of zoledronic acid monohydrate are well-known.

No new non-clinical data have been supplied with these applications and none are required for applications of this type. The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

A suitable justification has been provided for the non-submission of the environmental risk assessment.

There are no objections to the approval of these products from a non-clinical point of view.

III.3 CLINICAL ASPECTS
CLINICAL PHARMACOLOGY
Pharmacokinetics
In accordance with Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1), a bioequivalence study is not requested if the test product is an aqueous intravenous solution containing the same active substance as
No new data have been submitted and none are required for applications of this type.

**Pharmacodynamics**
No new data have been submitted and none are required for applications of this type.

**Clinical efficacy**
No new data have been submitted and none are required for applications of this type.

**Clinical safety**
Zoledronic acid monohydrate has an acceptable adverse event profile. No new safety data were supplied or required for these generic applications. Zoledronic acid monohydrate has a well-established side-effect profile and is generally well-tolerated.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling**
The SmPCs, PILs and labelling are medically satisfactory and consistent with those for the reference products.

**Clinical Expert Report**
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Marketing Authorisation Application (MAA) Form**
The MAA forms are medically satisfactory.

**Clinical Conclusion**
There are no objections to the approval of these products from a clinical point of view.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Zoledronic Acid 5 mg/100 ml Solution for Infusion and Zoledronic Acid 4 mg/5 ml Concentrate for Solution for Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL

No new efficacy data were submitted and none are required for applications of this type. As the safety profile of zoledronic acid monohydrate is well-known, no additional data were required. No new or unexpected safety concerns arose from this application.

The SmPCs, PILs and labelling are satisfactory.

RISK-BENEFIT ASSESSMENT

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 monohydrate is considered to have demonstrated the therapeutic value of the compound. The risk-benefit is, therefore, considered to be positive.
## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>10/01/2013</td>
<td>Label update</td>
<td>The product labels have been amended as follows:</td>
<td>Granted – 10/01/2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- The units used for content per ml have changed from micrograms to mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Some minor layout changes have been made</td>
<td></td>
</tr>
<tr>
<td>10/01/2013</td>
<td>Type 1B variation</td>
<td>To remove osteoporosis as an indication for the medicinal product. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC and the PIL have been updated. <strong>This variation applies to Zoledronic Acid 5 mg/100 ml Solution for Infusion (PL 29831/0480) only</strong></td>
<td>Granted – 21/03/2013</td>
</tr>
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</table>