Public Assessment Report

Decentralised Procedure

Alendronic Acid 10 mg Tablets
Alendronic Acid Once weekly 70 mg Tablets

(Alendronate sodium)

Procedure No: UK/H/1156/02-03/DC

UK Licence No: PL 20075/0070-0071

Accord Healthcare Limited
Lay Summary
Alendronic Acid 10 mg Tablets
Alendronic Acid Once weekly 70 mg Tablets
(Alendronate sodium)

This is a summary of the Public Assessment Report (PAR) for Alendronic Acid 10 mg Tablets and Alendronic Acid Once weekly 70 mg Tablets (UK/H/1156/02-03/DC; PL 20075/0070-0071). Alendronic Acid 10 mg Tablets and Alendronic Acid Once weekly 70 mg Tablets will be referred to as Alendronic Acid Tablets throughout this report, for ease of reading.

This summary explains how Alendronic Acid Tablets were assessed and their authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Alendronic Acid Tablets.

For practical information about using Alendronic Acid Tablets, patients should read the package leaflets or contact their doctor or pharmacist.

What are Alendronic Acid Tablets and what are they used for?
Alendronic Acid Tablets are ‘generic medicines’. This means that they are similar to ‘reference medicines’, already authorised in the UK called Fosamax® 10 mg Tablets and Fosamax® Once Weekly 70 mg tablets (PL 00025/0326 and PL 00025/0399; Merck Sharp & Dohme Limited).

Alendronic acid prevents the loss of bone that occurs in men, post-menopausal women and patients receiving glucocorticoids, such as prednisolone and methylprednisolone. Alendronic acid has also been shown to help rebuild bone and make bone less likely to fracture in men and post-menopausal women with osteoporosis.

How do Alendronic Acid Tablets work?
Alendronic Acid Tablets contain the active substance alendronate (as alendronate sodium) which belongs to a group of non-hormonal medicines called bisphosphonates. These medicinal products prevent the breakdown of bones.

How are Alendronic Acid Tablets used?
Alendronic Acid Tablets are taken orally. A single tablet should be swallowed with a full glass of plain water only (not less than 200 ml or 7 fluid ounce) in empty stomach. The tablets should not be crushed, chewed or dissolved in the mouth. After swallowing this medicine, patients should stay fully upright (sitting or standing) for at least 30 minutes and until after their first food of the day.

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

Alendronic Acid 10 mg Tablets
The recommended dose for the treatment of male osteoporosis or post-menopausal osteoporosis is one ‘alendronic acid’ 10 mg tablet once a day.

The usual dose for prevention of steroid induced osteoporosis in post-menopausal women not receiving hormone replacement therapy (HRT) with an oestrogen is 10 mg once a day.
Alendronic Acid Once weekly 70 mg Tablets

The usual dose for the treatment of post-menopausal osteoporosis is one 'alendronic acid' 70 mg tablet once weekly.

These medicinal products can only be obtained with a prescription.

How have Alendronic Acid Tablets been studied?
Because Alendronic Acid Tablets are generic medicines, studies in patients have been limited to tests to determine that they are bioequivalent to the medicinal products, Fosamax® 10 mg Tablets and Fosamax® 70 mg tablets once weekly. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the benefits and risks of Alendronic Acid Tablets?
As Alendronic Acid Tablets are generic medicines that are bioequivalent to Fosamax 10 mg Tablets and Fosamax® 70 mg tablets once weekly, their benefits and risks are taken as being the same as Fosamax 10 mg Tablets and Fosamax® 70 mg tablets once weekly.

Why are Alendronic Acid Tablets approved?
It was concluded that, in accordance with EU requirements, Alendronic Acid Tablets have been shown to have comparable quality and to be bioequivalent to Fosamax® 10 mg Tablets and Fosamax® 70 mg tablets once weekly. Therefore, the view was that, as for Fosamax® 10 mg Tablets and Fosamax® 70 mg tablets once weekly the benefits outweigh the identified risks.

What measures are being taken to ensure the safe and effective use of Alendronic Acid Tablets?
A satisfactory pharmacovigilance system has been provided to monitor the safety of these products.

Other information about Alendronic Acid Tablets
Italy, Slovenia, The Netherlands and the UK agreed to grant a Marketing Authorisation for Alendronic Acid 10 mg Tablets on 28 August 2008. The Marketing Authorisation was granted in the UK on 26 September 2008.

Cyprus, Estonia, Italy, Lithuania, Slovenia, The Netherlands, The Republic of Ireland and the UK agreed to grant a Marketing Authorisation for Alendronic Acid Once weekly 70 mg Tablets on 28 May 2008. The Marketing Authorisation was granted in the UK on 26 September 2008.

The full PAR for Alendronic Acid Tablets follows this summary.

For more information about treatment with Alendronic Acid Tablets, read the package leaflets or contact your doctor or pharmacist.

This summary was last updated in May 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 applications for Alendronic Acid 10 mg Tablets (UK/H/1156/02/DC; PL 20075/0070) and Alendronic Acid Once weekly 70 mg Tablets (UK/H/1156/03/DC; PL 20075/0071) are approvable.

These products are prescription-only medicines (POM), indicated in adults for the treatment of postmenopausal osteoporosis. Alendronic acid also reduces the risk of vertebral and hip fractures.

These applications were submitted using the Decentralised Procedures (DCPs), with the UK as Reference Member State (RMS) and Italy, Slovenia and The Netherlands as Concerned Member States (CMSs) for Alendronic Acid 10 mg Tablets and Cyprus, Estonia, Italy, Lithuania, Slovenia, The Netherlands, The Republic of Ireland as CMSs for Alendronic Acid Once weekly 70 mg Tablets.

These applications were made under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products. The applicant has cross referred to Fosamax® 10 mg Tablets and Fosamax® Once Weekly 70 mg tablets, which were first licensed to Merck Sharp & Dohme Limited (PL 00025/0326 and PL 00025/0399) on 28 July 1995 and 10 November 2000 respectively.

Alendronic Acid 10 mg Tablets and Alendronic Acid Once weekly 70 mg Tablets contain the active ingredient alendronate, as alendronate sodium. Alendronate sodium is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation. Preclinical studies have shown preferential localisation of alendronic acid to sites of active resorption. Activity of osteoclasts is inhibited, but recruitment or attachment of osteoclasts is not affected. The bone formed during treatment with alendronic acid is of normal quality.

No new non-clinical studies were conducted, which is acceptable given that these applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

Since Alendronic Acid 10 mg Tablets and Alendronic Acid Once weekly 70 mg Tablets are intended for generic substitution, their use will not lead to an increased exposure to the environment. An Environmental Risk Assessment (ERA) is, therefore, not deemed necessary.

A bioequivalence study was submitted to support these applications comparing the test product Alendronate sodium 70 mg tablets with the reference product Fosamax 70 mg Tablets in healthy adult male subjects, under fasting conditions. The applicant has stated that the bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that these applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.
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 MHRA as certification that acceptable standards of GMP are in place at those non-Community sites.

A satisfactory pharmacovigilance system has been provided to monitor the safety of these products.

The RMS and CMSs considered that these applications could be approved at the end of procedure (Day 210) on 28 August 2008. After a subsequent national phase, licences were granted in the UK on 26 September 2008.
II Quality aspects

II.1 Introduction
These applications were submitted according to Article 10(1) of Directive 2001/83/EC, as amended. The applicant has specified Fosamax® 10 mg Tablets and Fosamax® Once Weekly 70 mg tablets (PL 00025/0326 and PL 00025/03990) as the UK reference medicinal products (MA Holder: Merck Sharp & Dohme Limited).

Each tablet contains 10 mg or 70 mg alendronic acid (as alendronate sodium) as active ingredient. The excipients present in each tablet are lactose anhydrous, cellulose microcrystalline (E460), croscarmellose sodium and magnesium stearate.

The only excipient used that contains material of animal or human origin is lactose anhydrous. The applicant has provided a declaration that the milk used in the production of lactose anhydrous is sourced from healthy animals under the same conditions as that for human consumption. Confirmation has also been given that the magnesium stearate used in the tablets is of vegetable origin.

The 10 mg tablets are packed in opaque white polyvinylchloride (PVC)/aluminium blister containing 14, 28, 30, 50, 56, 84, 90, 98, 112* or 140* tablets. The 112 and 140 tablets are not for UK market.

The 70 mg tablets are packed in oriented polyamide (OPA)-aluminium(AL)-polyvinylchloride (PVC)/Al blister containing 4 and 12* tablets. The 12 tablet pack size is not for UK market.

No genetically modified organisms (GMO) have been used in the preparation of these products.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance
Alendronate sodium
INN: Alendronate sodium
Chemical Name: (4-amino-1-hydroxybutylidene)bisphosphonic acid monosodium salt trihydrate
Structure:

\[
\text{H}_2\text{N} \quad \text{O} \quad \text{P} \quad \text{Ona} \quad \text{3 H}_2\text{O}
\]

Molecular formula: \(\text{C}_4\text{H}_{12}\text{NNaO}_7\text{P}_2\cdot3\text{H}_2\text{O}\)
Molecular weight: 325.1 g/mol
Appearance: A white or almost white crystalline powder.
Solubility: Soluble in water, practically insoluble in methanol and in methylene chloride.
Alendronic Acid 10 mg Tablets and Alendronic Acid Once weekly 70 mg Tablets

UK/H/1156/02-03/DC

Alendronate sodium is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, alendronate sodium, are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

II.3 Medicinal Product

Pharmaceutical development

The objective of the development programme was to formulate safe, efficacious tablets containing 10 mg and 70 mg of alendronate sodium per tablet, that are generic versions of the reference products Fosamax® 10 mg Tablets and Fosamax® Once Weekly 70 mg tablets (Merck Sharp & Dohme Limited). A satisfactory account of the pharmaceutical development has been provided.

Comparative in-vitro dissolution and impurity profiles have been provided for the proposed and originator products.

Manufacture of the products

Satisfactory batch formulae have been provided for the manufacture of the finished products, together with appropriate accounts of the manufacturing processes. The manufacturing processes have been validated at commercial scale batch sizes and have shown satisfactory results.

Finished Product Specifications

The finished product specifications proposed are acceptable. The 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 products

Stability studies were performed in accordance with current guidelines on batches of the finished product, packed in the packaging proposed for marketing. The data from the studies of support a shelf-life of 3 years with no special storage conditions.

Suitable post approval stability commitments have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of Marketing Authorisations is recommended.

III Non-clinical aspects

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of alendronate sodium 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 Alendronic Acid 10 mg Tablets and Alendronic Acid Once weekly 70 mg Tablets are intended for generic substitution, their use 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
No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

There are no objections to the approval of these applications from a non-clinical viewpoint.

IV Clinical aspects

IV.1 Introduction
The clinical pharmacology of alendronate sodium is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

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

Based on the data provided, Alendronate sodium 70 mg tablets can be considered to be bioequivalent to Fosamax 10 mg and 70 mg tablets (Merck Sharp & Dohme Limited).

IV.2 Pharmacokinetics
In support of these applications, the applicant submitted the following bioequivalence study:

An open label, balanced, randomised, two-treatment, two-sequence, two-period, single dose, crossover oral bioequivalence study of Alendronate sodium 70 mg tablets versus the reference product, Fosamax 70 mg Tablets, in healthy, adult, male subjects, under fasting conditions.

Results

Table 1: Summary of the results (N= 86)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Test (Alendronate sodium) (mean +sd)</th>
<th>Reference (Fosamax) (mean +sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ae$_{0.4}$ (ng)</td>
<td>622760.2 (396848.5)</td>
<td>676782.5 (40811.2)</td>
</tr>
</tbody>
</table>
### IV.3 Pharmacodynamics
No new pharmacodynamics data are required for these applications and none have been submitted.

### IV.4 Clinical efficacy
No new clinical efficacy data are required for these applications and none have been submitted.

### IV.5 Clinical safety
No new data have been provided and none are required for these applications.

### IV.6 Pharmacovigilance System
A satisfactory pharmacovigilance system has been provided to monitor the safety of these products.

### IV.7 Discussion on the clinical aspects
The grant of marketing authorisations is recommended for these applications.

### 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, as amended. The language used for the purpose of user testing the package information leaflet (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

QUALITY
The important quality characteristics of Alendronic Acid 10 mg Tablets and Alendronic Acid Once weekly 70 mg Tablets 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 is needed for these applications.

No new or unexpected safety concerns arose from these applications.

CLINICAL
Clinical studies have demonstrated the efficacy of alendronate sodium in the prevention and treatment of osteoporosis.

The product literature is satisfactory and consistent with those for the innovator products.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical concerns have been identified.
The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

The current approved UK labelling for Alendronic Acid 10 mg Tablets and Alendronic Acid Once weekly 70 mg Tablets are listed below:
Alendronic Acid 10 mg Tablets and Alendronic Acid Once weekly 70 mg Tablets

Unvarnished area for pasting

Alendronic Acid Once weekly 70 mg Tablets

Each tablet contains 70 mg alendronic acid (as alendronate sodium)

70mg accord

PL 20075/0071
P.L. Holder: Accord Healthcare Limited,
Sage House, 319 Pinner Road,
North Harrow, Middlesex HA1 4HF,
United Kingdom

POM

Alendronic Acid Once weekly 70 mg Tablets

4 Tablets
Contains lactose anhydrous.
Please see enclosed leaflet.
Oral use.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Any unused product or waste material should be disposed of in accordance with local requirements.

4 Tablets

Alendronic Acid Once weekly 70 mg Tablets

4 Tablets

Code: G9j/Drugs/1339
Table of content of the PAR update for MRP and DCP
Steps taken after the initial procedure with an influence on the Public Assessment Report
(Type II variations, PSURs, commitments)

The following table lists a non-safety update to the Marketing Authorisations for these products that has been approved by the MHRA since the products were first licensed. The table includes updates that are detailed in the annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to these Marketing Authorisations.

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure numbers</th>
<th>Product information affected</th>
<th>Date of start of the procedures</th>
<th>Date of end of procedures</th>
<th>Approval / non approval</th>
<th>Assessment report attached Y/N (version)</th>
</tr>
</thead>
<tbody>
<tr>
<td>To register an additional bioequivalence study (no. 999-14) in reference to the Article 31 referral related to medicinal products for which studies have been carried out by GVK Biosciences - Hyderabad site (procedure number: EMEA/H/A-31/1408).</td>
<td>UK/H/1156/002-03/II/019</td>
<td>N/A</td>
<td>15/12/2015</td>
<td>29/04/2016</td>
<td>Approved</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Annex 1

Reference: PL 20075/0070-1-0028
Product: Alendronic Acid 10 mg Tablets and Alendronic Acid Once weekly 70 mg Tablets

Marketing Authorisation Holder: Accord Healthcare Limited

Active Ingredient: Alendronate sodium

Reason:
To register an additional bioequivalence study (no. 999-14) in reference to the Article 31 referral related to medicinal products for which studies have been carried out by GVK Biosciences - Hyderabad site (procedure number: EMEA/H/A-31/1408).

Supporting evidence
The applicant has presented an additional bioequivalence study.

Study design – Bioequivalence Study: 999-14
The bioequivalence study was designed as an open label, balanced, randomised, two treatment, four period, two sequence, full-replicate, crossover bioequivalence study of test and reference formulations of Alendronic Acid 70 mg Tablets in fasting, healthy adult human subjects.

Blood samples were collected pre-dose in duplicate and at 0.167, 0.333, 0.500, 0.667, 0.833, 1.000, 1.250, 1.500, 1.750, 2.000, 2.500, 3.000, 3.500, 4.000, 5.000, 6.000, 7.000, 8.000, 10.000, 12.000, 16.000, 24.000 and 36.000 hours post-dose. The wash-out period between dosing periods was 7 days.

The design is acceptable. Sampling over 36 hours is sufficient to characterise the absorption profile of an immediate release oral formulation of alendronic acid. The sampling scheme is adequate to estimate the $C_{\text{max}}$, which is expected at ~ 1 hour. A fasted study is appropriate, since alendronic acid should be taken on an empty stomach according to the Summary of Product Characteristics (SmPC) of the reference product. The washout period of 7 days is adequate, based on the expected half-life of ~8 hours; this is confirmed by the general absence of measurable plasma levels of alendronate at the start of dosing periods.

This replicate design (two dosing periods for both the test and reference product) allowed bioequivalence criteria for $C_{\text{max}}$ only to be widened, based upon the coefficient of variation for the reference product. In this instance, the intra-subject coefficient of variance (CV) of the reference product for ln-transformed $C_{\text{max}}$ was found to be > 30%, thus the calculated confidence interval limits for $C_{\text{max}}$ were widened to 74.01 – 135.13%. However, it is noted that widened $C_{\text{max}}$ limits proved unnecessary for the demonstration of bioequivalence; compliance with the standard confidence limits of 80.00 – 125.00% for $C_{\text{max}}$ was demonstrated.

Satisfactory information is presented to support the choice of the reference and test products. The batch size for the test product and reference product is acceptable, representing more than one tenth of the maximum commercial scale of 600,000 tablets.
A total of 51 subjects (all of whom were male) were enrolled according to standard inclusion and exclusion criteria. Of these, 48 subjects were planned for inclusion, with an age range of 31.1 ± 6.50 years and a body mass index (BMI) range of 22.9 ± 2.9 kg/m².

As per the protocol, 48 subjects were dosed in period I of the study. Of these 48 subjects a total of 42 subjects completed all clinical phases of the study. Pharmacokinetic and statistical analyses were performed on data from 42 subjects.

**Bioanalytical methods**
Analysts were blinded to treatment sequence. Content of alendronic acid in plasma was determined by solid phase extraction, followed by HPLC separation method with tandem mass spectrometric detection (LC–MS/MS). Alendronic acid-d6 was used as an internal standard. Chromatographic separation was performed with a Zorbax 5µ 300-SCX column with gradient elution of mobile phase. The method has been demonstrated to be linear between the lower limit of quantification (LLOQ) of 0.301 ng/ml and the upper limit of quantification (ULOQ) of 150.252 ng/ml. Adequate information, supported by certificates of analysis is provided for the reference and internal standards used during these analyses. Validation data support the suitability of the method in terms of selectivity, sensitivity, recovery, carry-over and matrix effects, precision, accuracy and stability.

Bioanalysis was initiated on 21 July 2015 and completed on 29 August 2015. Sample storage did not exceed 88 days, which has been verified by long-term (-65°C) plasma sample stability studies.

The analytical sequence included in addition to test specimens, blank plasma, blank plasma with internal standards, a set of calibration standards, including the LLOQ and ULOQ in duplicate and two sets of QC samples.

Standard acceptance criteria in line with the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009) were adopted and satisfied. To confirm method reliability, incurred sample reanalysis was performed, comprising at least 5% of the total number of samples reanalysed on a different day, using the same protocol. Of these, at least 67% were required to lie within 20% of the original value. A proportion (343 samples) was selected for incurred sample reanalysis. Of these, 98.3% of incurred samples reanalysed were within ± 20%. All requirements for bioanalytical study acceptance were met.

Satisfactory method validation is provided to support the validity and performance of the bioanalytical method.

**Pharmacokinetic (PK) Variables**
The primary PK parameters were AUC0-t, AUC0-∞, and Cmax. Secondary PK parameters included T1/2 and Tmax. The chosen PK parameters are acceptable.

**Statistical methods**
The acceptance criteria for AUC0-t and AUC0-∞ were prospectively defined as 80.00-125.00%. Based on the full-replicate design, widened acceptance criteria were applied to Cmax.

The log-transformed PK parameters AUC0-t, Cmax and AUC0-∞ were analysed using an ANOVA model, including the effect of period and sequence. 90% confidence intervals were calculated for the ratio of test and reference geometric means.
The statistical methods are appropriate. Confidence interval criteria are in line with ICH guidance on the Investigation of Bioequivalence, given the study design.

**Results**

**Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{\text{max}}$ median, range) for test and reference products**

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>Mean ± SD (Un-transformed data)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test Product-T (N = 84 Observations)</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (h)*</td>
<td>1.250 (0.500 - 2.033)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>41.993 ± 35.6910</td>
</tr>
<tr>
<td>AUC$_{0-1}$ (ng.h/mL)</td>
<td>137.462 ± 103.7912</td>
</tr>
<tr>
<td>AUC$_{0-\infty}$ (ng.h/mL)</td>
<td>149.523 ± 111.0066</td>
</tr>
<tr>
<td>$\lambda_c$ (1/h)</td>
<td>0.071 ± 0.0767</td>
</tr>
<tr>
<td>$t_{\text{v}}$ (h)</td>
<td>15.751 ± 7.6441</td>
</tr>
<tr>
<td>AUC %Extrap.obs (%)</td>
<td>8.435 ± 4.3349</td>
</tr>
</tbody>
</table>

* $t_{\text{max}}$ is represented as median (min-max) value.

**Ln-transformed confidence intervals**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Geometric Least Squares Means</th>
<th>90% Confidence Interval</th>
<th>Acceptance Criteria (%)</th>
<th>Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test Product-T (N = 84 Observations)</td>
<td>Reference Product-R (N = 84 Observations)</td>
<td>Ratio (T/R) %</td>
<td>74.01 - 135.13</td>
</tr>
<tr>
<td>ln$C_{\text{max}}$</td>
<td>32.793</td>
<td>30.507</td>
<td>107.5</td>
<td>95.72 - 120.72</td>
</tr>
<tr>
<td>lnAUC$_{0-1}$</td>
<td>109.001</td>
<td>100.241</td>
<td>108.7</td>
<td>96.78 - 122.18</td>
</tr>
<tr>
<td>lnAUC$_{0-\infty}$</td>
<td>119.183</td>
<td>109.744</td>
<td>108.6</td>
<td>96.90 - 121.72</td>
</tr>
</tbody>
</table>

Based on the submitted bioequivalence study, the test product, Alendronic Acid Once Weekly 70 mg Tablets is considered bioequivalent to the reference product, Fosamax 70 mg Tablets (Merck, Sharp & Dohme Limited).

The 90% confidence intervals for AUC$_{0-1}$ and $C_{\text{max}}$ are within 80.00-125.00%. For $C_{\text{max}}$, the study design allowed a wider range of acceptance limits for 90% confidence intervals of 74.01 – 135.13%. The calculated 90% confidence intervals for $C_{\text{max}}$ met the more stringent limits of 80.00-125.00%.
Biowaiver
To bridge to Alendronic Acid 10 mg Tablets, a biowaiver of strengths is presented. To qualify, the following criteria from the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) require to be satisfied.

a) the pharmaceutical products are manufactured by the same manufacturing process,

b) the qualitative composition of the different strengths is the same,

c) the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),

If there is some deviation from quantitatively proportional composition, condition c is still considered fulfilled if condition i) and ii) or i) and iii) below apply to the strength used in the bioequivalence study and the strength(s) for which a waiver is considered

i. the amount of the active substance(s) is less than 5 % of the tablet core weight, the weight of the capsule content

ii. the amounts of the different core excipients or capsule content are the same for the concerned strengths and only the amount of active substance is changed

iii. the amount of a filler is changed to account for the change in amount of active substance. The amounts of other core excipients or capsule content should be the same for the concerned strengths

d) appropriate in vitro dissolution data should confirm the adequacy of waiving additional in vivo bioequivalence testing

Criteria a), b) and c) are accepted as satisfied. Satisfactory comparative dissolution data have been presented for Alendronic Acid 10 mg and 70 mg Tablets to satisfy criterion d).

Safety results
Safety was monitored by vital signs, and a subject questionnaire to assess adverse events, at pre-dose and at scheduled intervals post-dosing. Medical examinations were conducted at check-in, and check-out. Clinical laboratory testing was conducted at check-in for each study period.

A total of eight adverse events were recorded by six subjects during the study. Of these, four followed administration of the reference product and four followed administration of the test product. One adverse event was graded as serious in nature (renal colic) and two as significant (backache, dysuria); these subjects were withdrawn from the study on medical grounds; however these adverse events are considered unlikely to be linked to the administration of the study products.

No safety concerns are raised following assessment of the safety data.

Conclusion
The additional data provided were acceptable. The variations were approved on 29 April 2016.