Public Assessment Report

Decentralised Procedure

RISEDRONATE SODIUM
75 MG FILM-COATED TABLETS

(risedronate sodium)

Procedure No: UK/H/4896/001/DC

UK Licence No: PL 04569/1277

Generics (UK) Limited
LAY SUMMARY

On 21 March 2013, Italy, Belgium, Luxembourg, Spain, France and the UK agreed to grant a Marketing Authorisation to Generics (UK) Limited for the medicinal product Risedronate Sodium 75 mg Film-coated Tablets (PL 04569/1277; UK/H/4896/001/DC). The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, a Marketing Authorisation was granted in the UK on 10 May 2013.

This is a prescription-only medicine (POM), used for the treatment of osteoporosis in postmenopausal women. It contains the active ingredient risedronate sodium, which belongs to a group of non-hormonal medicines called bisphosphonates. Postmenopausal osteoporosis is a condition which occurs in women after the menopause where the bones become weaker, more fragile and more likely to break after a fall or strain. Risedronate sodium works directly on the bones to make them stronger and, therefore, less likely to break.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Risedronate Sodium 75 mg Film-coated Tablets outweigh the risks and a Marketing Authorisation was granted.
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# Module 1
## Information about initial procedure

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Risedronate sodium 75 mg film-coated tablets</th>
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<tbody>
<tr>
<td>Type of Application</td>
<td>Generic, Article 10(1)</td>
</tr>
<tr>
<td>Active Substances</td>
<td>Risedronate sodium</td>
</tr>
<tr>
<td>Form</td>
<td>Film-coated Tablet</td>
</tr>
<tr>
<td>Strength</td>
<td>75 mg</td>
</tr>
<tr>
<td>MA Holder</td>
<td>Generics (UK) Limited, 24 Station Close, Potters Bar, Hertfordshire, EN6 1TL, UK</td>
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<tr>
<td>Reference Member State (RMS)</td>
<td>UK</td>
</tr>
<tr>
<td>Concerned Member States (CMS)</td>
<td>Italy, Belgium, Luxembourg, Spain, France</td>
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<td>Procedure Number</td>
<td>UK/H/4896/001/DC</td>
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<tr>
<td>Timetable</td>
<td>Day 210 – 21 March 2013</td>
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</table>
Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that have been 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 for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4
Labelling

The following text is the approved label text for Risedronate Sodium 75 mg Film-coated Tablets (PL 04569/1277). No label mock-ups have been provided for this product. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained.

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</th>
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<tbody>
<tr>
<td>CARTON</td>
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</table>

1. **NAME OF THE MEDICINAL PRODUCT**

   Risedronate Sodium 75 mg Film-coated Tablets (risedronate sodium)

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

   Each film-coated tablet contains 75 mg of risedronate sodium (equivalent to 69.6 mg risedronic acid)

3. **LIST OF EXCIPIENTS**

   Contains glucose and sorbitol [E420]. See leaflet for further information

4. **PHARMACEUTICAL FORM AND CONTENTS**

   **Blisters**
   - 2 film-coated tablets
   - 4 film-coated tablets
   - 6 film-coated tablets
   - 8 film-coated tablets
   - 12 film-coated tablets

   **Bottles**
   - 28 film-coated tablets

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

   For oral use. Take two tablets a month, on the same two consecutive days each month.

   Swallow the tablets whole. Do not suck or chew them.

   Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

   Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

   Take two tablets a month, on the same two consecutive days each month.
8. **EXPIRY DATE**

**EXP:**

*After first opening, use within 100 days.* (Applicable when bottle is packed into carton)

9. **SPECIAL STORAGE CONDITIONS**

This medicinal product does not require any special storage conditions.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Generics [UK] Ltd t/a Mylan
Potter's Bar,
Hertfordshire, EN6 1TL
United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 04569/1277

13. **BATCH NUMBER**

Batch:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Risedronate Sodium 75 mg Film-coated Tablets
**MINIMUM PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**BOTTLE LABEL**

1. **NAME OF THE MEDICINAL PRODUCT**

Risedronate Sodium 75 mg Film-coated Tablets
(risedronate sodium)

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 75 mg of risedronate sodium (equivalent to 69.6 mg risedronic acid)

3. **LIST OF EXCIPIENTS**

Contains glucose and sorbitol [E420]. See leaflet for further information

4. **PHARMACEUTICAL FORM AND CONTENTS**

28 film-coated tablets

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

For oral use. Take two tablets a month, on the same two consecutive days each month.

Swallow the tablets whole. Do not suck or chew them.

Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

Take two tablets a month, on the same two consecutive days each month.

8. **EXPIRY DATE**

EXP:

After first opening, use within 100 days.
Opened:
9. SPECIAL STORAGE CONDITIONS

This medicinal product does not require any special storage conditions.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Generics [UK] Ltd. t/a Mylan
Potters Bar,
Hertfordshire, EN6 1TL
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 04569/1277

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Risedronate Sodium 75 mg Film-coated Tablets
(risedronate sodium)

2. NAME OF THE MARKETING AUTHORIZATION HOLDER

Generics [UK] Ltd. t/a Mylan
Potters Bar,
Hertfordshire, EN6 1TL
United Kingdom

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. OTHER

Take two tablets a month, on the same two consecutive days each month
Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Risedronate Sodium 75 mg Film-coated Tablets (PL 04569/1277; UK/H/4896/001/DC) could be approved. The application was submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS) and Italy, Belgium, Luxembourg, Spain and France as Concerned Member States (CMS).

This product is a prescription-only medicine (legal classification POM).

This was an application made under the Decentralised Procedure (DCP), according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Actonel 75 mg Film-coated Tablets (Warner Chilcott UK Limited). The originator product was Actonel 5 mg Film-coated Tablets, which was originally granted a marketing authorisation in Sweden on 07 October 1999 and was subsequently authorised in the UK on 16 March 2000, via a mutual recognition procedure. The product used in the bioequivalence study was Actonel 75 mg Tablets (Warner Chilcott, Italy), which is identical to the currently authorised reference product in the UK.

Risedronate Sodium 75 mg Film-coated Tablets are indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fractures.

Risedronate sodium is a pyridinyl bisphosphonate that binds to bone hydroxyapatite and inhibits osteoclast-mediated bone resorption. It inhibits bone turnover without directly suppressing bone formation, resulting in increased bone mass and mineralisation.

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.

With the exception of the bioequivalence study, no new 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.

A bioequivalence study was performed, which compared the pharmacokinetics of Risedronate Sodium 75 mg Film-coated Tablets (Generics UK Limited) versus Actonel 75 mg Tablets (Warner Chilcott, Italy). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

The RMS and CMS considered that the application could be approved with the end of procedure on 21 March 2013. After a subsequent national phase, a licence was granted in the UK on 10 May 2013.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Risedronate Sodium 75 mg Film-coated Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Risedronate Sodium</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Bisphosphonates (M05BA)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Film-coated Tablets, 75 mg</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/4896/001/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>UK</td>
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<tr>
<td>Member States concerned</td>
<td>Italy, Belgium, Luxembourg, Spain and France</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 04569/1277</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Generics (UK) Limited, 24 Station Close, Potters Bar, Hertfordshire, EN6 1TL, UK</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substances - Risedronate Sodium

rINN: Risedronate sodium

Chemical name: [1-hydroxy-2-(3-pyridinyl) ethylidene] bisphosphonic acid monosodium salt hemipentahydrate

Structure:

![Structure](image)

Molecular formula: C_{17}H_{10}NaO_{7}P_{2}.2.5H_{2}O
Molecular weight: 350.13 g/mol
Appearance: White to off-white powder, which is soluble in water and is insoluble in methanol and in isopropanol.

An Active Substance Master File (ASMF) has been provided, which covers the manufacture and control of the active substance risedronate sodium.

Synthesis of the drug 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. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and 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 to support a suitable retest period when stored in the proposed packaging.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients. In the tablet core these are mannitol (E421), microcrystalline cellulose, crospovidone (Type A), colloidal anhydrous silica and magnesium stearate. The film-coating consists of Opadry II Pink (40L94556), which contains the excipients titanium dioxide (E171), Polydextrose FCC (contains glucose and sorbitol [E420]), HPMC 2910/Hypromellose 3cP, HPMC 2910/Hypromellose 6cP, triacetin, HPMC 2910/Hypromellose 50cP, Macrogol/PEG 8000 and iron oxide (E172).
With the exception of Opadry II Pink (40L94556), which complies with suitable in-house standards, all excipients comply with their respective European Pharmacopoeia monographs.

None of the excipients are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

**Pharmaceutical Development**
The objective of the development programme was to formulate a globally acceptable, stable and bioequivalent product that could be considered a generic medicinal product of the innovator product, Actonel 5 mg Film-coated Tablets (Warner Chilcott UK Limited).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed product and its respective reference product.

**Manufacturing Process**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product.

Suitable validation data have been provided for three commercial-scale batches produced by the finished product manufacturer.

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

**Container-Closure System**
The finished product is packaged as follows:
Aclar/polyvinylchloride/aluminium blisters, which are packed into cardboard cartons in pack sizes of 2, 4, 6, 8 or 12 tablets.

Aclar/polyvinylchloride/aluminium calendar blisters, which are packed into cardboard cartons in pack sizes of 2 tablets.

A high-density polyethylene bottle with a polypropylene screw-cap, for a pack size of 28 tablets.

The marketing authorisation holder has stated that not all pack sizes are intended for marketing. However, they have committed to providing the relevant licensing authority with the mock-ups for any pack size before marketing it in that country.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

**Stability of the product**
Stability studies were performed in accordance with current guidelines on batches of finished product manufactured by the finished product manufacturer and packed in the packaging proposed for marketing. The results from these studies support a shelf-life of 24 months (unopened) and 100 days (after opening), with no special storage conditions.
Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are acceptable from a pharmaceutical perspective.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) form
The MAA form is satisfactory from a pharmaceutical perspective.

Quality Overall Summary (Expert report)
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of risedronate sodium are well-known, no further non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

Suitable justification has been provided for the non-submission of an environmental risk assessment. As this product is intended for generic substitution with products that are currently marketed, no increase in environmental burden is expected.

There are no objections to the approval of this product from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS
Pharmacokinetics
In support of this application, the Marketing Authorisation Holder has submitted the following bioequivalence study:

An open-label, balanced, randomised, two-treatment, two-period, two-sequence, crossover, single-dose evaluation of bioavailability of Risedronate Sodium 75 mg Film-coated Tablets (Generics UK Limited) versus Actonel Tablets 75 mg (Warner Chilcott, Italy) in healthy adult human subjects under fasting conditions.

Following a supervised overnight fast of at least 8 hours, subjects were administered a single 75 mg dose of the test or reference product with 240 ml of water. Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 72 hours post-dose. The two periods were separated by an 18-day washout period.
The pharmacokinetic results for plasma levels of risedronate sodium are presented below:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$AUC_{0-72}$ $\text{ng/ml/h}$</th>
<th>$C_{\text{max}}$ $\text{ng/ml}$</th>
<th>$t_{\text{max}}$ h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>$168.360 \pm 116.522$</td>
<td>$46.006 \pm 26.421$</td>
<td>$1.00 (0.50-3.00)$</td>
</tr>
<tr>
<td>Reference</td>
<td>$173.370 \pm 117.034$</td>
<td>$47.071 \pm 32.236$</td>
<td>$1.00 (0.33-4.00)$</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>$96.73%$ ($84.27 - 111.03$)</td>
<td>$97.77%$ ($86.04-111.11$)</td>
<td></td>
</tr>
</tbody>
</table>

*$AUC_{0-t}$ Area under the plasma concentration curve from administration to last observed concentration at time $t$.

*$AUC_{0-72}$ can be reported instead of $AUC_{0-t}$ in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products.

*$AUC_{\infty}$ Area under the plasma concentration curve extrapolated to infinite time.

*$C_{\text{max}}$ Maximum plasma concentration

*$t_{\text{max}}$ Time until $C_{\text{max}}$ is reached

*In-transformed values

Compared with the reference product, the 90 % confidence intervals for the test product are within 80.00-125.00 % for $C_{\text{max}}$ and $AUC$. Risedronate Sodium 75 mg Film-coated Tablets are therefore considered to be bioequivalent to Actonel Tablets 75 mg (Warner Chilcott, Italy).

**Efficacy**

No new data on efficacy have been submitted and none are required for this type of application.

**Safety**

With the exception of the data submitted during the bioequivalence study, no new safety data have been submitted and none are required. No new or unexpected safety issues have been raised by the bioequivalence data.

**SmPC, PIL and Labels**

The SmPC, PIL and labels are acceptable from a clinical perspective. The SmPC is consistent with that for the reference product.

**Pharmacovigilance System and Risk Management Plan**

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.

Suitable justification has been provided for not submitting a risk management plan for this product.

**Clinical Expert Report**

The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Conclusion**

The grant of a Marketing Authorisation is recommended.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Risedronate Sodium 75 mg Film-coated 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 were submitted and none are required for applications of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s product and the reference product Actonel Tablets 75 mg (Warner Chilcott, Italy).

No new or unexpected safety concerns arose from this application.

The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s product and the reference product are interchangeable. Extensive clinical experience with risedronate sodium is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is therefore considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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