Risedronaatnatrium Jenson wekelijks 35 mg, tablets
Jenson Pharmaceutical Services Ltd, United Kingdom

risedronate (as sodium)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB’s knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1877/001/DC
Registration number in the Netherlands: RVG 106328

23 August 2011

Pharmacotherapeutic group: drugs affecting bone structure and mineralization; bisphosphonates
ATC code: M05BA07
Route of administration: oral
Therapeutic indication: postmenopausal osteoporosis; osteoporosis in men at high risk of fractures.
Prescription status: prescription only
Date of authorisation in NL: 3 May 2011
Concerned Member States: Decentralised procedure with BE, BG, CZ, DE, DK, ES, FI, FR, IE, IS, NO, PT, SE, SK and UK
Application type/legal basis: Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.
I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Risedronaatnatrium Jenson wekelijks 35 mg, tablets from Jenson Pharmaceutical Services Ltd. The date of authorisation was on 3 May 2011 in the Netherlands.

The product is indicated for:

- Treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures. Treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures.
- Treatment of osteoporosis in men at high risk of fractures.

A comprehensive description of the indications and posology is given in the SPC.

Risedronate sodium is a pyridinyl bisphosphonate that binds to bone hydroxyapatite and inhibits osteoclast-mediated bone resorption. The bone turnover is reduced while the osteoblast activity and bone mineralisation is preserved. In preclinical studies risedronate sodium demonstrated potent anti-osteoclast and antiresorptive activity, and dose dependently increased bone mass and biomechanical skeletal strength. The activity of risedronate sodium was confirmed by measuring biochemical markers for bone turnover during pharmacodynamic and clinical studies. In studies of post-menopausal women, decreases in biochemical markers of bone turnover were observed within 1 month and reached a maximum in 3-6 months. Decreases in biochemical markers of bone turnover were similar with risedronate sodium once a week 35 mg and risedronate sodium 5 mg daily at 12 months.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Optinate Septimum 35 mg film-coated tablets which has been registered in Sweden by sanofi-aventis AB since 2002. Optinate 5 mg was first authorised in Sweden in 1999. In the Netherlands, the 35 mg product has been registered since 2003 through MRP SE/H/0192/003 under the name Actonel Wekelijks 35 mg, film-coated tablets (NL License RVG 28338). In addition, reference is made to Optinate/Actonel authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Actonel 35 mg tablets, registered in the UK. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.
II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is risedronate sodium, an established active substance described in the Pharmacopoeia of the United States (USP*). The drug substance is a white to off-white powder, which is soluble in water and practically insoluble in organic solvents. Risedronate sodium hemi-pentahydrate is produced by the manufacturing process; this polymorphic form is confirmed by X-ray diffraction and other means. Other existing polymorphic forms are several other hydrates, alcohol solvates, anhydrates and amorphous forms.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The drug substance is synthesised in a two-stage process. The manufacturing process is described in detail including a flow-chart of the process. In general adequate specifications for the starting material, adequate in-process controls and specifications are applied.

Quality control of drug substance
The drug substance tests include several test parameters from the USP monograph and appropriate in-house methods. All analytical methods are clearly described, and sufficiently validated. The in-house HPLC method has been validated for the specified impurities. Batch analysis results are provided for 3 production-scale batches. All results meet the set requirements.

Stability of drug substance
Stability studies were performed in line with ICH guidelines. For three batches normal testing data (25°C/60% RH) up to 24 months and accelerated data (40°C/75% RH) up to 6 months are available. No significant changes have been observed among the available stability results. Based on these results the claimed re-test period of 36 months without specific storage conditions can be granted.

* USP is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the USA.

Medicinal Product

Composition
Risedronaatnatrium Jenson contains 35 mg risedronate sodium (as hemipentahydrate) equivalent to 32.5 mg risendronic acid. It is a light orange, round, biconvex, bevelled edge film-coated tablet, debossed with M on one side of the tablet and 714 on the other side.

The tablets are packed in HDPE container with PP child-resistant cap or PVC/Aclar/Aluminium blisters in a carton box.
The excipients are:
*Tablet core* – mannitol, microcrystalline cellulose, crospovidone, colloidal anhydrous silica, magnesium stearate.

*Coating* - titanium dioxide (E171), polydextrose, hypromellose, polyethylene glycol, glycerol triacetate, iron oxide yellow (E172), iron oxide red (E172).

**Pharmaceutical development**
The objectives of the formulation development trials were to develop a formula and a manufacturing process capable of producing a finished dosage form which would be pharmaceutically equivalent to the reference product. The choice of manufacturing process, excipients and packaging material has been sufficiently justified.

The commercial formulation was used in the bio-equivalence study. Dissolution profiles were conducted on the 35 mg Risedronate sodium Jenson tablets and the reference product, Actonel tablets, in the selected release media, showing identical dissolution profiles. Comparative profiles are provided for dissolution studies at three pH values.

**Manufacturing process**
The manufacturing process comprises usual steps of blending, milling, roller compaction, final blending, compression and film-coating. All steps are described in sufficient detail, a flow chart is provided. Adequate in-process controls are given for the stages of the final blend, compression and film-coating. The MAH performed a process validation study on two pilot-scale batches. The validation protocol for the proposed maximum commercial batch size is provided in the dossier.

**Control of excipients**
The core excipients meet the requirements of corresponding Ph. Eur. monographs. For iron oxide yellow and Iron oxide red in reference is made to EC directive 2009/53/EC. Polydextrose complies with the standards of the Food Chemicals Codex of the USP. These specifications are acceptable.

**Quality control of drug product**
Identical release and shelf-life specifications are applied for appearance, identification of drug substance, uniformity of dosage units, water content, dissolution, assay and related substances. Microbial purity requirements are included. All analytical methods have been described and validated. The method for related substances has been tested using stress conditions for the drug product and appears to be stability indicating. Batch analysis results were provided for the two validation batches, with results meeting the set requirements. The MAH committed to provide analytical results of a third batch as soon as available.

**Container Closure System**
The product is packed in HDPE bottles with a plastic closure seal (cap) or child resistant closure seal (cap), both provided with PE liners, or in PVC-alu blisters. The bulk tablets are packed in double PE bags placed in fibre drums or white production boxes.

**Stability of drug product**
Two batches of the tablets were stored in either the blister packaging or the bottles for 18 months at long-term conditions (25°C/60% RH) and 6 months at accelerated conditions (40°C/75% RH). For both storage conditions no significant changes in physical or chemical parameters have been found; no trends regarding results from assay, dissolution or degradation products were observed. Forced degradation studies demonstrated that the drug product is stable under all stress conditions applied, and that the product is photo-stable and that light protection measures are not necessary. Based on these results, a shelf life of 24 months without specific storage conditions can be granted for both packagings. The MAH will continue the stability studies up to the approved shelf life. The first three commercial batches in the blister pack will be placed on long-term stability program.

**Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies**
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded. Magnesium stearate is of vegetable origin.

II.2 Non-clinical aspects

This product is a generic formulation of Optinate, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of risedronate released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Risedronate is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Risedronaatnatrium Jenson wekelijks 35 mg (Jenson Pharmaceutical Services Ltd., UK) is compared with the pharmacokinetic profile of the reference product Actonel 35 mg tablets (Procter Gamble Pharmaceuticals UK Ltd.).

The choice of the reference product

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 130 healthy male subjects, aged 18-44 years. Each subject received a single dose (35 mg) of one of the 2 risedronate formulations. The tablet was orally administered with 240 ml water after an overnight fast. Meals were provided no less than 4 hours after drug administration. Demineralised water (240 ml) was allowed 1.25 hours pre-dose, and 1 hour after dosing regular tap water was allowed ad libitum. There were 2 dosing periods, separated by a washout period of 21 days. Blood samples were taken before dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours after administration of the products.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Two subjects did not show up in the second period, two subjects withdrew their consent in the second period and one was withdrawn due to adverse events. Out of the 130 male volunteers included in the study, 125 subjects completed the study. The dropouts were not included in the statistical analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t\text{max} (median, range)) of risedronate under fasted conditions.
The 90% confidence intervals calculated for \( \text{AUC}_{0-t} \), \( \text{AUC}_{0-\infty} \) and \( C_{\text{max}} \) are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80-1.25. Based on the pharmacokinetic parameters of risedronate under fasted conditions, it can be concluded that Risedronaatnatrium Jensen wekelijks 35 mg and Actonel 35 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Safety
After administration of both test and reference drugs adverse events were recorded. After each drug 5 events were listed, mostly drug product related but no severe events were reported.

Mean oral bioavailability is decreased when risedronate sodium is administered with food. The SPC clearly states that risedronate should be taken without reference to food intake (before breakfast, at least 30 minutes before the first food). Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan
Risedronate was first approved in 1998, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of risedronate can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Actonel, and the Core Safety Profile an paediatric wording for risedronate has been included.
Readability test
The package leaflet has not been evaluated via a user consultation study. A waiver has been granted for user testing.
According to the published CMD(h) document “Consultation with target patient groups – Meeting the requirements of Article 59(3) without the need for a full test – Recommendations for bridging” bridging can be accepted for medicines within the same ‘drug class.’ That means similar key safety messages, similar indications, similar patient population and similar format and layout of the PIL. The MAH sufficiently demonstrated in the bridging report, that there are no important differences between the PIL for Risedronate Jenson and a tested PIL for another bisfosfonate containing product.
The layout of Risedronate Jenson differs from the layout of the tested PIL, but reference is made to other leaflets with the same in-house style which has been successfully tested.
No differences between the PILs were observed that are considered to influence readability. Therefore the bridging report was accepted.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Risedronaatnatrium Jenson wekelijks 35 mg, tablets has a proven chemical-pharmaceutical quality and is a generic form of Actonel 35 mg. Actonel is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other risedronate containing products.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Risedronaatnatrium Jenson wekelijks 35 mg, tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 15 March 2011. Risedronaatnatrium Jenson wekelijks 35 mg, tablets was authorised in the Netherlands on 3 May 2011.

A European harmonised birth date has been allocated (31 March 1998) and subsequently the first data lock point for risedronate is March 2012. The first PSUR will cover the period from authorisation to March 2012, after which the PSUR submission cycle is 1 year.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product
- The MAH committed to submit analytical results of a third batch as soon as the first three commercial batches are manufactured.
List of abbreviations

ASMF  Active Substance Master File
ATC   Anatomical Therapeutic Chemical classification
AUC   Area Under the Curve
BP    British Pharmacopoeia
CEP   Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP  Committee for Medicinal Products for Human Use
CI    Confidence Interval
Cmax  Maximum plasma concentration
CMD(h) Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV    Coefficient of Variation
EDMF  European Drug Master File
EDQM  European Directorate for the Quality of Medicines
EU    European Union
GCP   Good Clinical Practice
GLP   Good Laboratory Practice
GMP   Good Manufacturing Practice
ICH   International Conference of Harmonisation
MAH   Marketing Authorisation Holder
MEB   Medicines Evaluation Board in the Netherlands
OTC   Over The Counter (to be supplied without prescription)
PAR   Public Assessment Report
Ph.Eur. European Pharmacopoeia
PIL   Package Leaflet
PSUR  Periodic Safety Update Report
SD    Standard Deviation
SPC   Summary of Product Characteristics
t½    Half-life
tmax  Time for maximum concentration
TSE   Transmissible Spongiform Encephalopathy
USP   Pharmacopoeia in the United States
## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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