

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Risedronaatnatrium Apotex wekelijks 35 mg, film-coated tablets
Apotex Europe B.V., the Netherlands**

risedronic acid (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/1913/001/DC
Registration number in the Netherlands: RVG 106275**

1 March 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:	28 February 2011
Concerned Member States:	Decentralised procedure with BE, CZ, ES, IT, LU, 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 Apotex wekelijks 35 mg, film-coated tablets from Apotex Europe B.V. The date of authorisation was on 28 February 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 film-coated 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 powder, which is soluble in water/aqueous solutions and essentially insoluble in organic solvents; soluble in base, and very slightly soluble in acid aqueous solutions. Risedronate sodium hemi-pentahydrate is produced by the manufacturing process; this polymorphic form is confirmed by X-ray diffraction. Other existing polymorphic forms are several other hydrates, alcohol solvates, anhydrides 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 manufacturing process of the drug substance has been sufficiently described. There are two alternative starting materials, both providing high purity risedronate sodium hemi-pentahydrate. Sufficient in-process controls have been laid down.

Quality control of drug substance

The drug substance tests include test parameters from the USP monograph. All analytical methods are clearly described. In 10 batches of drug substance the results for maximum unknown were below 0.05%. Batch analysis data are provided from a sufficient number of production-scale batches from both starting materials.

Stability of drug substance

Stability studies were performed in line with ICH guidelines. For three initial batches and three second-crop batches from one starting material normal testing data are available up to 24 months and accelerated data up to 6 months. For drug substance from the other starting material, 1 production batch and 1 second batch up to 12 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. It was shown by PXRD data that the hemipentahydrate form does not change during storage.

* 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 Apotex wekelijks contains 35 mg risedronate sodium (as hemipentahydrate) equivalent to 32.5 mg risedronic acid. It is an orange, round, biconvex film-coated tablet with 'APO' engraved on one side and 'RIS' over '35' on the other side.

The film-coated tablets are packed in PVC/PVdC-Alu blister packs.

The excipients are:

Tablet core – anhydrous lactose, crospovidone, magnesium stearate (E572), colloidal anhydrous silica.

Coating – hypromellose (E464), hydroxypropylcellulose (E463), macrogol, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (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 development of the dissolution method has been adequately described. Both Risedronate Sodium by Apotex and the Actonel product (UK) demonstrated very rapid and dose-independent dissolution profiles in water ($\geq 85\%$ in 15 minutes). Dissolution profiles were obtained at different pH values and were shown to be comparable.

The pharmaceutical development of the product has been described in sufficient detail.

Manufacturing process

The main steps of the standard manufacturing process are milling, screening and blending of ingredients, lubricating, compression and film-coating. An adequate holding time has been defined based on bulk stability data. The MAH provided validation protocol and committed to validate three batches prior marketing. Considering that the manufacturing process is considered a standard process, the provided limited validation data are accepted.

Control of excipients

Red and yellow ferric oxide are meeting the requirements of USP-NF, and in accordance with Council Directive 94/36/EC and Commission Directive 95/45/EC and respective amendments. All other excipients do meet the requirements of the Ph.Eur. These specifications are acceptable.

Quality control of drug product

Adequate release and shelf-life specifications are applied for the drug product, in accordance with usual and pharmacopoeial requirements or current guidelines. Release specifications are applied for appearance, identification of drug substance, identification of titanium dioxide and ferric oxide, average weight, uniformity of dosage units, loss on drying, dissolution, assay, related substances, and microbiological purity. In view of the known propensity of biphosphonates to cause oesophagitis, a lower disintegration time limit for release and shelf life is applied. This is appropriate.

All analytical methods are adequately described and validated. Batch analysis results on three batches are in accordance with the set requirements.

Stability of drug product

Three batches were included in the stability studies; these have been stored for 18 months at normal and 6 months at accelerated conditions. 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 photostable.

Based on the provided stability data, a shelf life was granted of 2 years in alu-PVC/PVdC blister without specific storage condition.

The first three commercial batches in the blister pack will be placed on a long-term stability program.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

For the excipients magnesium stearate (100% vegetable origin) and lactose anhydrous (obtained from milk sourced from healthy animals in the same conditions as milk collected for human consumption) all necessary data were provided regarding the risk of BSE/TSE.

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 Apotex wekelijks 35 mg (Apotex Europe B.V., NL) is compared with the pharmacokinetic profile of the reference product Actonel 35 mg film-coated tablets (Sanofi-Aventis, UK). The product was also compared to Actonel from the Australian market. Only the UK reference product is considered relevant for this application. Therefore, only the data of this reference product were taken into account.

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, three-period, three-treatment, three-sequence, crossover bioequivalence study was carried out under fasted conditions in 69 healthy subjects (33 females/36 males), aged 21-55 years. Each subject received a single dose (35 mg) of one of the 3 risedronate formulations. The tablet was orally administered with 240 ml water after an overnight fast. To avoid possibility of oesophagus irritation, the subjects took the risedronate tablet while standing or sitting upright. Meals were provided no less than 4 hours after drug administration. Demineralized water was allowed *ad libitum* until 2 hours pre-dose and between approximately 2 hours and 4 hours after dosing; after which regular tap water was allowed *ad libitum*.

The volunteers were divided in two cohorts who were treated three days after each other. The washout period between the treatments was 28 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.75, 1, 1.33, 1.67, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 60 and 72 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 dropped out for medical reasons and were not included in the statistical analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{max} (median, range)) of risedronate under fasted conditions.

Treatment	AUC _{0-t}	AUC _{0-∞}	C _{max}	t _{max}	t _{1/2}
-----------	--------------------	--------------------	------------------	------------------	------------------

N=67	ng.h/ml	ng.h/ml	ng/ml	h	h
Test	58.67 ± 45.03	63.21 ± 48.35	16.08 ± 15.14	1.0 (0.33-4.0)	39.4 ± 8.1
Reference	60.78 ± 46.77	65.72 ± 50.15	16.32 ± 14.01	1.13 (0.33-3.0)	38.5 ± 8.9
*Ratio (90% CI)	1.03 (0.92-1.16)	1.02 (0.91-1.15)	1.04 (0.91-1.18)		
CV (%)	42	42	47		
AUC_{0-∞} area under the plasma concentration-time curve from time zero to infinity AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum concentration t_{1/2} half-life					

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} and C_{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 Apotex wekelijks 35 mg and Actonel 35 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

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 for risedronate has been included.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a preliminary round followed by 2 round of testing with 10 participants each. The preliminary round did not identify any major issues. Participants were recruited from senior day centres, churches, libraries and referrals from past

participants. The age and sex distribution of the participants was acceptable with regard to the indications. The test contained 17 questions specific to the product, which covered the main safety issues and 3 feedback questions about the user friendliness of the PIL. No revisions to the PIL were proposed during the test.

The leaflet passed the defined success criteria (90% of the test participants are able to find the information requested within the package leaflet of which 90% can show that they understand it in each round). Therefore the test was deemed to be successful. In addition there was mainly positive feedback on the lay-out of the PIL. The MAH did not identify any weaknesses of the PIL. However after taking a closer look at the results from the text regarding the intake with food in section 2, this section was amended.

The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Risedronaatnatrium Apotex wekelijks 35 mg, film-coated 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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Risedronaatnatrium Apotex wekelijks 35 mg, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 25 August 2010. Risedronaatnatrium Apotex wekelijks 35 mg, film-coated tablets was authorised in the Netherlands on 28 February 2011.

A European harmonised birth date has been allocated (31 March 1998) and subsequently the first data lock point for risedronate is March 2011. The first PSUR will cover the period from August 2010 to March 2011, after which the PSUR submission cycle is 1 year.

The date for the first renewal will be: 30 November 2013.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to place the first three commercial batches in the blister pack on a long-term stability program.

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
C _{max}	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
t _{1/2}	Half-life
t _{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached