CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Natriumrisedronaat Aurobindo 5 mg and 30 mg, film-coated tablets
Natriumrisedronaat Aurobindo Wekelijks 35 mg, film-coated tablets
Aurobindo Pharma 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/2263/001-003/MR
Registration number in the Netherlands: RVG 106807-106809

3 October 2011

Pharmacotherapeutic group:	drugs affecting bone structure and mineralization; bisphosphonates
ATC code:	M05BA07
Route of administration:	oral
Therapeutic indication:	postmenopausal osteoporosis (5 mg, 35 mg); osteoporosis in men at high risk of fractures (35 mg only); Paget's disease of the bone (30 mg only); prevention of osteoporosis (5 mg only); to maintain or increase bone mass in postmenopausal women undergoing long-term systemic corticosteroid treatment (5 mg only) (see next page)
Prescription status:	prescription only
Date of first authorisation in NL:	6 September 2010
Concerned Member States:	Mutual recognition procedure with DE, ES, FR, IE, IT, MT, UK; addtitionally for 35 mg strength – RO
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 Natriumrisedronaat Aurobindo 5 mg and 30 mg, film-coated tablets and Natriumrisedronaat Aurobindo Wekelijks 35 mg, film-coated tablets from Aurobindo Pharma B.V. The date of authorisation was on 6 September 2010 in the Netherlands.

The therapeutic indications are:

Natriumrisedronaat Aurobindo 5 mg
- Treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures.
- Treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures.
- Prevention of osteoporosis in postmenopausal women with increased risk of osteoporosis (see section 5.1).
- To maintain or increase bone mass in postmenopausal women undergoing long-term (more than 3 months), systemic corticosteroid treatment at doses ≥7.5mg/day prednisone or equivalent.

Natriumrisedronaat Aurobindo 30 mg
- Treatment of Paget's disease of the bone.

Natriumrisedronaat Aurobindo Wekelijks 35 mg
- 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 and in patients with Paget's disease, 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 35 mg and Risedronate sodium 5 mg daily at 12 months.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Actonel 5 mg, 30 mg and 35 mg, film-coated tablets which was first registered in Sweden by Procter & Gamble Pharmaceuticals UK Ltd since 1999 (original product). In the Netherlands, Actonel 5 mg and 30 mg (NL License RVG 25801, 24990) have been registered since 2000 and Actonel Wekelijks 35 mg, film-coated tablets (NL RVG 28338) since 2003 through MRP SE/H/0192/001-003.
In addition, reference is made to Actonel authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC. For the 35 mg strength in Italy and Romania, the legal basis is article 10(3) of Directive 2001/83/EC, as this strength is not available for the innovator in these CMSs.

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® once a week 35 mg, film-coated tablets obtained from 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 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/aqueous solutions and insoluble in organic solvents. Risedronate does not have a chiral center and does not show any optical isomerism. Risedronate sodium hemi-pentahydrate is produced by the manufacturing process in one polymorphic form.

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 synthesis processes, starting materials, solvents and reagents have been included in the description. The drug substance is formed in a two step process. The active substance has been adequately characterized. No class 1 organic solvents are used in the manufacturing process of the drug substance.

Quality control of drug substance
The drug substance specification is in line with requirements of the USP and has further been established in-house by the MAH. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for thee production-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three production-scaled batches stored at 25°C/60%RH (36 months) and 40°C/75%RH (6 months). Based on the results, the claimed re-test period of 36 months is justified. The drug substance does not require any special storage conditions.

**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
Natriumrisedronaat Aurobindo 5 mg contains 5 mg risedronate sodium (equivalent to 4.6 mg risedronic acid) and is a yellow colored, circular shaped, beveled edge, film-coated biconvex tablet debossed with 'X' on one side and '61' on the other side.
Natriumrisedronaat Aurobindo 30 mg contains 30 mg risedronate sodium (equivalent to 27.8 mg risedronic acid) and is a white to off-white colored, circular shaped film-coated biconvex tablet debossed with 'L' on one side and '30' on the other side.
Natriumrisedronaat Aurobindo 35 mg contains 35 mg risedronate sodium (equivalent to 32.4 mg risedronic acid) and is a light orange colored, circular shaped film-coated biconvex tablet debossed with 'F27' on one side and plain on the other side.

The film-coated tablets are packed in transparent PVC/PE/PVdC/Aluminium blisters**.**

The excipients are:
Tablet core - lactose monohydrate, cellulose microcrystalline, crospovidone, hydroxy propyl cellulose, magnesium stearate.
Coating – hypromellose, titanium dioxide (E171), macrogol 400, hydroxy propyl cellulose; iron oxide yellow (E172) (5 mg, 35 mg), macrogol 8000 (5 mg, 35 mg) silica colloidal anhydrous (5 mg, 35 mg), iron oxide red (E172) (35 mg).

The three tablet strengths are dose proportional.

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 Aurobindo and the innovator product Actonel product (UK) demonstrated very rapid and dose-independent dissolution profiles in water (≥ 85% in 15 minutes). Dissolution profiles were obtained at different pH values and were shown to be comparable with the tablets of the innovator product. The innovator product Actonel is marketed in the UK through MRP (SE/H/0192/003). So the use of the UK reference product is acceptable for the Netherlands, no further comparison is necessary.
For each strength a comparison was made of the impurity profiles and assay of the innovator and test product. Results for assay were comparable
The pharmaceutical development of the product has been described in sufficient detail.

Manufacturing process
The tablets are manufactured by means of a 17-step process including preparation of the granular, compression of lubricated blend, and coating of the compressed tablets. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 4 minimum-size production-scale batches of the common blend as well as two minimum-size production-scale batches of each tablet strength. The product is manufactured using conventional manufacturing techniques. Process validation on additional minimum sized production scaled batches and for maximum sized production scaled batches will be performed post authorization.

Control of excipients
All excipients comply with their specifications of the Ph.Eur. monographs. and additional requirements. For the coating material an acceptable in-house specification is provided.

Quality control of drug product
The product specification includes tests for appearance, average weight, uniformity of dosage units (content), water, identification, dissolution, assay, related substances, thickness, microbiological

contamination and identification of titanium dioxide and colorants. Release and end of shelf-life specification are identical except for water and related substances. The limits are acceptable. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on six minimum-size production-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for six production-scale batches stored at 25°C/60%RH (12 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PE/PVdC-Aluminum blisters as well as a simulated bulk pack. All results stayed within limits. Forced degradation studies showed no sensitivity to light. A shelf-life of 2 year was granted based on the provided data; the product does not require any special storage conditions.

Several commitments have been made with regard to the finished product; these can be found on page 8 of this report.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
For lactose monohydrate, relevant certification in compliance with EU regulations on TSE has been provided. Stearic acid of vegetable is used in the manufacture of Magnesium stearate.

II.2 Non-clinical aspects

This product is a generic formulation of Actonel, 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 Natriumrisedronaat Aurobindo Wekelijks 35 mg (Aurobindo Pharma B.V., NL) is compared with the pharmacokinetic profile of the reference product Actonel 35 mg once a week, film-coated tablets (Proctor &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 60 healthy male subjects, aged 19-48 years. Each subject received a single dose (35 mg) of one of the 2 risedronate sodium formulations. The tablet was orally administered with 240 ml water under fasted conditions. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48 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
One subject dropped out as he was absent for period-II check-in. The remaining 59 subjects completed the study and were included in the pharmacokinetc analysis.

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

Treatment N=59	**AUC_{0-72h}** ng*hr/ml	**C_{max}** ng/ml	**t_{max}** hr
Test	87 ± 42	25 ± 13	1.25 (0.5-2.5)
Reference	87 ± 42	24 ± 13	1.0 (0.5-4)
***Ratio (90% CI)**	1.01 (0.90-1.14)	1.03 (0.91-1.16)	-
CV (%)	40	41	-

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-72} 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 risedronic acid under fasted conditions, it can be concluded that Natriumrisedronaat Aurobindo Wekelijks 35 mg and Actonel 35 mg once a week, 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.

Safety
Twenty-four adverse events were reported during the entire duration of the study. Eighteen adverse events occurred during the in-house stay of the subjects in Period I. Six adverse events occurred during the in-house stay of the subjects in Period II. All post-study clinical laboratory test results were within normal range. Fourteen adverse events were observed after administration of the test product and ten after administration of the reference product. Musculoskeletal events were reported 11 times, myalgia 8 times, headache 4 times and nausea once. All adverse events resolved.

Extrapolation to different strengths
The results of this study with the 35 mg tablets can be extrapolated to the risedronate 5 mg and 30 mg tablets, since all conditions mentioned in the current Note for Guidance on Bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled:
- The tablets are manufactured by the same manufacturer and process
- The absorption after an oral dose is rapid (t_{max} is approximately 1 hour) and independent over the dose range studied.

- The qualitative composition of the 5 and 30 mg tablets is the same as the risedronate 35 mg tablet
- The risedronate 5 and 30 mg tablets are dose proportional with the 35 mg tablet
- The dissolution profiles of the 5 and 30 mg tablets are similar with the risedronate 35 mg tablet under identical conditions.

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. Reference is made to the results of a readability test with another bisphosphonate. Use of the parent PIL was justified, since the key messages for safe use have been adequately addressed. Both leaflets have the same font type, font size, layout and design (same inhouse style), and same text colour. In both PILs the headings are presented as white letters with black background which enhances the findability of relevant information. The critical safety sections in both parent and daughter PL are laid out in bullet points.
Furthermore, the content of the Daughter PL is exactly the same as the PL text of the innovator product Actonel (SE/H/0192/001-003).

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Natriumrisedronaat Aurobindo 5 mg and 30 mg, film-coated tablets and Natriumrisedronaat Aurobindo Wekelijks 35 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Actonel 5 mg, 30 mg and 35 mg, film-coated tablets. 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 Natriumrisedronaat Aurobindo 5 mg and 30 mg, film-coated tablets and Natriumrisedronaat Aurobindo Wekelijks 35 mg, film-coated tablets were authorised in the Netherlands on 6 September 2010.

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 Natriumrisedronaat Aurobindo 5 mg, 30 mg and 35 mg with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 20 June 2011.

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

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

Quality - medicinal product

- The MAH committed to validate the manufacturing process for the first commercial batches of the minimum batch size of the common blend.
- The MAH committed to validate the first three production batches of the maximum sizes of the common blend.
- The MAH committed to validate the first three production batches of each strength.
- The MAH committed to place the first minimum-size commercial batch of each strength on long-term and accelerated stability studies.
- The first three maximum-size commercial batches of each strength will be subjected to long term and accelerated stability studies.

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
$t_{½}$	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