CBG MEB

Public Assessment Report

Scientific discussion

Risedronaatnatrium Aurobindo 75 mg, film-coated tablets

(risedronate sodium)

NL/H/2263/004/DC

Date: 13 January 2017

This module reflects the scientific discussion for the approval of Risedronaatnatrium Aurobindo 75 mg, film-coated tablets. The procedure was finalised on 23 December 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Risedronaatnatrium Aurobindo 75 mg, film-coated tablets from Aurobindo Pharma B.V.

The product is indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fractures (see SmPC section 5.1).
A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Actonel 75 mg film-coated tablets, registered in the Netherlands through mutual recognition procedure SE/H/0192/005 by Actavis Group PTC ehf since 25 January 2008. The originator product is Actonel 35 mg, film-coated tablets, registered in the community for more than 10 years, i.e. since 1999 (SE/H/0192/003).

The concerned member states (CMS) involved in this procedure were Germany, Spain, Italy and Romania.

Three lower strengths (5 mg, 30 mg and 35 mg) have already been authorised in the reference member state (RMS) and CMS by the same Marketing Authorisation Holder (MAH) through procedure NL/H/2263/001-003/MR. A bioequivalence study with the 35 mg strength was approved in this procedure. The MAH refers to this study and applies for a biowaiver for the new 75 mg strength (see section IV of this report).

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Risedronaatnatrium Aurobindo 75 mg is a light pink to pink coloured, circular shaped film coated biconvex tablet debossed with ‘L’ on one side and ‘62’ on the other side. Each film-coated tablet contains 75 mg risedronate sodium (equivalent to 69.6 mg risedronic acid).

The film-coated tablet is packed in clear PVC-Aluminium foil blister packs.

The excipients are:
Tablet core - lactose monohydrate, microcrystalline cellulose, crospovidone (Type A), hydroxy propyl cellulose (low viscosity grade) and magnesium stearate.
Coating - hypromellose (6 cps), macrogol 400, titanium dioxide (E171) and red iron oxide (E172).

II.2 Drug Substance

The active substance is risedronate sodium, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to off-white powder, which is soluble in water and practically insoluble in methanol. It dissolves in dilute solutions of alkali hydroxides and mineral acids.. Risedronate sodium does not have a chiral centre and does not show any optical isomerism. It exists in different hydrates such as anhydrous, monohydrate and hemi-pentahydrate. The manufacturer produces risedronate sodium hemi-pentahydrate.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general

monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with requirements of the Ph.Eur and the CEP and contains additional requirements for particle size and microbial contamination. The specification is accepted. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

Stability of drug substance
The active substance is stable for 3 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The development of the 75 mg tablets is based on the pharmaceutical development previously described and approved for the 5 mg, 30 mg and 35 mg film-coated tablets. The tablets are dose proportional. The choice of excipients is justified and their functions explained.

Comparative dissolution profiles for 5 mg, 30 mg and 35 mg as well as 75 mg tablets are provided. The dissolution profile of Risedronaatnatrium Aurobindo 75 mg, film-coated tablets is similar to Risedronaatnatrium Aurobindo 35 mg, film-coated tablets used in the bioequivalence study. Based on this acceptable bioequivalence study, a biowaiver was requested for the 75 mg film-coated tablets. More than 85% of the drug is released with in 15 minutes independent of the pH. The company requested a bio-waiver for the 75 mg tablets.

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 two minimum sized production scaled batches of the 75 mg tablet strength. The product is manufactured using conventional manufacturing techniques. Process validation on 1 additional minimum sized production scaled batches and for 3 maximum sized production batches will be performed post authorisation.

Control of excipients
All excipients comply with their specifications of the Ph.Eur. monographs. For the ready to use coating material an acceptable in-house specification is provided. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, average weight, uniformity of dosage units (content), water, identification, dissolution, assay, related substances, thickness, microbiological contamination, disintegration time and identification of titanium dioxide and colourants. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from 2 minimum sized production scaled from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided for 2 production scaled batches as 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 the proposed packaging.

Results stayed within limits. Forced degradation studies showed no sensitivity to light. A shelf-life of 2 year can be granted based on the provided data; the product does not require any special storage conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is of animal origin (milk). Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Risedronaatnatrium Aurobindo 75 mg, film-coated tablets has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Risedronaatnatrium Aurobindo 75 mg, film-coated tablets is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Actonel which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Risedronate sodium is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

Bioequivalence study
The MAH provided the bioequivalence study for procedure NL/H/2263/001-003/MR in which the pharmacokinetic profile of the test product Risedronaatnatrium Aurobindo 35 mg, film-coated tablets (Aurobindo Pharma B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Actonel 35 mg, film-coated tablets (Procter & Gamble Pharmaceuticals UK Ltd, United Kingdom).

The choice of the reference product
The choice of the UK reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula that is currently marketed.

Biowaiver
The selection of a lower strength than the highest is approved. The MAH provided sufficient support that risedronate sodium is a highly soluble substance, in line with the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) appendix III, section III.1. A biowaiver can be granted for the 75 mg strength as per following criteria:

- Risedronaatnatrium 35 mg and 75 mg, film-coated tablets are manufactured by the same manufacturer using the same manufacturing process.
- Absorption after an oral dose is relatively rapid (t_{max} ~1 hour) and is independent of the studied dose range.
- The qualitative composition of Risedronaatnatrium Aurobindo 75 mg is the same as that of Risedronaatnatrium Aurobindo 35 mg, film-coated tablets.
- Risedronaatnatrium Aurobindo 75 mg, film-coated tablets are dose proportional with Risedronaatnatrium Aurobindo 35 mg, film-coated tablets. Thus, the ratio of amount of active substance and the excipients is the same for all the strengths.
- The dissolution profile of Risedronaatnatrium Aurobindo 75 mg, film-coated tablets is similar to Risedronaatnatrium Aurobindo 35 mg, film-coated tablets. Hence in different media (0.01N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer) the test and reference product were found similar.

Design
A single-dose, open-label, 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.

The design of the study is acceptable. Mean oral bioavailability is decreased when risedronate sodium is administered with food. The SmPC 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 fasted conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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 was dropped out as he was absent for period-II check in. The remaining 59 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=59	**AUC_{0-72}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
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
CV coefficient of variation

**ln-transformed values*

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.

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-72} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Risedronaatnatrium Aurobindo 35 mg, film-coated tablets is considered bioequivalent with Actonel 35 mg, film-coated tablets.

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).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Risedronaatnatrium Aurobindo 75 mg, film-coated tablets.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Osteonecrosis of the jaw • Hypocalcaemia • Gastrointestinal events in particular gastritis, oesophagitis, and ulcerations of the oesophagus and gastroduodenum • Ocular adverse events • Anaphylactic reaction
Important potential risks	• Atypical femoral fracture • Renal disorder/dysfunction
Missing information	• Use during pregnancy and lactation • Use in patients below 18 years of age • Patients with severe renal impairment

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Actonel. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The content and wording of the PL of Risedronaatnatrium Aurobindo 75 mg is exactly the same as the content and wording of the PL of the innovator product Actonel 75 mg (SE/H/0192/003). Therefore, the MAH has not performed a user test with the PL of Risedronaatnatrium Aurobindo, but instead submitted a bridging report only focussing on the lay out of the PL. The bridging report makes reference to the PL of Metoprolol Aurobindo 50 mg and 100 mg film-coated tablets (SE/H/1201/001-002/DC). The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Risedronaatnatrium Aurobindo 75 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Actonel. 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 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 Aurobindo 75 mg, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23 December 2015.

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
Change in the (invented) name for nationally authorised products	NL/H/2263/ 4/IB/013	IB	22-2-2016	23-3-2016	Approval	No