Public Assessment Report

Scientific discussion

Risedronaatnatrium Wekelijks 35 mg PCH, film-coated tablets

(risedronate sodium)

NL/H/4180/001/DC

6 December 2017

This module reflects the scientific discussion for the approval of Risedronaatnatrium Wekelijks. The procedure was finalised on 18 September 2008. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Risedronaatnatrium Wekelijks 35 mg PCH, film-coated tablets, from Pharmachemie B.V. 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.

Risedronate sodium is a pyridinyl bisphosphonate that binds to bone hydroxyapatite and inhibits osteoclast-mediated bone resorption.

This decentralised procedure concerns a generic application claiming essential similarity with the reference product Optinate Septimum by sanofi-aventis AB, registered since 1999 in Sweden.
The reference product used to establish bioequivalence is Actonel 35 mg film-coated tablets, Aventis Pharma from the German market.

The marketing authorisation is granted based on article 10.1 of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Each Risedronaatnatrium Wekelijks film-coated tablet contains 35 mg of risedronate sodium (equivalent to 32.5 mg of risedronic acid).

The tablets are orange, round, film-coated tablets, debossed with “R35”on one side and plain on the other.

Risedronaatnatrium Wekelijks is packed in transparent PVC/PVdC – Aluminium blisters in a cardboard carton in pack sizes of 1, 2, 4, 8, 10, 12, 12 (3x4), 14, 16, 16 (4x4) or 30 tablets and in hospital packs of 4 (4x1), 10 (10 x 1) or 50 tablets (50 x 1). However, not all pack sizes may be marketed.

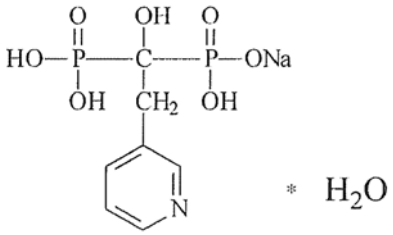
The excipients in the tablet core are: Lactose monohydrate; maize starch; pregelatinised starch (maize); silica, colloidal anhydrous; sodium stearyl fumarate and magnesium stearate.
The coating consists of: Hypromellose; titanium dioxide (E171); macrogol 400; iron oxide yellow (E172); polysorbate 80 (E433); Sunset yellow aluminium lake (E110) and iron oxide red (E172).

Compliance with Good Manufacturing Practice
The RMS 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.

II.2 Drug Substance

INN: Risedronate sodium
Chemical name(s): [1-hydroxy-2-(3-pyridinyl)ethylidene]bis[phosphonic acid]monosodium salt
Molecular formula: $C_7H_{10}NO_7P_2Na\ H_2O$
Molecular mass: 323.10

Structural formula:



Risedronate sodium is a white to pale yellow (or off-white) solid. Risedronate sodium is soluble in water and in aqueous solutions, and essentially insoluble in common organic solvents.

A Drug Master File has been provided for documentation on the drug substance risedronate sodium.

The drug substance risedronate sodium is not described in any pharmacopoeia; therefore, in-house specifications have been established for the control of the drug substance. The control tests and specifications are adequately drawn up.

The synthesis of the drug substance has been adequately described in the restricted part of the DMF.

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. An appropriate retest period and storage condition has been set based on the data submitted.

II.3 Medicinal Product

The development of the product has been described, the choice of excipients is justified and their functions explained.

The manufacturing process is a standard wet granulation process. Adequate process validation data for pilot scale batches has been provided.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on 3 pilot scale batches from one of the manufacturing sites and 2 pilot scale batches from the alternative site. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for the drug product are adequately drawn up.

A shelf-life of 36 months with no special storage conditions for the drug product is accepted.

III. NON-CLINICAL ASPECTS

This product is a generic formulation of Optinate Septimum 35 mg film-coated tablets, 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.

Pharmacodynamic, pharmacokinetic and toxicological properties of risedronate sodium are well known. Overview based on literature review is, thus, appropriate.

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 sodium 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

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

For this generic application, the MAH has submitted 2 bioequivalence studies under fasting conditions in which the pharmacokinetic profile of the test product Risedronaatnatrium Wekelijks 35 mg PCH, film-coated tablets is compared with the pharmacokinetic profile of the reference product Actonel 35 mg film-coated tablets, Aventis Pharma, from the German market.

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.

Study no. XXXX-923
The study was an open-label, randomised, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fasting conditions with a wash out period of 7 days between the two administrations. 35 mg was administered in each period.

Blood samples were collected pre-dosing and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 12, 16 and 24 hours post administration of a single-dose 35 mg tablet with 240 ml of water for the analyses of risedronic acid.

80 healthy non-smoking male subjects (19-53 years; 62 Caucasians, 10 Black and 3 Asian (of the 75 included in data analysis)) participated in the study. 75 subjects completed the study and were used for the pharmacokinetic and statistical analysis.
Drop-outs: Subject no. 2 was dismissed during period 1 due to an episode of emesis (5.97 hour post-dose), subject no. 4 was withdrawn following completion of period 1 due to adverse events, subject no. 10 and 45 withdrew prior to period 2 check-in and subject no. 20 withdrew before period 2 due to personal reasons.

The parameters calculated were AUC_{0-t}, $AUC_{0-\infty}$, $AUC_{0-t}/AUC_{0-\infty}$, C_{max}, t_{max}, K_{el} and $t_{½\ el}$. Primary variables were AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}.

In order to establish bioequivalence, the 90% confidence intervals of the relative mean AUCs of the test to reference product should be between 80 and 125%. The 90% confidence intervals of the relative mean C_{max} of the test to reference product should be between 75 and 133%.

A justification for the widening of the 90% CI for C_{max} to 75-133% was given. The intra-subject variability for C_{max} is known to be high (up to 50%), which is mainly due to the extremely low bioavailability (≈0.63%). Risedronate can be administered once daily as a 5 mg dose or once weekly as a 35 mg dose. There is a significant difference in the maximum concentrations obtained with these two dosage regimens. Therefore, the maximum concentration cannot be related to clinical efficacy as the different dosing regimens produce the same clinical effect.
According to the current opinion throughout Europe a widening of the 90% CI for C_{max} is not acceptable although the drug exhibits high intra-subject variability. However, since the results are just outside the general acceptance range of 80-125% and an additional study has been carried out showing results within 80-125%, no concern was raised.

Results

Analyte: Risedronic acid (N = 75)					
Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra-Subject (CV%)
	Treatment A	Treatment B			
AUCt (ng*h/mL)	37.819 47.705 (76)	40.170 49.104 (66)	94.15	83.20 - 106.53	48
AUCinf (ng*h/mL)	40.624 51.527 (76)	43.114 53.000 (66)	94.22	83.12 - 106.82	48
Cmax (ng/mL)	11.10572 14.30459 (80)	12.27467 14.92302 (66)	90.48	79.09 - 103.50	53
Tmax[a] (h)	1.26 (58)	1.19 (52)	-	-	-
Kel[a] (1/h)	0.1614 (75)	0.1502 (84)	-	-	-
Thalf[a] (h)	7.58 (72)	8.66 (78)	-	-	-
[a]Presented as arithmetic mean (CV%) only.					

The 90% confidence interval for the AUCs is within the acceptance range of 80-125%, whereas the 90% confidence interval for C_{max} is just outside the lower limit of the acceptance range (79.09-103.5%). As stated above a widening of the limits is not considered acceptable; however, taking into account the additional confirmative study (see below), bioequivalence between the test and reference product can be concluded.

Study no. XXXX-1430

The confirmative study was an open-label, randomised, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fasting conditions with a wash out period of 7 days between the two administrations. 35 mg was administered in each period.

Blood samples were collected pre-dosing and at 0.167, 0.33, 0.50, 0.67, 0.833, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3, 4, 5, 6, 8, 12, 16, 24 and 36 hours post administration of a single-dose 35 mg tablet with 240 ml of water for the analyses of risedronic acid.

117 healthy male subjects (20-55 years; 77 Caucasian, 23 Black and 13 Asian (of the 113 completing the study)) participated in the study. 113 subjects completed the study and were used in the pharmacokinetic and statistical analysis.
Drop-outs: Subject no. 41, 60 and 63 was withdrawn from the study prior to period 2 dosing due to non-compliance (subject no. 41 and 60 were positive for cotinine and subject no. 63 was positive for THC). Subject no. 106 withdrew from the study prior to period 2 dosing due to personal reasons.

The parameters calculated were AUC_{0-t}, $AUC_{0-\infty}$, $AUC_{0-t}/AUC_{0-\infty}$, C_{max}, t_{max}, K_{el} and $t_{½\ el}$. Primary variables were AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}.

In order to establish bioequivalence, the 90% confidence intervals of the relative mean AUCs of the test to reference product should be between 80 and 125%. The 90% confidence intervals of the relative mean C_{max} of the test to reference product should be between 75 and 133%.

A justification for the widening of the 90% CI for C_{max} to 75-133% was given. The intra-subject variability for C_{max} is known to be high (up to 50%), which is mainly due to the extremely low bioavailability (≈0.63%). Risedronate can be administered once daily as a 5 mg dose or once weekly as a 35 mg dose. There is a significant difference in the maximum concentrations obtained with these two dosage regimens. Therefore, the maximum concentration cannot be related to clinical efficacy as the different dosing regimens produce the same clinical effect.

According to the current opinion throughout Europe a widening of the 90% CI for C_{max} is not acceptable although the drug exhibits high intra-subject variability. However, since the results are within the general acceptance range of 80-125%, no concern was raised.

Results

Analyte: Risedronic acid (N = 113)					
Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra-Subject (CV%)
	Treatment A	Treatment B			
AUCt (pg*h/mL)	14351.59 19287.56 (109)	15001.99 21622.33 (131)	95.66	85.17 - 107.46	57
AUCinf (pg*h/mL)	15808.41 20188.56 (108)	16145.10 22534.06 (134)	97.91	87.48 - 109.60	52
Cmax (pg/mL)	5443.44 7462.65 (105)	5622.86 8256.96 (128)	96.81	86.04 - 108.93	57
Tmax[a] (h)	1.06 (59)	1.01 (57)	-	-	-
Kel[a] (1/h)	0.3660 (38)	0.3536 (41)	-	-	-
Thalf[a] (h)	2.58 (89)	3.21 (155)	-	-	-
[a]Presented as arithmetic mean (CV%) only.					

The 90% confidence intervals for all primary variables (AUCs and C_{max}) are within 80-125%.

Pharmacokinetic conclusion

Based on the submitted bioequivalence studies Risedronaatnatrium Wekelijks 35 mg PCH, film-coated tablets are considered bioequivalent with Actonel 35 mg film-coated tablets, Aventis Pharma.

The RMS 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).

IV.2 Risk management plan & Pharmacovigilance system

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 postauthorisation 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.

The Pharmacovigilance system described fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the identification and notification of any a potential risks occurring either in the Community or in a third country.

V. PRODUCT INFORMATION

SmPC and Package leaflet

The content of the SmPC and package leaflet approved during the decentralised procedure is in accordance with that accepted for the reference product Optinate Septimum marketed by sanofi-aventis.

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 language used for the purpose of user testing the package leaflet was English. The test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Risedronaatnatrium Wekelijks 35 mg PCH, film-coated tablets have a proven chemical-pharmaceutical quality and are a generic form of Optinate Septimum film-coated tablets. Optinate Septimum 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 SmPC, package leaflet and labelling are in the agreed templates and are in agreement with other risedronate containing products.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that essential similarity has been demonstrated for Risedronaatnatrium Wekelijks 35 mg PCH, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 18 September 2008.

A European harmonised birth date has been allocated (1998-03-31) and subsequently the first data lock point for risedronate is 2009-03. The first PSUR will be submitted with a DLP of 2009-03, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 1 December 2012.

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

- Process validation will be performed on the first 3 production scale batches manufactured at proposed manufacturing site(s).
- Certificates of analysis performed on the first 3 consecutive production scale batches should be forwarded when available.
- The enclosed stability studies will be continued.
- The first 3 production batches will be put on stability and tested according to the stability protocol as presented in section P.8.1.