

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

**Melenor 5 mg, 30 mg and 35 mg film-coated tablets
Medochemie Limited, Cyprus**

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/2145/001-003/DC
Registration number in the Netherlands: RVG 108741-108743**

30 April 2014

Pharmacotherapeutic group:	bisphosphonates
ATC code:	M05BA07
Route of administration:	oral
Therapeutic indication:	5 mg - Treatment of postmenopausal osteoporosis, to reduce the risk of fractures; prevention of osteoporosis in postmenopausal women with increased risk of osteoporosis; to maintain or increase bone mass in postmenopausal women undergoing long-term systemic corticosteroid treatment 30 mg - Paget's disease of the bone 35 mg - Postmenopausal osteoporosis, to reduce the risk of fractures; treatment of osteoporosis in men at high risk of fractures
Prescription status:	prescription only
Date of authorisation in NL:	11 October 2011
Concerned Member States:	Decentralised procedure with CY (all strengths) and CZ, EE, EL, LT, LV, SK (only 35 mg)
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 (SmPC), 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 Melenor 5 mg 30 mg and 35 mg film-coated tablets, from Medochemie Limited. The date of authorisation was on 11 October 2011 in the Netherlands.

The product is indicated for treatment of:

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.
- To maintain or increase bone mass in postmenopausal women undergoing long-term (more than 3 months), systemic corticosteroid treatment at doses ≥ 7.5 mg/day prednisone or equivalent.

30 mg

- Paget's disease of the bone.

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.

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

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 antiosteoclast 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 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 once a week and Risedronate sodium 5 mg daily at 12 months. In a study in men with osteoporosis, decreases in biochemical markers of bone turnover were observed at the earliest time point of 3 months and continued to be observed at 24 months.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Optinate 5 mg, 30 mg and 35 mg, film-coated tablets which has been registered in Sweden by Sanofi Aventis AB since 1999 (original product). In the Netherlands, reference is made to Actonel 5 mg film-coated tablets have been registered since 2000 (NL license RVG 25801). 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 one bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Actonel 30 mg tablets, registered in the Netherlands. 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 generic medicinal products.

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. Risedronate sodium is described in PharmEuropa (Ph. Eur^{*}). Risedronate sodium is a white to off-white powder, which is sparingly soluble in 0.1N sodium hydroxide solution. The structure of risedronate sodium has been adequately proven. Polymorphism has been adequately discussed; the hemipentahydrate form is produced.

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.

Manufacture

The manufacturing process consists of one synthesis step and a salt forming step.

Quality control of drug substance

The active substance specification generally includes relevant tests and the limits for impurities have been justified. The analytical methods applied are suitably described and validated. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches from the drug substance manufacturer and for two batches issued by the finished product manufacturer. As soon as the monograph for risedronate sodium becomes official in the Ph.Eur., the specifications and limits as mentioned in the monograph should be adopted.

Stability of drug substance

Stability studies under ICH conditions have been conducted (on seven batches) and the data provided are sufficient to confirm the proposed re-test period of 4 years when adequately packed.

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

Medicinal Product

Composition

Melenor 5 mg – are light-yellow coloured, round, film-coated tablets of 4.6 mm diameter, debossed with the letter "J" on one side and "5" on the other.

Melenor 30 mg – are white to off-white, round, film-coated tablets of 9.1 mm diameter, debossed with "J" on one side and "30" on the other.

Melenor 35 mg – are light orange coloured, round, film-coated tablets of 9.1 mm diameter, debossed with "J" on one side and "35" on the other.

The excipients are:

Tablet core: lactose monohydrate, microcrystalline cellulose, crospovidone, and magnesium stearate.
Film-coating: hypromellose, macrogol, hydroxypropyl cellulose, colloidal anhydrous silica, and titanium dioxide E171; Iron oxide yellow E172 (5 mg and 35 mg); Iron oxide red E172 (35 mg)

The three strengths are dose proportional.

The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The product development objective was to develop a robust, stable and bioequivalent formulation of risedronate sodium 5 mg, 30 mg and 35 mg film-coated tablets, comparable in performance to the innovator's product.

Direct compression process was used as technological procedure of the tablet core preparation. Critical steps in the manufacturing process were identified and the process was optimized.

The dissolution method was developed by generation of data on the innovator product. Different dissolution media were evaluated for drug release. The dissolution profiles for test (from bioequivalence study) and reference are similar. The different tablet strengths of the test and reference products show fast dissolution, with >85% released in 15 minutes in all three dissolution media. The biowaiver for the 5 mg and 35 mg strength is acceptable from a quality point of view.

The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

Excipients

The excipients comply with the Ph.Eur. and the specifications are acceptable. For the Opadry coating agents in-house specifications are designed and are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identification of risedronate sodium by HPLC and UV, identification of colorants, water, average mass, diameter, thickness, disintegration, uniformity of dosage units by content uniformity, dissolution, related substances, assay and microbial quality.

The test and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose. Validations of the analytical methods have been adequately performed.

Batch analytical data have been provided on two batches per strength, demonstrating compliance with the release specifications.

Microbiological attributes

The test for microbial contamination is included as a part of finished product specification to check the microbiological quality of the drug product, since some excipients may tend to support microbial growth. The tablets comply with the criteria for *Microbiological quality of pharmaceutical preparations (5.1.4)* of the European Pharmacopoeia.

Stability tests on the finished product

Stability data on the product has been provided for two batches per strength stored in Al-Al blisters at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The photostability study has been performed according to the Note for Guidance on the Photostability Testing of New Active Substances and Medicinal Products. From the results it is evident that the product is not sensitive to light.

All stability data reported comply with the proposed specifications and no obvious trends were seen. The proposed shelf-life of 2 years is justified based on the stability data provided. No special storage

conditions are considered necessary. A bulk storage time of 6 months is judged as acceptable, when stored in the proposed bulk pack not above 25°C.

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

All materials used in the product have demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of Transmitting animal Spongiform Encephalopathy agents via human or veterinary medicinal products (EMA/410/01). 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.

II.2 Non-clinical aspects

This product is a generic formulation of Optinate 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.

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 one bioequivalence study in which the pharmacokinetic profile of the test product Melenor 30 mg film-coated tablets (Medochemie Limited, Cyprus) is compared with the pharmacokinetic profile of the reference product Actonel 30 mg tablets (Procter & Gamble Pharmaceuticals, the Netherlands).

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.

Bioequivalence study

A randomized, open label, two treatment, four period, two sequence (ABAB and BABA), single dose, replicate, crossover bioequivalence study was carried out under fasted conditions in 60 (Group 1 – 48 subjects and Group 2 – 12 subjects) male volunteers, aged 18-36 years. The criteria for inclusion were: Healthy human adult non smoker subjects between 18-45 years of age (inclusive) having a BMI (Body Mass Index) criteria 18.5-24.9 kg/m² (both inclusive) and weight between 50-80 kg (both inclusive) who had no evidence of underlying disease or clinically significant abnormal.

After a supervised overnight fast of at least 10 hours subjects were given study products (test or reference) with 240 ml of water according to the randomization schedule. Fasting continued for at least 4 hours after dosing. Blood samples were collected pre-dose (within 1 hour before dosing) and at 0.167, 0.333, 0.5, 0.667, 0.833, 1.0, 1.333, 1.667, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0 and 24.0 hours post dosing. A wash-out period of 16 days separated each period.

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

Only male subjects were included in the trial, although the protocol stated that male and female subjects can be included and the medication is predominantly prescribed for female patients. This is not considered a problem as the pharmacokinetic properties of risedronate are the same in male and female subjects.

Results

Forty-four subjects completed the study. Five subjects were withdrawn due to protocol deviation, five subjects did not check in for period III, one subject did not check in for period IV and five subjects were withdrawn due to adverse events. In accordance with the study protocol, pharmacokinetic and statistical analyses were performed on data from first 40 evaluable subjects

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

Treatment N=40	AUC _{0-t} pg.h/ml	AUC _{0-∞} pg.h/ml	C _{max} pg/ml	t _{max} h
Test - first administration	64912 \pm 44253	67453 \pm 44897	20320 \pm 14547	0.8 (0.33-3.0)
Test - second administration	62405 \pm 41084	64837 \pm 42231	20364 \pm 13490	1.0 (0.5-3.0)
Reference –first administration	56141 \pm 26805	58333 \pm 27576	17822 \pm 8184	1.0 (0.33-3.0)
Reference –first administration	56287 \pm 27089	58772 \pm 28141	18159 \pm 10220	0.9 (0.33-3.0)
*Ratio (90% CI)	1.04 (0.94-1.15)	1.04 (0.94-1.15)	1.06 (0.95-1.17)	---
CV (%)	39	39	39	---
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours AUC_{0-∞} area under the plasma concentration-time curve from time zero to infinity C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration				

**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 Melenor 30 mg film-coated tablets and the Actonel 30 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

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 fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Safety

All 60 subjects who received at least one dose of study medication were included in safety analysis. There were 45 adverse events (AEs) in the study. 24 AEs occurred in treatment group A of which 20 were possibly due to the study medication and 04 AEs were unrelated to the medication. 19 AEs occurred in treatment group B of which 18 AEs were possibly due to the medication and one AE was considered unrelated to the medication. All adverse events were followed up till resolution. Both products were well tolerated.

A total of five study subjects were withdrawn from the study due to adverse effects. The number and nature of the adverse events observed in this study, is similar for the test and reference formulation. Most of the reported adverse events are mentioned in the current SmPC of the reference product.

Extrapolation of results

- The pharmacokinetics of risedronate is linear in the therapeutic dose range
- the different strengths are produced using the same process and by the same manufacturer
- the qualitative composition of the tablet core is the same for the different strengths
- the ratio between amounts of active substance and excipients is the same
- the *in vitro* dissolution profile is similar for the different tablet strengths

The results of the bioequivalence study performed with the 30 mg tablets therefore apply to the 5 mg and 35 mg strengths.

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 postauthorisation which are not adequately covered by the current SmPC. 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

Readability test

5 mg:

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. A pilot study including 2 subjects was carried out. After this the PL was tested in 2 test rounds, each including 10 subjects. A total 20 females, aged from 46 to 76 and with varying educational background, participated. The subjects were recruited by placing advertisement in the local newspaper. Inclusion and exclusion criteria are defined and acceptable.

The subjects were asked 18 questions related to safety and compliance issues, such as indication, dosage, warnings and side effects plus 3 additional questions regarding the general design and layout of the leaflet. The questions were open and randomly ordered. The most important aspects of the leaflet are covered by the test, and the questionnaire is considered acceptable. Each subject got enough time to read through the PL and answer the questions. Each interview lasted up to 45 minutes. The test was performed by face-to-face interviewing. There were clear instructions for the interviewer to follow. Subjects were asked to give their answer in their own words and show where in the leaflet the information was found.

The general impression of the leaflet (content, layout and language) was mostly positive according to the responses given on the general question(s). No weaknesses were identified during the test. Before the user testing the leaflet was reviewed by the test administrator, some minor changes were done to the leaflet.

Results

Overall, the test methodology follows the Readability Guideline. Both the first and the second test round met the success criteria of 90% of the subjects being able to locate the requested information, and of those, 90% being able to give the correct answer, to indicate that they understood the information presented. The general impression of the PL (content, language and layout) was mostly positive. In conclusion, the user test is considered acceptable.

30 mg:

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. A pilot study including 2 subjects was carried out. After this the PL was tested in 2 test rounds, each including 10 subjects. A total 10 males and 10 females, aged from 20 to 58 and with varying educational background, participated. The subjects were recruited by placing advertisement in the local newspaper. Inclusion and exclusion criteria are defined and acceptable. The subjects were asked 18 questions related to safety and compliance issues, such as indication, dosage, warnings and side effects plus 3 additional questions regarding the general design and layout of the leaflet. The questions were open and randomly ordered. The most important aspects of the leaflet are covered by the test, and the questionnaire is considered acceptable. Each subject got enough time to read through the PL and answer the questions. Each interview lasted up to 45 minutes. The test was performed by face-to-face interviewing. There were clear instructions for the interviewer to follow. Subjects were asked to give their answer in their own words and show where in the leaflet the information was found.

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Results

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35 mg:

A bridging report has been provided regarding the content and the layout of the leaflet. The RMS finds the bridging acceptable as most sections (i.e., contraindications, instructions, warnings and interactions) are identical between the Parent PIL and the Daughter PIL. In sections that differ a comprehensive table has been provided in the report. The difference of additional words and more information in the Parent PIL does not increase the complexity of the text when compared to the Daughter PIL in contrary it makes the Parent PIL more complex.

The MAH has proposed a bridging to a user test carried out on the products Risedronate sodium Jubilant 5 mg and a cross reference to Risedronate sodium Jubilant 30 mg.

A comparison between the mother PL and the daughter PL (including lay-out) together with a critical discussion has been provided. The user test of the Risedronate sodium Jubilant 5 mg and Risedronate sodium Jubilant 30 mg leaflet was assessed and accepted.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Melenor 5 mg, 30 mg and 35 mg film-coated tablets have a proven chemical-pharmaceutical quality and are a generic form of Optinate 5 mg, 30 mg and 35 mg film-coated tablets. Optinate 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.

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 Melenor 5 mg, 30 mg and 35 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 18 July 2011. Melenor 5 mg, 30 mg and 35 mg film-coated tablets were authorised in the Netherlands on 11 October 2011.

The date for the first renewal will be November 2017.

There were no post-approval commitments made during the procedure.

List of abbreviations

AE	Adverse Event
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
SmPC	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
Addition of a finished product manufacturing/packaging site; change in batch size; minor, other change to test procedure	NL/H/2145/001-003/IB/001/G	IB/G	1-5-2012	31-5-2012	Approval	N