CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Acenocoumarol PharmaMatch 1 mg, tablets
Pharmamatch B.V., the Netherlands

acenocoumarol

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.
It reflects the scientific conclusion reached by the MEB 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.

Registration number in the Netherlands: RVG 113318

12 November 2013

Pharmacotherapeutic group:	antithrombotic agents; vitamin K antagonists
ATC code:	B01AA07
Route of administration:	oral
Therapeutic indication:	prophylaxis and treatment of thromboembolic events
Prescription status:	prescription only
Date of authorisation in NL:	9 July 2013
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 Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Acenocoumarol PharmaMatch 1 mg, tablets from Pharmamatch B.V. The date of authorisation was on 9 July 2013 in the Netherlands.

The product is indicated for prophylaxis and treatment of thromboembolic events.

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

Acencocoumarol is a vitamin K antagonist. To initiate blood clotting, vitamin K causes gamma-carboxylation of certain glutamic acid molecules on the coagulation factors II, VII, IX and X, and of protein C and its cofactor protein S. Coumarin derivatives, such as acenocoumarol, prevent gamma-carboxylation of these proteins by vitamin K, although the precise nature of this antagonism has yet to be established. Depending on the initial dosage, acenocoumarol prolongs the coagulation time. Following withdrawal of acenocoumarol, the coagulation time usually reverts to normal after a few days.

This national procedure concerns a generic application claiming essential similarity with the innovator product Acenocoumarol Sandoz 1 mg, tablets (NL License RVG 04464) which has been registered by Sandoz B.V. since 22 February 1965.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Acenocoumarol Sandoz 1 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 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 acenocoumarol, an established active substance described in the British Pharmacopoeia (BP*). The active substance is an almost white to buff powder, which is practically insoluble in water. Acenocoumarol has one chiral centre; the drug substance is a racemic mixture. Acenocoumarol exhibits polymorphism. Consistency of the polymorphic form of the drug substance has been demonstrated.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process of acenocoumarol consists of three steps and has been adequately described. No class 1 organic solvents or metal catalysts are used. The active substance has been adequately characterized. Acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The drug substance specification is in line with the BP monograph with additional requirements for residual solvents, specific optical rotation, heavy metals and particle size. Acceptable batch analytical data demonstrating compliance with the drug substance specification have been provided for three full batches.

Stability of drug substance
Stability data on the active substance have been provided for three full-scale batches stored at 25°C/60% RH (18 months) and at 40°C/75% RH (6 months). All parameters tested remained relatively stable at both storage conditions. Based on the stability data provided, a re-test period of 30 months has been granted.

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

Medicinal Product

Composition
Acenocoumarol PharmaMatch 1 mg is a white to off-white round, flat, beveled edge, uncoated tablet plain on one side other side embossing with '1'.

The tablets are packed in PVC-Al blisters and HDPE containers with PP closure.

The excipients are: lactose monohydrate, pregelatinised maize starch, hydroxypropyl cellulose, silica colloidal anhydrous, talc and magnesium stearate.

Pharmaceutical development

The development of the product has been adequately described, the choice of the excipients is justified and their functions explained. The main development studies performed were formulation studies and manufacturing process development. The excipients are well known and the choices of the packaging and manufacturing process have been sufficiently justified.
Bioequivalence studies were performed versus the reference product. The test batch used in the bioequivalence studies has the same composition and is manufactured in the same way as the future commercial batches. The dissolution profiles of the test and reference product were shown to be essentially similar. The pharmaceutical development of the product is considered adequate.

Manufacturing process
The manufacturing process is divided in the following steps: sifting, dry mixing, lubrication, compression and packaging. The product is manufactured using conventional manufacturing techniques. The manufacturing process has been adequately validated according to the relevant European guidelines. Process validation data on the product has been presented for three full-scale batches.

Control of excipients
The excipients comply with Ph.Eur. requirements. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification, average mass, uniformity of mass, uniformity of content, uniformity of dosage units, disintegration time, dimensions, hardness, loss on drying, dissolution, assay, related substances and microbiological purity. The release and shelf life limits are identical except for hardness, loss on drying and assay. The release and shelf-life limits are considered acceptable.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data of the product has been provided on three full-scale batches stored at 25°C/60% RH (24 months), at 30°/65% RH (24 months) and at 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-Al blister and HDPE containers with PP closure. No out of specification results were observed. The following trends were observed in both blister and container: a decrease in assay, a slight increase in related substances. The following trends were observed in the blister only: an increase in loss on drying and an increase in disintegration time. All results remained within specification limits. Photostability was tested after light exposure for 12, 24 and 48 hours. The provided results in combination with the proposed storage condition are considered acceptable. The results from the studies show that no significant change in the drug product has been observed in any of the test parameters tested. Based on the stability data provided a shelf life of 36 months without special storage condition can be granted.

Stability data has been provided demonstrating that the product remains stable for 90 days following first opening of the container, when stored at long term conditions. Given the tested period (i.e. 90 days), the container size (i.e. 100 tablets) and the similarity to the trends observed at long term conditions for the unopened container, a declaration of an in-use shelf life is not considered necessary.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is the only excipient of animal origin. Statements of the suppliers of the drug substances and excipients regarding BSE/TSE safety have been provided.

II.2 Non-clinical aspects

This product is a generic formulation of Acenocoumarol Sandoz, which is available on the European market. 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 Board agreed that no further non-clinical studies are required.

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 acencocoumarol 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

Acenocoumarol 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 Board agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Acenocoumarol PharmaMatch 1 mg (Pharmamatch B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Acenocoumarol Sandoz 1 mg tablets (Sandoz B.V., 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.
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 28 healthy male subjects, aged 18-40 years. Each subject received a single dose (1 mg) of one of the 2 acenocoumarol formulations. The tablet was orally administered after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.3, 0.7, 1.0, 1.3, 1.6, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 12.0, 24.0 and 48.0 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. The samples were analysed for the enantiomers R-acenocoumarol and S-acenocoumarol.

The design of this study is acceptable. The periods are separated by a sufficiently long wash-out period, the sampling schedule is adequate to estimate pharmacokinetic parameters and the analysed compounds, the two enantiomers, are acceptable.

Results
Twenty-six subjects completed both study periods, as two subjects dropped-out after the first study period; one was withdrawn due to abnormal lab results and the other due to a medical condition. The subjects who completed the study were eligible for pharmacokinetic analysis.

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

Treatment	AUC_{0-t}	$AUC_{0-\infty}$	C_{max}	t_{max}	$t_{1/2}$

N=26	ng.h/ml	ng.h/ml	ng/ml	h	h
Test	107 ± 44	126 ± 53	17.1 ± 4.2	1.8 (0.66-4.5)	13.3 ± 2.6
Reference	112 ± 42	131 ± 50	16.3 ± 4.9	1.5 (0.66-4.5)	12.7 ± 2.1
***Ratio (90% CI)**	0.95 (0.90 – 1.00)	--	1.07 (0.97 – 1.19)	--	--
CV (%)	15	--	20	--	--
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity **AUC_{0-t}** area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration **$t_{1/2}$** half-life					

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of S-acenocoumarol under fasted conditions.

Treatment N=26	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	35.4 ± 26	37.4 ± 30	14.4 ± 4.6	1.5 (0.66-4.5)	3.2 ± 3.2
Reference	40.4 ± 33	43.0 ± 38	13.7 ± 4.8	1.3 (0.33-4.0)	4.3 ± 4.1
***Ratio (90% CI)**	0.90 (0.83 – 0.97)	--	1.06 (0.94 – 1.20)	--	--
CV (%)	45	--	25	--	--
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity **AUC_{0-t}** area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration **$t_{1/2}$** half-life					

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t} 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 R-acenocoumarol and S-acenocoumarol under fasted conditions, it can be concluded that Acenocoumarol PharmaMatch 1 mg and Acenocoumarol Sandoz 1 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Acenoumarol may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of the active substance. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan

Acenocoumarol Sandoz was first approved in 1965, and there are now decades of post-authorisation experience with the active substance. The safety profile of acenocoumarol 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 SmPC. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. A Risk Management Plan has been provided, which sufficiently covers potential and identified risks.

Product information

SmPC
The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product Acenocoumarol Sandoz.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The leaflet passed the defined success criteria in both rounds: 90% of the test participants were able to find the information requested within the package leaflet of which 90% were able to show that they understood it. No revisions were deemed necessary. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Acenocoumarol PharmaMatch 1 mg, tablets has a proven chemical-pharmaceutical quality and is a generic form of Acenocoumarol Sandoz 1 mg. Acenocoumarol Sandoz 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 is consistent with that of the reference product. The SmPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. Acenocoumarol PharmaMatch 1 mg, tablets was authorised in the Netherlands on 9 July 2013.

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

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
SmPC	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