LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

# Public Assessment Report

# Scientific discussion

# Warfarin Orion
# (warfarin sodium)

# SE/H/710/01/DC

**This module reflects the scientific discussion for the approval of Warfarin Orion. The procedure was finalised at 28 June 2010. For information on changes after this date please refer to the module 'Update'.**

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# I. INTRODUCTION

Orion Corporation has applied for a marketing authorisation for Warfarin Orion, tablet, 2,5 mg claiming essential similarity to Marevan, tablet, 2,5 mg marketed in Norway by Nycomed AB. The product contains warfarin sodium as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bioequivalence study is Waran, tablet, 2,5 mg marketed by Nycomed AB in Sweden.

# II. QUALITY ASPECTS

## II.1 Introduction

Warfarin Orion is presented in the form of tablets containing 2.5 mg of warfarin sodium. The excipients are lactose, maize starch, calcium phosphate, povidone and magnesium stearate. The tablets are packed in plastic bottles.

## II.2 Drug Substance

The drug substance warfarin sodium is described in a Ph. Eur. monograph.

Warfarin sodium is a white powder, hygroscopic, very soluble in water and in alcohol, soluble in acetone, and very slightly soluble in methylene chloride.

The active substance specification includes relevant tests and the limits for impurities/ degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies have been conducted and the data provided are sufficient to confirm the retest period.

## II.3 Medicinal Product

Warfarin Orion tablets are formulated using excipients described in the current Ph. Eur. The only ingredient of animal origin is lactose. The supplier confirms that the lactose is sourced from healthy animals under the same conditions as milk collected for human consumption and the calf rennet used for production of whey is in accordance with EMEA/CPMP/571/02.

The development and the manufacturing process of the drug product have 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.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with no special storage precautions.

# III. NON-CLINICAL ASPECTS

## III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

# IV. CLINICAL ASPECTS

## IV.1 Pharmacokinetics

A standard two-way crossover trial in healthy male volunteers performed during fasting conditions was submitted in the application. The study was performed at Accutest Research Laboratories, Khairane, Navi Mumbai, India from the 30$^{th}$ of September until the 9$^{th}$ of November 2008. A total of 78 (72 + 6 standby subjects) healthy male volunteers were enrolled.

Warfarin in plasma was determined with an achiral LC-MS/MS method at the bioanalytical facilities at Accutest Research Laboratories, Khairane, Navi Mumbai, India. The use of an achiral method is deemed acceptable based on the requirements outlined in the new bioequivalence guideline. As the requirements in the new BE guideline may be seen as a clarification of the old guideline, this is not controversial.

The new guideline states that an enatioselective analysis should be performed when all the following conditions are met:

(1) the enantiomers exhibit different pharmacokinetics
(2) the enantiomers exhibit pronounced difference in pharmacodynamics
(3) the exposure (AUC) ratio of enantiomers is modified by a difference in the rate of absorption.

Based on literature, we may conclude that bullet 1 and 2 are met. When it comes to bullet 3, no specific data is found. On the other hand, numerous publications states that, R- and S-warfarin exhibit complete absorption which implies that no non-linearity should be present in the absorption of warfarin. Based on this reasoning, we cannot see that the AUC ratio of R- and S-warfain could be modified by a difference in the rate of absorption. An achiral method is thus acceptable. One aspect that also is reassuring is that there appears to be no difference in tmax between the test and reference products (test 0.67 h (0.33-4.00), ref 0.50 h (0.17-4.00)) which indicate that the two products are absorbed at a similar rate.

Regarding the statistical analysis, log-transformed $C_{max}$, $AUC_{0-t}$ and $AUC_{0-\infty}$ were analysed using ANOVA. The standard bioequivalence criterion, 80-125 %, was applied to all parameters. See table 1 for results.

**Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ median, range)**

| Treatment | $AUC_{0-t}$ ng/ml/h | $AUC_{0-\infty}$ ng/ml/h | $C_{max}$ ng/ml | $t_{max}$ h |
|---|---|---|---|---|
| **Test** | 13696±3191 | 16906±4285 | 360.9±78.57 | 0.67 (0.33-4.00) |
| **Reference** | 12977±3143 | 16449±4198 | 337.6±75.00 | 0.50 (0.17-4.00) |
| ***Ratio (90% CI)** | 105.7 (103.0-108.4) | 102.8 (100.0-105.6) | 107.2 (102.4-112.2) | |

$AUC_{0-t}$ area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ 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 general, Sweden approves generic versions of narrow therapeutic index drugs, such as warfarin, based on the normal acceptance range of 80-125 % and bioequivalence was thus shown. When it comes to interchangeability, this is a separate issue which is handled nationally following approval.

### IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

## V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Warfarin Orion Pharma 3 mg and 5 mg tablet, which was assessed and accepted in FI/H/567/01-02. The bridging report submitted by the applicant has been found acceptable.

The risk/benefit ratio is considered positive and Warfarin Orion, 2,5 mg, tablet is recommended for approval.

## VI. APPROVAL

The Decentralised procedure for Warfarin Orion, 2,5 mg, tablet was successfully finalised on 28 June 2010.

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# Public Assessment Report – Update

| Scope | Procedure number | Product Information affected | Date of start of the procedure | Date of end of procedure | Approval/ non approval | Assessment report attached |
|---|---|---|---|---|---|---|
| | | | | | | Y/N (version) |

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