LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Fosinopril Medis, tablets, 5, 10 and 20 mg

Fosinopril

SE/H/530/01-03/E01

This module reflects the scientific discussion for the approval of Fosinpril Medis. The procedure was finalised at April 15th 2009. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Actavis Group PTC ehf. has applied for a marketing authorisation for Fosinopril Medis, tablets, 5 mg, 10 mg and 20 mg claiming essential similarity to Monopril tablets, 10 mg and 20 mg marketed in the EU by Bristol-Myer Squibb. The product contains fosinopril sodium as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence studies are Fosinorm 10 mg (Bristol-Myer Squibb, Germany) and Staril 20 mg (E.R. Squibb and Sons, UK).

II. QUALITY ASPECTS

II.1 Introduction

Fosinopril Medis is presented in the form of tablets containing 5 mg, 10 mg and 20 mg, respectively, of fosinopril sodium. The excipients are lactose monohydrate, croscarmellose sodium, pregelatinised maize starch, microcrystalline cellulose, glycerol dibehenate. The tablets are packed in Al/Al blisters or in PP containers with desiccant.

II.2 Drug Substance

Fosinopril sodium does not have a monograph in the Ph. Eur. However a draft monograph has been published in Pharmeuropa 19.4.

Fosinopril sodium is a white to off-white, crystalline powder which is freely soluble in water, methanol and 1N NaOH, sparingly soluble in ethanol and practically insoluble in ethyl acetate, acetone and 1N HCl. The structure of fosinopril sodium has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism and chirality is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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 under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Fosinopril Medis tablets are formulated using excipients described in the current Ph. Eur. All raw materials used in the product has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as polymorphism and stability.

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.

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, when stored below 25°C.

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

Fosinopril is a pro-drug which, during absorption, is hydrolysed in the gastrointestinal tract and liver to the active angiotensin converting enzyme (ACE) inhibitor fosinoprilat. About 30-35% of an oral dose of fosinopril is absorbed, whereof 50-100% is hydrolysed to fosinoprilat. Concomitant food intake reduces the rate but not the extent of absorption. The pharmacokinetics is linear within the therapeutic dose range.

Results from two bioequivalence studies of the 10 and 20 mg tablets were submitted in support of the application. The absence of a study with the 5 mg tablet strength is considered acceptable from a pharmacokinetic point of view as the pharmacokinetics of fosinopril and fosinoprilat is independent of dose. Both studies were single-dose 2-way cross over bioequivalence sudies under fasting conditions in 34 healthy volunteers. Bioequivalence was based on the active metabolite fosinoprilat using conventional acceptance criteria of 80-125%. Fosinoprilat in plasma were determined with a sufficiently validated LC/MS/MS method. In both studies bioequivalence was demonstrated regarding C_{max}, AUC_{0-t} and AUC_{0-inf} for fosinoprilat.

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 testing of the package leaflet has been performed and is acceptable.

The results of the conducted bioequivalence studies can be extrapolated to other strength since the criteria for biowaiver for additional strengths are fulfilled according to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence.

The risk/benefit ratio is considered positive and Fosinopril Medis, tablets, 5 mg, 10 mg and 20 mg is recommended for approval.

VI. APPROVAL

The mutual recognition repeat-use procedure for Fosinopril Medis, tablets, 5 mg, 10 mg and 20 mg was successfully finalised on 2009-04-15.

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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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