LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Perindopril arginine Actavis (perindopril arginine)

SE/H/1456/01-03/DC

This module reflects the scientific discussion for the approval of Perindopril arginine Actavis. The procedure was finalised on 2015-11-24. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Perindopril arginine Actavis, 2,5mg, 5mg, 10mg, film-coated tablets is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Actavis Group PTC ehf. applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and CZ, SK (5mg and 10mg only), HR, HU, IE, LT, MT, PL, RO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Perindopril Servier, 2mg, comprimé, authorised in France since 1988, with Les Laboratoires Servier as marketing authorisation holder.

The reference product used in the bioequivalence study is Coversyl®, 10 mg, film-coated tablets, from UK with Les Laboratoires Servier as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

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 have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

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

The pharmacokinetic documentation comprised two bioequivalence studies. In the first study bioequivalence was not indisputably shown for Cmax. An additional study with a higher power was therefore conducted.

Study 2998/13 was a single-dose, two-way crossover study conducted in 30 healthy volunteers, comparing Perindopril arginine Actavis, 10 mg, tablet with Coversyl, 10 mg, tablet under fasting conditions. The study was conducted at Lotus Labs Pvt Ltd, Bangalore, India between 19 and 27 Nov 2013. Blood samples were collected pre-dose and up to 12 hours post-dose. The study design is considered acceptable. Plasma concentrations of perindopril were determined with an adequately validated LC/MS/MS method. For AUC0-t the 90% confidence interval (CI) for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%. For Cmax the 90% CI was below the lower limit of 80.00. Hence, bioequivalence was demonstrated for AUC but not for Cmax. The study is considered inconclusive.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for perindopril, n=30.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test A	**158.93 ± 38.676**	**116.50 ± 36.849**	**0.75 0.50-2.50**
Reference C	**160.29 ± 41.961**	**139.16 ± 48.634**	**0.63 0.50-1.67**
***Ratio (90% CI)**	**99.36 (96.71-102.09)**	**84.95 (75.66-95.37)**	**-**

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 plasma concentration

**calculated based on ln-transformed data*

Study 3558/14 was a single-dose, two-way crossover study conducted in 40 healthy volunteers, comparing Perindopril arginine Actavis, 10 mg, tablet with Coversyl, 10 mg, tablet under fasting conditions. The study was conducted at Lotus Labs Pvt Ltd, Bangalore, India between 17 and 23 July 2014. Blood samples were collected pre-dose and up to 12 hours post-

dose. The study design is considered acceptable. Plasma concentrations of perindopril were determined with an adequately validated LC/MS/MS method. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%. Bioequivalence was demonstrated.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for perindopril, n=40.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**160.74 ± 32.416**	**140.06 ± 33.553**	**0.75 0.50-1.67**
Reference	**159.25 ± 36.205**	**132.34 ± 38.239**	**0.75 0.50-2.50**
***Ratio (90% CI)**	**101.57 (98.65-104.58)**	**107.04 (101.04-113.39)**	**-**

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 plasma concentration

**calculated based on ln-transformed data*

Overall pharmacokinetic conclusion

The first study (2998/13) was inconclusive since bioequivalence was not demonstrated: the 90% CI for Cmax was outside the acceptance range of 80.00-125.00%. In the second study (3558/14) bioequivalence was demonstrated for both AUC and Cmax. Since the second study had higher power (n=40 compared to n=30), one might suggest that the results from the second study should overrule the first. It is however noted that the results for Cmax is slightly contradictory in the two studies. In 2998/13 Cmax for the test formulation was lower compared to the reference (T/R-ratio 84.95) while it was higher in 3558/14 (T/R-ratio 107.04).

The deviating results of the two studies is likely caused by the slightly faster dissolution characteristics of the EU-reference batch used in the first study compared to the reference batch used in the second study and also in comparison to other reference batches (a third EU-reference batch and an Australian reference batch). Study 3558/14, in which bioequivalence was shown, had also higher power compared to study 2998/13, in which bioequivalence could not be indisputably shown. Taken together, the results from Study 3558/14 are considered reliable.

Bioequivalence between Perindopril arginine Actavis, 10 mg, tablet and Coversyl, 10 mg, tablet has been sufficiently demonstrated. From a pharmacokinetic point of view, absence of studies with the additional strength(s) is acceptable since the pharmacokinetics of perindopril is linear.

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.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and

interventions designed to identify, characterise, prevent or minimise risks relating to Perindopril arginine Actavis.

Safety specification
Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks	Electrolyte abnormalities (hyperkalaemia) Symptomatic hypotension Severe hypersensitivity reactions Angioedema Acute renal impairment Hepatotoxicity Blood dyscrasias Risks related to the use during the second and third trimesters of pregnancy
Important potential risks	Risks related to the use during the first trimester of pregnancy
Missing information	Use in children Use after kidney transplantation Use during breast-feeding

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The RMP is approved.

V. 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 Perindopril arginine/Indapamide, SE/H/1426/001-003/DC. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Perindopril arginine Actavis, 2.5 mg, 5 mg, 10 mg, film-coated tablets are recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

Area[1]	Description
Quality	Within 6 months after the DCP has been finalised, the Applicant has committed to providing the drug product manufacturer's analytical method description and method validation for the determination of palladium in the active substance perindopril arginine.

1. Areas: Quality, Non-clinical, Clinical, Pharmacovigilance

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Perindopril arginine Actavis, 2.5 mg, 5 mg, 10 mg, film-coated tablets was positively finalised on 2015-11-24.

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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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