

Public Assessment Report

Scientific discussion

Losartan Mylan **(Losartan potassium)**

SE/H/611/01-04/DC

This module reflects the scientific discussion for the approval of Losartan Mylan. Please note that the marketing authorisation was first approved with the name “Losartan Merck NM” and therefore this name is used throughout the document. The procedure was finalised at 2007-11-27. For information on changes after this date please refer to the module ‘Update’.

I. INTRODUCTION

Merck NM AB has applied for a marketing authorisation for Losartan Merck NM, film-coated tablets, 12.5 mg, 25 mg, 50 mg and 100 mg claiming essential similarity to Cozaar film-coated tablets, 12.5, 50 and 100 mg marketed in Sweden by Merck, Sharp & Dohme. The product contains losartan potassium as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Cozaar, 12.5 mg and 100 mg film-coated tablets marketed by Merck Sharp & Dohme in Spain.

II. QUALITY ASPECTS

II.1 Introduction

Losartan Merck NM is presented in the form of film-coated tablets containing 12.5 mg, 25 mg, 50 mg and 100 mg respectively of losartan potassium which corresponds to 11.44 mg, 22.88 mg, 45.76 and 91.52 mg of losartan. The excipients are Lactose monohydrate, pregelatinised maize starch, microcrystalline cellulose, magnesium stearate, hydroxypropylcellulose, hypromellose and titanium dioxide (E171). The film-coated tablets are packed in Aluminium-PE/PVDC blisters.

II.2 Drug Substance

Losartan potassium does not have a monograph in the Ph. Eur.

Losartan potassium is a white to off-white powder which is freely soluble in water. The structure of losartan potassium 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

Losartan Merck NM, film-coated tablets is formulated using excipients described in the current Ph Eur, except for brilliant blue FCF aluminium lake (E133) which is controlled according to acceptable in house specifications. 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 (EMA/410/01).

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

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, 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 total of two bioequivalence studies (12.5 mg) and (100 mg)) comparing the pharmacokinetic profiles of Losartan Merck NM, 12.5 and 100 mg, tablets with the corresponding reference formulations were performed. The study employed in both cases was a randomised, 2 periods, 2-way crossover study performed in healthy, adult, male and female volunteers under fasting conditions.

The same bioanalytical method was used in both studies. Losartan and E-3174 in plasma was determined with an HPLC-MS/MS method with fluorescence detection.

Bioequivalence was satisfactorily demonstrated.

12.5 mg study:

Pharmacokinetic parameters of losartan and E-3174.

	Treatment N=40	AUC_{0-t} ng/ml/h	AUC_{0-∞} ng/ml/h	C_{max} ng/ml	t_{max} h	T_{1/2} h
Losartan	Test	93.6±35.4	98.6±36.0	35.8±21.4	0.75 (0.25-5.0)	3.1±0.86
	Reference	93.9±36.0	98.4±37.0	38.5±26.1	0.75 (0.25-5.5)	3.0±0.93
	*Ratio (90% CI)	99.7 95.3-104	100 96.0-105	96.7 80.9-116		
E-3174	Test	541.5±186.4	560.4±188.1	45.2±19.2	6.0 (3.5-12)	6.7±1.1
	Reference	556.1±190.9	577.3±193.3	47.6±19.8	6.0 (3.5-12)	6.8±1.1
	*Ratio (90% CI)	97.4 92.8-102	97.1 92.5-102	95.7 89.9-102		
AUC_{0-∞} 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						

100 mg study:

Pharmacokinetic parameters of losartan and E-3174.

	Treatment t N=39	AUC_{0-t} ng/ml/h	AUC_{0-∞} ng/ml/h	C_{max} ng/ml	t_{max} h	T_{1/2} h
Losartan	Test	750.5±283.1	793.7±282.5	508.3±321.5	1.0 (0.50-3.0)	3.0±1.4
	Reference	765.3±299.2	805.8±305.0	510.8±344.4	1.0 (0.50-4.0)	2.7±1.1
	*Ratio (90% CI)	98.8 93.4-107	101 94.2-107	104 88.4-121		
E-3174	Test	3718±1628	3816±1635	648.3±352.6	2.5 (1.3-4.0)	6.5±1.8
	Reference	3688±1648	3791±1653	609.6±345.6	2.5 (1.3-5.5)	6.8±2.1
	*Ratio (90% CI)	101 94.4-108	101 94.4-108	106 97.8-115		
AUC_{0-∞} 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						

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 risk/benefit ratio is considered positive and Losartan Merck NM, 12.5 mg, 25 mg, 50 mg and 100 mg, film-coated tablets is recommended for approval.

Specific obligation

The issue whether ACE inhibitors and ARBs should be contraindicated throughout pregnancy or during the second and third trimester only is currently evaluated by the Pharmacovigilance Working Party. The Applicant commits to make a type II variation, changing the wording according to forthcoming recommendations from the CHMP.

VI. APPROVAL

The Decentralised procedure for Losartan Merck NM, 12.5 mg, 25 mg, 50 mg and 100 mg, film-coated tablets was successfully finalised on 2007-11-27.

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)