LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Lodinsarta
(amlodipine besilate, valsartan)

SE/H/1524/01-03/DC

This module reflects the scientific discussion for the approval of Lodinsarta. The procedure was finalised on 2016-10-17. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

The application for Lodinsarta, 5 mg/80 mg, 5 mg/160 mg, 10 mg/160 mg, film-coated tablets, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Sigillata Ltd, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Exforge, 5 mg/80 mg, film-coated tablets authorised in the Union since 2007, with Novartis Europharm Limited as marketing authorisation holder.
The reference product used in the bioequivalence study is Exforge, 10 mg/160 mg, film-coated tablets from DE and UK (member states of source).

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 results from one pivotal bioequivalence study were submitted with the application. Study 3154/13 was a single-dose, two-treatment, three-period, three-sequence, semi-replicated crossover study conducted in 78 healthy volunteers, comparing Amlodipine/valsartan by Actavis, 10 mg/160 mg, tablet with Exforge, 10 mg/160 mg, tablet under fasting conditions. The study was conducted at Lotus Labs Pvt Ltd, Bangalore, India between 30 June and 18 Aug 2014. Blood samples were collected pre-dose and up to 72 hours post-dose. The overall design of the study is considered acceptable. Plasma concentrations of amlodipine and valsartan were determined with an adequately validated LC/MS/MS method.

For amlodipine and valsartan AUC and Cmax the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%. Thus, bioequivalence was satisfactorily demonstrated. The results are presented below.

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

Treatment	AUC_{0-72} ng*h/ml	C_{max} ng/ml	t_{max} h
Test n=71	**298.7 ± 64.8**	**7.4 ± 1.4**	**8.0 4.5-12.0**
Reference 1 n=72	**299.9 ± 67.3**	**7.3 ± 1.4**	**8.5 3.5-12.0**
Reference 2 n=66	**297.2 ± 68.0****	**7.4 ± 1.3**	**7.5 4.5-12.0**
Reference intra subject variability (%)	**9.03**	**12.21**	**-**
***Ratio (90% CI)**	**100.83 (98.71-103.00)**	**101.24 (98.57-103.98)**	**-**

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*
***n=65*

Table 2. Valsartan pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range).

Treatment	AUC_{0-t} µg*h/ml	C_{max} µg/ml	t_{max} h
Test n=71	**34.2 ± 13.3**	**5.7 ± 2.4**	**3.5 1.5-6.5**
Reference 1 n=72	**33.6 ± 14.6**	**5.5 ± 2.2**	**3.25 1.5-4.5**
Reference 2 n=66	**35.2 ± 14.7**	**5.6 ± 2.0**	**3.75 1.5-5.0**
Reference intra subject variability (%)	**22.43**	**24.62**	**-**
***Ratio (90% CI)**	**101.98 (96.69-107.57)**	**103.46 (97.46-109.84)**	**-**

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*

Absence of studies with the additional strengths is acceptable since all biowaiver criteria for additional strength(s) are fulfilled. Conductance of the study with the highest strength is adequate as the pharmacokinetics of both amlodipine and valsartan is linear within the therapeutic dose range.

The pharmacokinetic documentation is sufficient.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 the products concerned in this report.

Safety specification

Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks:	Renal impairment (especially in patients with renal artery stenosis, pre-existing renal impairment, heart failure, post-myocardial infarction, dual blockade of RAAS)
	Hypersensitivity reactions including angioedema
	Cardiovascular events and death – in patients with congestive heart failure
	Foetotoxicity during 2nd and 3rd trimesters of pregnancy
	Hyperkalaemia
	Hypotension
	Drug interactions (e.g. with aliskiren, CYP3A4 inhibitors, lithium and grape fruit juice)
	Pulmonary oedema in patients with pre-existing heart failure NYHA grades III and IV
Important potential risks:	Risk of teratogenicity during the first trimester of pregnancy
Missing info:	Safety in patients with recent kidney transplantation
	Safety and efficacy Use in hypertensive crisis
	Use in pregnancy, breast feeding and fertility

Pharmacovigilance Plan

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

Risk minimisation measures

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

Summary of the RMP

The RMPis approved.

Updated RMPs should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

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 language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Lodinsarta, is found adequate. There are no objections to approval of Lodinsarta, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable.
The application is therefore recommended for approval.

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

N/A

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

N/A

VII. APPROVAL

The Decentralised procedure for Lodinsarta, 5 mg/80 mg, 5 mg/160 mg, 10 mg/160 mg, film-coated tablets was positively finalised on 2016-10-17.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se