LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Isomex
(isosorbide mononitrate)

SE/H/1620/01/DC

This module reflects the scientific discussion for the approval of Isomex. The procedure was finalised on 2017-01-18. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Isomex, 30 mg, prolonged-release tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, RPH Pharmaceuticals AB, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK and NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Imdur, 30 mg, prolonged-release tablet authorised in Sweden since 1993, with AstraZeneca AB as marketing authorisation holder.
The reference product used in the bioequivalence study is Imdur, 30 mg, prolonged-release tablet from Sweden with AstraZeneca AB 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

Pharmacokinetics
Bioequivalence with the reference product was evaluated in two bioequivalence studies:

- Study LBS 016-15: A fasted single-dose crossover study with the 30 mg tablet.
- Study LBS 017-15: A fed single-dose crossover study with the 30 mg tablet.

Waiving a multiple-dose bioequivalence study is considered justified since lack of accumulation was sufficiently shown in the single-dose studies.

Single-dose study fasting (LBS-016-15)
This was a single-dose, two-way crossover study conducted in healthy volunteers, comparing Isosorbid-5-mononitrate 30 mg prolonged-release tablet with Imdur 30 mg prolonged-release tablet under fasting conditions. Blood samples were collected pre-dose and up to 36 hours post-dose. The study design is considered acceptable. Plasma concentrations of isosorbide-5-moninitrate were determined with an adequately validated LC/MS/MS method.

For AUC0-t, AUC0-∞, AUC0-12, AUC12-36 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%. The results are presented below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for isosorbide-5-mononitrate fasting conditions.

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	AUC_{0-12} ng*h/ml	AUC_{12-36} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**5014.2±786.4**	**5120.7±828.2**	**3184.4±370.0**	**1829.8±523.6**	**349.6±46.0**	**4.5 2.5-6.0**
Reference	**4759.0±825.3**	**4858.5±870.9**	**3061.3±399.1**	**1697.7±546.8**	**330.4±43.5**	**3.75 2.5-5.5**
***Ratio (90% CI)**	**105.62 (101.00-110.44)**	**105.68 (101.00-110.57)**	**104.04 (100.39-107.82)**	**108.71 (100.83-117.20)**	**105.78 (102.49-109.17)**	**-**

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
AUC_{0-12} area under the plasma concentration-time curve from time zero 12 hours
AUC_{12-36} area under the plasma concentration-time curve from time 12 to 36 hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

Single-dose study fed (LBS-017-15)
This was a single-dose, two-way crossover study conducted in healthy volunteers, comparing Isosorbid-5-mononitrate 30 mg prolonged-release tablet with Imdur 30 mg prolonged-release tablet after intake of a high-fat, high-calorie meal. Blood samples were collected pre-dose and up to 36 hours post-dose. The study design is considered acceptable. Plasma concentrations of isosorbide-5-mononitrate were determined with an adequately validated LC/MS/MS method.

For AUC0-t, AUC0-∞, AUC0-12, AUC12-36 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%. The results are presented below

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for isosorbide-5-mononitrate fed conditions.

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	AUC_{0-12} ng*h/ml	AUC_{12-36} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**5433.5±689.8**	**5571.9±736.7**	**2962.8±323.0**	**2470.8±555.7**	**326.6±32.5**	**4.75 3.25-12.0**
Reference	**4943.0±801.8**	**5092.9±848.0**	**2680.3±260.4**	**2262.7±667.0**	**301.8±30.2**	**4.625 3.0-12.0**
***Ratio (90% CI)**	**110.30 (105.06-115.81)**	**109.81 (104.55-115.33)**	**110.02 (106.66-113.48)**	**111.42 (101.73-122.02)**	**107.93 (104.01-112.0)**	**-**

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
AUC_{0-12} area under the plasma concentration-time curve from time zero 12 hours
AUC_{12-36} area under the plasma concentration-time curve from time 12 to 36 hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

Overall conclusion
Bioequivalence between Isomex 30 mg prolonged-release tablet and Imdur 30 mg prolonged-release tablet has been satisfactorily demonstrated.

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 (RMP) 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 Isomex.

Following comments from the RMS during the procedure, version 2.0 of the RMP was approved with the following list of safety concerns:

Summary of safety concerns	
Important identified risks	Concomitant treatment with Phosphodiesterase type 5-inhibitors Hypotension and related conditions
Important potential risks	None
Missing information	Use in pregnancy and lactation

Pharmacovigilance Plan
Routine pharmacovigilance and no additional pharmacovigilance activities were proposed by the applicant, which was endorsed.

Risk minimisation measures
Routine risk minimisation and no additional risk minimisation activities were proposed by the applicant, which was endorsed.

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, Isomex, is found adequate. There are no objections to approval of Isomex, 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 Isomex, 30 mg, prolonged-release tablet was positively finalised on 2017-01-18.

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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)

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