LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Furosemid Medical Valley
(furosemide)

SE/H/2109/01-02/DC

This module reflects the scientific discussion for the approval of Furosemid Medical Valley. The procedure was finalised on 2021-12-01. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Furosemid Medical Valley, 20 mg, 40 mg, Tablet.

The active substance is furosemide. A comprehensive description of the indication and posology is given in the SmPC.

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

The application for Furosemid Medical Valley, 20 mg and 40 mg, tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Medical Valley Invest AB applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK and NL as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is:

- For 20 mg (SE/H/2109/01/DC) Lasilix faible, 20 mg, tablet authorised in FR since 1977 with Sanofi-Aventis France as marketing authorisation holder.
- For 40 mg (SE/H/2109/02/DC) Lasix, 40 mg, tablet authorised in SE since 1965, with sanofi-aventis AB as marketing authorisation holder. The product has been withdrawn in Sweden since 2007.

The reference product used in the bioequivalence study is Lasix, 40 mg, tablet from PT with Sanofi - Produtos Farmacêuticos, Lda as marketing authorisation holder.

European Reference Product (ERP)

For SE/H/2109/01/DC:
A European Reference Product is used in RMS and CMS DK and NL: Lasilix faible, 20 mg, tablet authorised in FR since 1977 with Sanofi-Aventis France as marketing authorisation holder.
The justification to use this product is based on information received from FR. The ERP information received from FR was circulated during validation period.

For SE/H/2109/02/DC:
A European Reference Product is used in CMS DK and NL: Lasix, 40 mg, tablet authorised in Sweden since 1965, with sanofi-aventis AB as marketing authorisation holder. The product is withdrawn in Sweden since 2007.
The justification to use this product is based on RMS's own files.
The ERP information from Sweden was circulated during validation period.

Potential similarity with orphan medicinal products

According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

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

Pharmacodynamic, pharmacokinetic and toxicological properties of active substance are well known. As active substance is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since product name is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Furosemid Medical Valley from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Furosemid Medical Valley with the reference product Lasix.

Pharmacokinetic properties of the active substance
Absorption: Furosemide is a weak carboxylic acid which exists mainly in the dissociated form in the gastrointestinal tract. Furosemide is rapidly but incompletely absorbed (60-70%) on oral administration and its effect is largely over within four hours. The optimal absorption site is the upper duodenum at pH 5.0.

Distribution and biotransformation: Furosemide is bound to plasma albumin and little biotransformation takes place. Regardless of route of administration, 69-97% of activity from a radio-labelled dose is excreted in the first 4 hours after the furosemide is given.

Elimination: Furosemide is mainly eliminated via the kidneys (80-90%); a small fraction of the dose undergoes biliary elimination and 10-15% of the activity can be recovered from the faeces.

Study ARL/13/104

Methods

This was a single-dose, two-treatment, three-period, three-sequence crossover study conducted in 53 healthy volunteers, comparing Furosemid Medical Valley, 40 mg, tablet with Lasix, 40 mg, tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of furosemide were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The clinical part of the study was conducted between 06 May 2013 and 22 May 2013.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for furosemide (n=50).

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**3621.06 ± 1181.97**	**1599.01 ± 715.94**	**1.63 (0.50-5.00)**
Reference	**3893.40 ± 1150.7**	**1668.68 ± 639.86**	**1.50 (0.50-5.00)**
***Ratio (90% CI)**	**90.0856 (85.73- 94.66)**	**91.3063 (82.95-100.51)**	**-**
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*

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%.

A biowaiver was sought for the additional strength of 20 mg.

Discussion and overall conclusion

The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr). The bioanalytical method was adequately validated.

Based on the submitted bioequivalence study, Furosemid Medical Valley, 40 mg, tablet is considered bioequivalent with Lasix, 40 mg, tablet.

Absence of studies with the additional strength of 20 mg is acceptable, as all conditions for biowaiver for additional strength, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr) are fulfilled and since the pharmacokinetics of furosemide is linear between 20 and 40 mg.

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, this is considered adequate.

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 Furosemid Medical Valley. In response to

questions raised the applicant updated the RMP to be in line with the last PSUSA for furosemide 2018 (PSUSA/00001491/201801).

Safety specification

List of important risks and missing information	
Important identified risks	None
Important potential risks	• Medication errors • Lack of efficacy
Missing information	• Use in pregnant and lactating women

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 submitted Risk Management Plan, version 0.2 signed 31 May-2021 is considered acceptable. The MAH has satisfactorily responded to the questions raised and updated the RMP accordingly. **Issue is resolved.**

An updated RMP 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 PlL 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, Furosemid Medical Valley, is found adequate. There are no objections to approval of Furosemid Medical Valley, 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 benefit/risk is considered positive, and the application is therefore recommended for approval.

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

N/A

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

N/A

VII. APPROVAL

The decentralised procedure for Furosemid Medical Valley, 20 mg, 40 mg, Tablet was positively finalised on 2021-12-01.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	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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