IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Furosemide Pinewood 20 mg Tablets
Furosemide
PA0281/263/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Furosemide Pinewood 20mg & 40mg Tablet, from Pinewood Laboratories Ltd on 20th October 2023 for the management of fluid retention and for the management of mild to moderate hypertension, either alone or as an adjunct.

This application for a national marketing authorisation was submitted in accordance with Article 10(1) of Directive 2001/83/EC and is referred to as a "generic" application.

Furosemide Pinewood 20mg & 40mg Tablets are prescription only, for supply through pharmacy and for promotion to healthcare professionals only.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Furosemide Pinewood 20mg Tablet
Name(s) of the active substance(s) (INN)	Furosemide
Pharmacotherapeutic classification (ATC code)	C03CA01
Pharmaceutical form and strength(s)	20mg Tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA0281/263/001
Marketing Authorisation Holder	Pinewood Laboratories Ltd
MRP/DCP No.	IE/H/1219/001/DC
Reference Member State	IE
Concerned Member State	MT

II. QUALITY ASPECTS

II.1. Introduction

This application is for Furosemide Pinewood 20mg & 40mg Tablets.

II.2 Drug substance

The active substance is furosemide, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The product consists of the active substance Furosemide (20 mg or 40 mg), lactose monohydrate, maize starch, pregelatinised starch, sodium starch glycolate and magnesium stearate.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European and ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with the European Pharmacopoeia and are adequately controlled.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for tablets and ICH Q6A, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur. and EU legislation requirements for use with foodstuffs.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Furosemide tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance has been available on the European/Irish market for more than 10 years. Preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available.

III.2 Pharmacology, Pharmacokinetics and Toxicology

The pharmacodynamic, pharmacokinetic and toxicological properties of furosemide are well known. Furosemide is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. The overview provided based on literature review is, thus, appropriate.

III.5 Ecotoxicity/environmental risk assessment

The applicant has not provided a full environmental risk assessment (ERA) in accordance with the guideline (CHMP/SWP/4447/00). Instead, justification for the absence of a full ERA is supplied.

Since Furosemide Pinewood 20 mg and 40 mg tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of furosemide are well known. As furosemide is a widely used, well-known active substances, and this is a generic application, the applicant has not provided additional nonclinical studies and further studies are not required. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology provided is adequate. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

Furosemide is a well-known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Lasix 20mg tablets (PA 0540/052/004) and Lasix 40mg tablets (PA 0540/052/005) from Sanofi-Aventis Ireland, registered since 1st April 1977.

For this generic application, the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test product furosemide 40mg tablets is compared with the pharmacokinetic
profile of the reference product LASIX (furosemide 40 mg) Tablets, manufactured by Sanofi-Aventis, Portugal.

A randomized, balanced, open label, single dose, three-sequence, two-treatment, three-period, reference replicate, crossover, bioequivalence study was carried out. Test product furosemide 40mg tablets was compared to the reference product LASIX (furosemide 40 mg) Tablets, manufactured by Sanofi-Aventis, Portugal. Based on the pharmacokinetic parameters of active substance furosemide, the reference tablet LASIX (furosemide 40 mg) Tablets, manufactured by Sanofi-Aventis, Portugal and test tablet furosemide 40mg tablets are bioequivalent with extent
to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

A justification for a biowaiver for the 20mg strength was provided in accordance with the CHMP Guideline on the Investigation of Bioequivalence.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

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 4 hours. The optimal absorption site is the upper duodenum at pH 5.0. Regardless of route of administration 69-97% of activity from a radio-labelled dose is excreted in the first 4 hours after the drug is given. Furosemide is bound to plasma albumin and little biotransformation takes place. 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.

IV.3 Pharmacodynamics

Furosemide is a sulfonamide-type, loop diuretic. It inhibits the re-absorption of electrolytes, the main effect on the ascending limb of the loop of Henle and also the distal renal tubules. Excretion of calcium, chloride, potassium and sodium is increased and excretion of water enhanced.

IV.4 Clinical Efficacy

The efficacy of furosemide in the proposed indications is established in clinical use. No additional efficacy clinical studies to demonstrate efficacy have been included in the application and none are required for a generic application.

IV.5 Clinical Safety

The overall safety profile of furosemide is established and generally known. No new safety studies are provided and none are required.

The reported adverse events in the bioequivalence study were mild to moderate in severity and resolved and no serious adverse events were observed.

The safety information in the SmPC and Package Leaflet are in line with those of the reference product and other similar products.

Risk Management Plan

A risk management plan was submitted, 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 Furosemide Pinewood 20mg and 40mg tablets.

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

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

Periodic safety update reports (PSURs) shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

IV.6 Discussion on the clinical aspects

As this is a generic application under Article 10(1) of Directive 2001/83/EC, additional non-clinical and clinical studies to demonstrate efficacy and safety are not required. The applicant has submitted the results of a suitable bioequivalence study with the 40mg strength which has demonstrated the similarity of the test products against the reference products, in accordance with the relevant guidance. Justification for a biowaiver for the 20mg strength was provided. No additional tests are required for this application.
The applicant has also submitted a clinical overview and summary of the evidence demonstrating the efficacy and safety of this product in clinical practice.

V. OVERALL CONCLUSIONS

Furosemide Pinewood 20mg & 40mg Tablet, from Pinewood Laboratories Ltd is a generic form of Lasix 20mg tablets (PA 0540/052/004) and Lasix 40mg tablets (PA 0540/052/005) from Sanofi-Aventis Ireland, registered since 1st April 1977. Lasix 20mg tablets (PA 0540/052/004) and Lasix 40mg tablets (PA 0540/052/005) is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown for the 40mg strength and a biowaiver for the 20mg strength has been justified in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product and other similar products.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Furosemide Pinewood 20mg & 40mg Tablet, from Pinewood Laboratories Ltd demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

10.08.2028