IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Furosemide 10 mg/ml Solution for Injection
Furosemide
PA2299/036/001

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

This product was initially authorised under procedure number UK/H/1241/1/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 06/12/2018 under procedure number IE/H/0864/1/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA2299/036/001
Marketing Authorisation Holder: Baxter Holding BV

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

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, Denmark, Finland, Germany, Ireland, Italy, The Netherlands, Norway, Sweden and the UK considered that the application for Furosemide 10mg/ml Solution for Injection could be approved. The product is a prescription only medicine (POM) for the following indications:

- Oedema caused by cardiac or hepatic diseases
- Oedema caused by renal diseases (in case of nephrotic syndrome, treatment of the underlying disease is essential)
- Pulmonary oedema (e.g. in case of acute heart failure)

This application for Furosemide 10mg/ml Solution for Injection is submitted as an abridged standard application according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product to Lasix 20mg/2ml Injection, first authorised in the European Economic Area (EEA) to Sanofi-Aventis since April 1977.

The product contains the active substance furosemide, a loop diuretic, the site of action being the renal tubules. It causes loss of potassium ions, and some retention of sodium ions. This causes a reduction in oedema (excessive accumulation of fluids in tissues aka water retention) and oliguria (abnormal reduced urine production).

No new preclinical studies were conducted, which is acceptable given that the product contains a widely-used, well-known active substance. No clinical studies have been performed and none are required for this application as the pharmacology of furosemide is well-established. No clinical pharmacology data is required for this generic injection solution.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

II. QUALITY ASPECTS

III SCIENTIFIC OVERVIEW AND DISCUSSION

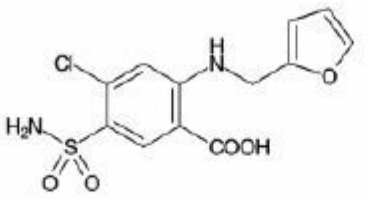
III.1 QUALITY ASPECTS

S. Active substance

INN/Ph.Eur name: Furosemide

Chemical name: 5-(aminosulfonyl)-4-chloro-2-[(2-furanylmethyl)amino]benzoic acid;
4-chloro-N-furfuryl-5-sulfamoylanthranilic acid;
4-chloro-N-(2-furylmethyl)-5-sulfamoylanthranilic acid

Structural formula:



Molecular formula: $C_{12}H_{11}C1N_2O_5$

Appearance: A white to pale yellow, brownish – pale yellow or reddish – pale yellow, hygroscopic powder.
Practically insoluble in water and methylene chloride, soluble in acetone, sparingly soluble in alcohol. Dissolves in dilute solutions of alkali hydroxides.

Molecular formula: $C_{12}H_{11}C1N_2O_5$

Molecular weight: 330.7

Chirality: This does not have a chiral centre.

Furosemide is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture of the active substance furosemide from its starting materials are controlled by a Certificate of Suitability.

An appropriate retest period has been proposed based on stability data submitted for the active substance furosemide.

An appropriate specification is provided for the active substance, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specification.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

P. Medicinal Product

Other Ingredients

Other ingredients consist of pharmaceutical excipients sodium hydroxide, sodium chloride and water for injections.

All excipients comply with their European Pharmacopoeia monograph.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development
The objective of the development programme was to produce a product that could be considered a generic medicinal product of Lasix 20mg/2ml Injection (Sanofi-Aventis, April 1977).

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative impurity profiles have been provided for the finished product versus the reference product Lasix 20mg/2ml Injection (Sanofi-Aventis).

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. The applicant has committed to perform process validation with the first three full scale batches of the drug product.

Finished Product Specification
The finished product specification proposed for the product is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container-Closure System
The product is packaged in ampoules composed of type I amber glass.
Specifications and certificates of analysis for the packaging used have been provided. The product is packaged in sizes of 5ml and 2ml ampoules.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the European Pharmacopoeia Type I and relevant regulations regarding use of materials in contact with food.

Stability of the product
Stability studies were performed on batches of the finished product in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of two years for an unopened product with storage conditions "Keep the ampoules in the outer carton in order to protect from light." and "Store in the original package in order to protect the product from moisture".

Once opened, the product should be used almost immediately, with storage conditions "From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions."
For storage conditions of the diluted medicinal product "Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C protected from light only with neutral and weak alkaline solution.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL and labelling are pharmaceutically acceptable.

User testing results have been submitted for a typical PIL for this product. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA forms
The MAA form is pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of a marketing authorisation is recommended.

III. NON-CLINICAL ASPECTS

III.2 PRE-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of furosemide are well-known. As furosemide is a widely used, well-known active substance, the applicant has not provided any additional studies and none are required.

The pre-clinical expert report is based on literature sources and has been written by an appropriately qualified person.

IV. CLINICAL ASPECTS

III.3 CLINICAL ASPECTS

1. Introduction

This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier. For more details, the reader should refer to the company's clinical overview and summary and to the clinical file.

The clinical overview has been written by an appropriately qualified physician. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

2. Clinical study reports

No bioequivalence studies have been performed and none are required for this application, as the applicant's product is similar to the reference product in terms of qualitative and quantitative composition and is expected to perform identically *in vivo*. A human bioavailability study is not relevant to this application as the compound is intended for intravenous infusion.

3. Post marketing experience

Furosemide has a well-recognised efficacy and an acceptable level of safety in the indications approved for Lasix 20mg/2ml, and corresponding products have been widely used in many countries. Therefore, the submission of PSUR at the renewal of the marketing authorisation is supported.

4. Benefit-Risk assessment

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant's product and the innovator product are interchangeable. Extensive clinical experience with furosemide is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

5. Conclusions

The grant of a marketing authorisation for Furosemide 10mg/ml Solution for Injection is recommended from a clinical viewpoint.

V. OVERALL CONCLUSIONS

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Furosemide 10mg/ml Solution for Injection are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

CLINICAL

No bioequivalence studies have been performed and none are required for this application, given the composition of the product and its intended route of administration.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with furosemide is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

VI. REVISION DATE

28/02/2022

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From UK/H/1241/1/DC to IE/H/0864/1/DC			