IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Furosemide 8 mg/ml oral solution
Furosemide
PA22697/011/002

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/5871/1-3/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 12/04/2019 under procedure number IE/H/1026/1-3/DC
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA22697/011/001-003
Marketing Authorisation Holder: SYRI Limited, t/a Thame Laboratories

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, the UK and Ireland considered that the applications for Furosemide 4mg/ml, 8mg/ml and 10mg/ml Oral Solution (PL 39307/0047-0048; UK/H/5871/001-003/DC) could be approved. These are prescription-only medicines (POM), which are indicated in the treatment of all conditions requiring prompt diuresis in patients who are unable to take solid dose forms. Indications include cardiac, pulmonary, hepatic and renal oedema, peripheral oedema due to mechanical obstruction or venous insufficiency and hypertension.

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Ireland as Concerned Member State (CMS). The applications for Furosemide 4mg/ml and 8mg/ml Oral Solution were submitted under Article 10(3) of Directive 2001/83/EC, as amended, as hybrid applications. The application for Furosemide 10mg/ml Oral Solution was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. Furosemide 4mg/ml, 8mg/ml and 10mg/ml Oral Solution cross-refer to the reference product Lasix 10mg/ml oral solution (Sanofi-Aventis, France), which were authorised in France on 20 October1987. The corresponding reference product in the UK is Lasix 10mg/ml oral solution, which was first authorised on 14 May 1993 to Hoechst UK Limited and was cancelled on 27 September 2005. However, there are other generic furosemide oral solution products still marketed in the UK.

The active ingredient, furosemide is a potent loop diuretic which inhibits the co-transport system (reabsorption) of Na+, K+ and 2CL-, located on the luminal cell membrane on the ascending limb of the loop of Henle. Secondary effects of increased elimination of sodium are the increase of urinary excretion and increase of potassium secretion at the distal tube.

In accordance with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), a bioequivalence study was not required to support these applications for oral aqueous solution products, containing the same active substance as the reference product.

No new non-clinical or other clinical data were submitted, which is acceptable given that these applications were based on the products being hybrid/generic medicinal products of an originator product that has been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of these products.

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

The RMS and CMS considered that the applications could be approved at the end of procedure on 03 September 2015. After a subsequent national phase, licences were granted in the UK on 15 September 2015.

II. QUALITY ASPECTS

II QUALITY ASPECTS

II.1 Introduction

The submitted documentation concerning the proposed products is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The products are clear colourless to pale brown coloured solutions with cherry flavour.

Each ml of Furosemide 4mg/ml Oral Solution contains 4mg of furosemide as the active ingredient.

Each ml of Furosemide 8mg/ml Oral solution contains 8 mg of furosemide as the active ingredient.

Each ml of Furosemide 10mg/ml Oral solution contains 10 mg of furosemide as the active ingredient.

The products also contain the pharmaceutical excipients citric acid monohydrate (E330), ethanol (96% v/v), sodium hydroxide (E524), liquid maltitol (E965), cherry flavour [containing propylene glycol (E1520), disodium phosphate and anhydrous (E339)] and purified water. Appropriate justification for the inclusion of each excipient has been provided.

The finished products are supplied in European Pharmacopoeia Type III amber glass bottles with tamper evident, child resistant, plastic (polypropylene/polyethylene) caps with expanded polyethylene (EPE) liners. The products are packaged with 10ml oral syringes with 0.5ml graduation markings, supplied with low density polyethylene (LDPE) syringe adaptors.

Furosemide Oral Solution is available in pack sizes of 100ml, 150ml and 300ml.

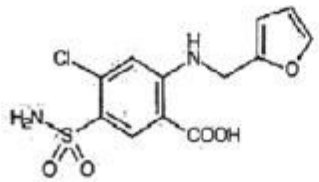
Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for the primary packaging materials have been provided. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

II.2 DRUG SUBSTANCE

Furosemide

INN:	Furosemide
Chemical Name:	3-Ethyl 5-methyl (4*RS*)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate
Molecular Formula:	$C_{12}H_{11}ClN_2O_5S$
Structure	



M_r:	330.75
Appearance:	White or almost white crystalline powder

Solubility	Practically insoluble in water, soluble in acetone, sparingly soluble in ethanol (96 per cent), practically insoluble in methylene chloride. It dissolves in dilute solutions of alkali
Isomerism	Furosemide does not exhibit optical isomerism

Furosemide is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, furosemide, are covered by European Directorate for the Quality of Medicine and Healthcare (EDQM) Certificates of Suitability.

II.3 MEDICINAL PRODUCT

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, stable, oral solutions containing 4mg/ml, 8mg/ml and 10mg/ml of furosemide that could be considered comparable in performance to the innovator reference product Lasix 10mg/ml oral solution (Sanofi-Aventis S.p.A., Italy). Suitable pharmaceutical development data have been provided for these applications.

Comparative *in-vitro* dissolution profiles have been provided for these products and the reference product. The dissolution profiles were satisfactory.

With the exception of cherry flavour, all the excipients comply with their respective European Pharmacopoeia monographs. Cherry flavour is controlled to a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate description of the manufacturing process. Based on full-scale production batches, the manufacturing process has been validated and has shown satisfactory results.

The Marketing Authorisation Holder has committed to performing process validation studies on future full-scale production batches.

Control of Finished Product

The finished product specifications are acceptable. Test methods have been described and have been validated adequately. Batch data that comply with the release specifications have been provided. Certificates of Analysis have been provided for all working standards used.

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results a shelf life of 12 months for the unopened products has been accepted. The opened products should be discarded 60 days after first opening. The special storage conditions for the unopened and opened products are 'Do not store above 25°C.'

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished products.

Bioequivalence/Bioavailability

Bioequivalence studies were not necessary to support these applications for oral aqueous solutions.

II.4 Discussion on chemical, pharmaceutical and biological aspects

It is recommended that Marketing Authorisations are granted for Furosemide 4mg/ml, 8mg/ml and 10mg/ml Oral Solution.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

The SmPCs, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

III. NON-CLINICAL ASPECTS

III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of furosemide are well known. No new non-clinical data have been submitted for these applications and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

Not applicable, see Section III.1 Introduction, above.

III.3 Pharmacokinetics

Not applicable, see Section III.1 Introduction, above.

III.4 Toxicology

Not applicable, see Section III.1 Introduction, above.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)

Suitable justification has been provided for non-submission of an Environmental Risk Assessment in accordance with regulatory guidelines (EMEA/CHMP/SWP/4447/00). As the products are intended for substitution with products that are already marketed, no increase in environmental exposure to furosemide is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

III.6 Discussion of the non-clinical aspects

It is recommended that Marketing Authorisations are granted for Furosemide 4mg/ml, 8mg/ml and 10mg/ml, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of furosemide is well-known. No new clinical pharmacology data have been submitted and none are required for applications of this type.

In accordance with the guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) for aqueous oral solutions, the guidance states that "If the test product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an approved oral solution, bioequivalence studies may be waived. However if the excipients may affect gastrointestinal transit (e.g. sorbitol, mannitol, etc.), absorption (e.g. surfactants or excipients that may affect transport proteins), in vivo solubility (e.g. co-solvents) or in vivo stability of the active substance, a bioequivalence study should be conducted, unless the differences in the amounts of these excipients can be adequately justified by reference to other data […]".

The applicant has provided evidence to justify eligibility for biowaivers as described in the guideline. The RMS considers that comparability of the physicochemical properties and overall quality of the test and reference products has been demonstrated. Furthermore, it is agreed as the Applicant argues, that the composition of Furosemide 4mg/ml, 8mg/ml and 10mg/ml Oral Solution are similar to other currently licensed furosemide oral solution products (such as Furosemide Focus PL 20046/0037-39 and Furosemide Pinewood PL 04917/0072-7) for which biowaivers have been accepted on the basis that the excipients (including liquid maltitol) were not expected to affect gastrointestinal absorption. Therefore no bioequivalence studies were required for these applications.

IV.2 Pharmacokinetics

The clinical pharmacokinetic properties of furosemide are well known and are adequately described in the applicant's non-clinical overview. No new pharmacokinetic data were submitted and none are required for applications of this type.

IV.3 Pharmacodynamics

The clinical pharmacodynamics properties of furosemide are well-known. No new pharmacodynamic data were submitted and none are required for applications of this type.

IV.4 Clinical Efficacy

The clinical efficacy of furosemide is well-known. No new efficacy data are presented or are required for applications of this type.

IV.5 Clinical Safety

No new safety data have been submitted with these applications and none are required. No new or unexpected safety concerns arose from these applications.

IV.6 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 Furosemide 4mg/ml, 8mg/ml and 10mg/ml Oral Solution.

A summary of safety concerns is listed in the table below table:

Summary of safety concerns	
Important identified risks	• Hypersensitivity • Hypovolaemia and dehydration • Hypotension • Electrolyte disturbances, particularly hypokalaemia and hyponatraemia and acid-base disturbances • Lack of efficacy of furosemide due to interaction with indomethacin, ketorolac, phenytoin, corticosteroids barbiturates and sucralfate • Increased exposure to furosemide as result of concomitant use with antivirals (nelfinavir, ritonavir or saquinavir) • Drug toxicity (lithium toxicity, salicylic toxicity, probenecid and methotrexate) • Cardiac Toxicity • Nephrotoxicity • Ototoxicity • Use in patients having difficulty with micturition including patients with prostatic hypertrophy • Hepato-biliary disorders, including hepatic encephalopathy • Nephrocalcinosus/nephrolithiasis/patent ductus arteriosus in preterm infants
Important potential risks	• Effect on ability to drive and use machine due to reduced mental alertness • Use in pregnancy and lactation
Missing information	• Use in patients with acute porphyria • Use in children • Effect on fertility

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns, except for overdose and medication error for which the provision of a double ended dosing spoon and child resistant cap are proposed additional risk minimisation measures, as detailed in the table below.

IV.7 Discussion of the clinical aspects

It is recommended that Marketing Authorisations are granted for Furosemide 4mg/ml, 8mg/ml and 10mg/ml Oral Solution.

V. USER CONSULTATION

A 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 pack leaflet 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.

V. OVERALL CONCLUSIONS

VI. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY

The important quality characteristics of Furosemide 4mg/ml, 8mg/ml and 10mg/ml Oral Solution 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.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type. As the pharmacokinetics, pharmacodynamics and toxicology of furosemide are well-known, no additional data were required.

EFFICACY

No new efficacy data have been submitted and none are required for applications of this type.

SAFETY

The safety profile of furosemide is well-known. No new safety data have been submitted with this application and none are required. No new or unexpected safety concerns arose from these applications

PRODUCT LITERATURE

The SmPCs, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

BENEFIT/RISK ASSESSMENT

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

RECOMMENDATION

The grant of Marketing Authorisations is recommended.

VI. REVISION DATE

24/02/2022

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/5871/1-3/DC to IE/H/1026/1-3/DC			