26 March 2026
EMADOC-1829012207-45079
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Bopediat

International non-proprietary name: Furosemide

Procedure No. EMEA/H/C/006617/0000

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List of abbreviations

AAS	Atomic Absorption Spectrometry
AE	Adverse Event
ANOVA	Analysis of variance
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
BA	Bioavailability
BCS	Biopharmaceutics Classification System
BE	Bioequivalence
BMI	Body Mass Index
C	Degree Celsius
CFU	Colony Forming Units
CI	Confidence interval
Cmax	Maximum measured Plasma concentration
CoA	Certificate of Analysis
CPMA	Clinical Pharmacology and Medical Affairs
CRO	Contract Research Organization
CRS	Chemical Reference Substance (official standard)
Ct	Last measurable Plasma concentration
CV	Coefficient of Variation
DCGI	Drug Controller General of India
DSC	Differential Scanning Calorimetry
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDQM	European Directorate for the Quality of Medicines
EMA	European Medicines Agency
ERA	Environmental risk assessment
FPM	Finished Product Manufacturer
FTIR	Fourier-transform infrared spectroscopy
GCP	Good Clinical Practice
GLM	Generalized linear model
GLP	Good Laboratory Practice
H	Hour(s)
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C Virus
HDPE	High Density Polyethylene
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
ICF	Informed Consent Form
ICMR	Indian Council of Medical Research
IEC	Independent Ethics Committee
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
IPC	In-process control
IR	Infrared
IRB	Institutional Review Board
ISCV	Intra subject coefficient of variation
IU	International Units
LC-MS/MS	Liquid Chromatography/ Tandem Mass Spectrometry
LDPE	Low Density Polyethylene
ln	Logarithmic value to the base '*e*'

LOD	Limit of Detection
LOQ	Limit of Quantification
LTR	Lambda Therapeutic Research
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation holder
MS	Mass Spectrometry
MS	Method SOP
MV	Method Validation
N	Number
ND	Not detected
ng/mL	Nanogram per milliliter
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NOR	Normal Operating Range
NPC	Niemann-Pick Type C
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
ODT	Orodispersible tablet
OOS	Out of Specifications
PAR	Proven Acceptable Range
PDE	Permitted Daily Exposure
PE	Polyethylene
PEC	Predicted Environmental Concentration
PK	Pharmacokinetic(s)
PROC	Procedure
QA	Quality Assurance
Rcf	Relative Centrifugal Force
SAE	Serious Adverse Event
SAS	Statistical analysis system
SOP	Standard Operating Procedure
T/R	Test to reference ratio
t½	Terminal half-life
Tmax	Time of the maximum measured Plasma concentration
λz	First order terminal rate constant associated with the terminal (log-linear) portion of the curve

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Proveca Pharma Limited submitted on 7 March 2025 an application for a Paediatric Use marketing authorisation in accordance with Article 30 of Regulation (EC) No 1901/2006, to the European Medicines Agency (EMA) for Bopediat, through the centralised procedure under Article 31 of Regulation (EC) No 1901/2006. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 27 June 2024.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in a Member State on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

> Bopediat is indicated in children from birth to less than 18 years of age for the treatment of oedema of cardiac or renal origin, oedema of hepatic origin, and hypertension in patients with chronic kidney disease.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of composed of administrative information, complete quality data, a bioequivalence study with the reference medicinal product Lasilix Faible 20 mg tablets and appropriate clinical data.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Lasilix Faible, 20 mg tablet
- Marketing authorisation holder: Sanofi Winthrop Industrie
- Date of authorisation: (05/04/1977)
- Marketing authorisation granted by:
  - Member State (EEA): France
    - National procedure
- Marketing authorisation number: 6 930 493 8

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Lasilix Faible, 20 mg tablet
- Marketing authorisation holder: Sanofi Winthrop Industrie

- Date of authorisation: (05/04/1977)
- Marketing authorisation granted by:
  - Member State (EEA): France
    - National procedure
- Marketing authorisation number: 6 930 493 8

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Lasilix Faible, 20 mg tablet
- Marketing authorisation holder: Sanofi Winthrop Industrie
- Date of authorisation: (05/04/1977)
- Marketing authorisation granted by:
  - Member State (EEA): France
    - National procedure
  - Marketing authorisation number(s): 6 930 493 8
- Bioavailability study number(s): PRO/FUR/001

1.3. Information on paediatric requirements

Pursuant to Article 30 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P-03I5-2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P-03I5-2023 was completed.

The PDCO issued an opinion on compliance for the PIP P-03I5-2023.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

Relevant for the assessment are the Guideline on the Investigation of Bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev.1), the Guideline on the pharmacokinetic and clinical evaluation of modified-release dosage forms (EMA/CHMP/EWP/280/96 Rev.1), ICH M13A Guideline on bioequivalence for immediate-release solid oral

dosage forms" (EMA/CHMP/ICH/953493/2022), and one of the questions of the Questions & Answers: Positions on specific questions addressed to the Pharmacokinetics Working Party (EMA/618604/2008).

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP were:

Rapporteur: Jana Klimasová Co-Rapporteur: N/A

The application was received by the EMA on	7 March 2025
The procedure started on	27 March 2025
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	16 June 2025
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	30 June 2025
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 July 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	9 October 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	17 November 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 November 2025
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	11 December 2025
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	26 January 2026
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	11 February 2026
The CHMP agreed on a 2nd list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	26 February 2026
The applicant submitted the responses to the CHMP consolidated 2nd List of Outstanding Issues on	3 March 2026
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the 2nd List of Outstanding	11 March 2026

Issues to all CHMP and PRAC members on	
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Bopediat on	26 March 2026

2. Scientific discussion

2.1. Introduction

Furosemide is well-established loop diuretic, having been on the WHO list of essential medicines since 1977, and is indicated in all conditions requiring diuresis including cardiac, hepatic and renal oedema, and hypertension.

Although currently licenced from birth, oral formulations of furosemide specifically intended for children are only sporadically available in the EU and have their limitations. Due to its limited solubility in water, available paediatric liquid formulations of furosemide use ethyl alcohol as a solvent, at concentrations as high as 11.7%. The potential problems associated with the use of ethanol as an excipient are summarised in the Committee for Medicinal Products for Human Use (CHMP) reflection paper "Formulations of choice for the paediatric population" which states that there are severe acute and chronic concerns in the use of ethanol containing medicinal products in the paediatric population e.g., acute intoxication with accidental overdose and chronic toxicity associated with routine use for chronic medical conditions. In addition, the dosing of furosemide formulations containing alcohol in infants has been shown to cause elevation of blood acetaldehyde, a potentially toxic metabolite of ethanol.

Where licenced liquid formulations are unavailable, or in cases where the excipients are too high risk to administer to patients e.g., in neonates, unlicenced extemporaneous compounding is currently occurring. This compounding often involves crushing commercially available tablets and using a suspending vehicle to create an oral suspension. Unlike registered medications, these compounded products are not subjected to various tests for quality by regulatory authorities and therefore risk inadequate safety, quality and efficacy.

To address the issues with current paediatric solutions, an orodispersible tablet formulation of furosemide has been developed in strengths of 1 mg and 5 mg, with functional score line to enable flexible dosing.

This Paediatric Use Marketing Authorisation (PUMA) is submitted via centralised procedure as a hybrid application according to article 10(3) of Directive 2001/83/EC as amended by 2004/27/EC for Bopediat (furosemide) from Proveca Pharma Limited, Ireland.

The European reference medicinal product (ERP) is Lasilix Faible, 20 mg, tablets from Sanofi Winthrop Industrie, for which marketing authorisation was granted in France via national procedure on 05 April 1977. The justification to use this product is based on information received from France based on their own files.

The legal basis of this PUMA falls under Article 10(3) of Directive 2001/83/EC as amended ("hybrid application") due to the change in strength from the ERP (Lasilix Faible 20 mg). This hybrid application relies in part on the results of pre-clinical studies and clinical trials of the ERP.

The original paediatric investigation plan (PIP) was adopted by the European Medicines Agency on 9th August 2023 [PIP 07 August 2015 (Decision number P/0315/2023)].

A PIP compliance check (CC) request was submitted to the European Medicines Agency on 15th January 2025, procedure number EMA/PE/0000244107. Applicant received the CC positive opinion from EMA on the 28th of February 2025. Two studies PRO/FUR/001 and PRO/FUR/002 were assessed to be compliant within the CC procedure.

The applicant submitted one bioequivalence study (PRO/FUR/001) of furosemide orodispersible tablets (ODT) 5 mg administered as 4 x 5 mg tablets i.e, 20 mg (Proveca Pharma Limited) vs Lasilix Faible 1 x 20 mg tablet (Sanofi Winthrop Industrie) conducted in normal, healthy, adult human subjects under fasting conditions. This study compared the pharmacokinetics and drug exposure of the new furosemide ODT to a licensed tablet formulation. The bioequivalence study was to examine if the appropriate doses of furosemide are administered with the new ODT compared to the standard formulation, which is authorised for use in the paediatric population. Additionally, applicant requested a biowaiver for lower 1 mg strength.

The applicant also submitted the results of acceptability and palatability study with Bopediat, "Children's acceptability of furosemide (CHAFfinch) study in 10 paediatric participants" (PRO/FUR/002). The aim of the study was to investigate, within a small group of patients who are already prescribed and taking oral furosemide, how they react to the new formulation and if it is acceptable to them.

Initially, the MAA was submitted for 2 strengths, 1 mg and 5 mg in the form of an orodispersible tablet (ODT). The submitted bioequivalence study was performed with 5 mg strength only, and the applicant sought an exemption for lower strength (1 mg ODT). The criteria for the lower strength biowaiver for 1 mg ODT were not met, since the composition of the strengths (Bopediat 1 mg ODT and Bopediat 5 mg ODT) was not proportional and the dissolution data at pH 1.2 showed incomplete dissolution. As the major objection remained outstanding, the applicant withdrew marketing authorisation application for the lower strength (1 mg ODT).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as orodispersable tablets (ODTs) containing 5 mg of furosemide as active substance.

Other ingredients are mannitol (E 421), maize starch, croscarmellose sodium (E 468), povidone (E 1201), strawberry flavour (contains gum arabic, sodium, furaneol, sulphites, acetic acid), sodium stearyl fumarate, red iron oxide.

The product is available in PVC/PVDC/aluminium blister as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of furosemide is 4-Chloro-2-[[(furan-2-yl)methyl]amino]-5-sulfamoylbenzoic acid corresponding to the molecular formula $C_{12}H_{11}ClN_2O_5S$. It has a relative molecular mass of 330.74 g/mol and the following structure:

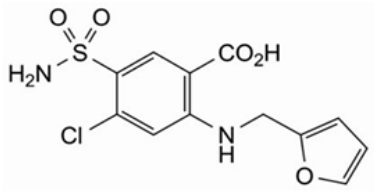


Figure 1: Active substance structure

The active substance is a white or almost white, crystalline powder practically insoluble in water, soluble in acetone, sparingly soluble in ethanol (96 %), practically insoluble in methylene chloride. It dissolves in dilute solutions of alkali hydroxides.

As there is a monograph of furosemide in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for furosemide which has been provided within the current Marketing Authorisation Application.

***Manufacture*, characterisation and process controls**

The active substance is manufactured by one manufacturing site. The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Specification

The active substance specification adopted by the finished product manufacturer includes tests for appearance (visual), identity (FTIR, TLC), appearance of the solution (Ph. Eur.), related substances (Ph. Eur.), chlorides (Ph. Eur.), sulfates (Ph. Eur.), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.) assay on dried basis (Ph. Eur.), residual EDTA disodium and particle size (in-house).

The presented specification from the finished product manufacturer is in line with Ph. Eur. monograph no. 0391 and with submitted EDQM CEP according to which an additional test for residual EDTA disodium is performed. Moreover, particle size tested by an in-house method by standard sieving is included in the specification due to check for agglomerates of the drug substance that might occur during its storage or transport.

The finished product manufacturer conducts testing according to Ph. Eur. or CEP methods and standard analytical techniques. Therefore, no validation of the analytical methods is required.

The certificates of analysis as issued by the finished product manufacturer were given for three batches of furosemide showing the compliance of the drug substance with the proposed specification. Overall, the proposed control of the drug substance by the finished product manufacturer is considered adequate and acceptable.

Stability

According to the CEP, the re-test period of the active substance furosemide is 5 years if stored in a black PE bag placed in a PE carboy.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The 5 mg strength is presented as pale red, round, flat with bevelled edge orodispersible tablet with 'F' debossed on one side and a score line on the other side. The tablet is 5.7 mm and can be divided into equal halves.

Initially a 1 mg strength was also proposed however, during assessment the proposed biowaiver for this strength was not considered acceptable, therefore, the applicant withdrew the 1 mg strength.

The finished product has been developed to be a hybrid equivalent to the reference medicinal product Lasilix Faible 20 mg tablets. The aim of the formulation development programme was to develop a stable, age-appropriate dosage form that would allow accurate and yet flexible dosing to paediatric patients from birth. To achieve a stable product with acceptability in children, an ODT formulation was selected for development. A detailed justification was provided regarding the development of medicinal product in accordance with the "Guideline on pharmaceutical development of medicines for paediatric use".

All excipients are well known pharmaceutical ingredients, and their quality is compliant with the Ph. Eur. standards, except of iron oxide red and strawberry flavour which comply with In House specifications. One co-processed excipient is used in the formulation. Information is provided in line with the Questions and Answers regarding co-processed excipients used in solid oral dosage forms. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. An active substance-excipient compatibility study was performed, indicating that selected excipients are compatible with the active substance.

Development work was initiated on both an oral liquid and an orodispersible tablet formulation but the 10 mg/mL oral liquid formulation proved challenging as due to the solubility of furosemide, the efficacy of preservatives diminished, and it was found that the preferred solubilisers interacted with the preservatives selected. Thus, development of a liquid formulation was stopped, and focus was turned to the ODT dosage form where achievement of a stable product with acceptability in children was deemed more promising.

During the formulation development, early prototypes, pilot scale batches and optimisation batches were manufactured to ensure that the formulation and manufacturing process is robust and would consistently provide ODTs with a rapid disintegration time. The process development of the finished product continued with the production of feasibility and clinical batches and scale-up trials were conducted. Critical process steps and parameters of manufacturing process, that should be monitored or controlled to ensure that the product is of the desired quality, are identified and discussed.

The method for dissolution is taken from the BP Furosemide Tablets monograph and does not require full ICH validation as the method is already validated for use. The method was verified to show that it is fit for purpose.

The disintegration time of an orodispersible tablet is a critical parameter, particularly for a paediatric dosage form where it is important that the tablet disintegrates fast to ensure the child does not spit it out. Therefore, disintegration time has been used to discriminate between 'good' and 'bad' batches during development. Different compaction forces and compression speeds led to the slightly different disintegration times and friability; however, all these batches met the specification criteria for disintegration. In order to demonstrate that the proposed finished products are equivalent to the reference medicinal product, a bioequivalence study has been performed. The in-vivo bioequivalence has been evaluated and demonstrated between the 5 mg

strength test formulation and the reference medicinal product; see clinical part for the assessment of the bioequivalence study.

To support the results obtained in the BE-study, the comparison of dissolution profiles of proposed orodispersible tablets of 20x 1 mg strength and 4x 5 mg strength and reference medicinal product 1x 20 mg tablets in four dissolution media: pH 1.2, pH 4.5, pH 6.8, and pH 5.8 (QC medium) has been conducted. Dissolution profiles in media with pH 6.8 and 5.8 have been found to be similar for all batches as more than 85 % of active substance was dissolved within 15 minutes. Similarity was not shown at lower pHs.

The applicant applied for a biowaiver of 1 mg strength; however, it was not accepted since it did not meet the requirements of the Guideline on Investigation on Bioequivalence (CHMP/EWP/QWP/1401/98 Rev 01). The 1 mg product is not quantitatively proportional to the 5 mg strength and the alternative compositional requirement for a biowaiver of strengths is not fulfilled, i.e. the amount of the active substance is not less than 5 % of the tablet core weight in all strengths. In addition, in vitro dissolution profiles for 20 x 1 mg compared to 4 x 5 mg orodispersable tablet at pH 1.2 are not considered similar.

A multidisciplinary major objection was raised by the CHMP with regards to the unacceptable biowaiver and additional comparative in-vitro dissolution profile of the clinical and validation batches. In response, the applicant stated that an additional comparative bioavailability study with the 1 mg test product is being conducted in order to confirm bioequivalence with the reference product and, therefore, biowaiver approach is no longer applicable. The applicant withdrew the 1 mg strength from this initial authorisation application.

Manufacturing process development was performed through the manufacturing of feasibility and clinical batches at the initial manufacturing site prior to being transferred to commercial manufacturing site. The Critical Quality Attributes (CQA) of the finished product were defined from the Quality Target Product Profile (QTPP) elements prior to scale up. Following the different stages of development, the final manufacturing process was established. For each manufacturing process step, the associated parameters with potential to impact the Critical Quality Attributes were identified as Critical Process Parameters via risk assessment. Based on the presented *in vitro* dissolution data it can be concluded that minor differences applied in the manufacturing process of clinical batches versus commercial batches do not affect *in vitro* furosemide release from the 5 mg strength.

The primary packaging is PVC/PVDC/aluminium blister. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. Patients may require medicine administration of furosemide via nasogastric tube (NGT) and the feasibility of administering the orodispersible tablets via this route was investigated. Dose recovery, repeat use and NGT blocking were considered and evaluated with polyurethane (PUR), silicone and PVC NGTs. It was concluded that a rinse volume of 5mL is sufficient for dose deliver, 30 seconds and approximately 40 movements is sufficient to provide a uniform dispersion, and no evidence of blockage was observed, showing that the orodispersible tablet dispersion could be successfully administered through NGTs of this internal dimension.

Manufacture of the product and process controls

The finished product is manufactured at one manufacturing site. Satisfactory evidence of GMP compliance has been provided for all sites involved in the manufacturing, testing and batch release of the finished product.

The manufacturing process consists of 5 main steps: wet granulation, fluid bed drying, blending, compression, and packaging. The manufacturing process is considered to be a standard process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this pharmaceutical form.

Product specification

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: appearance (visual), water content (KF), disintegration (Ph. Eur.), identity (UV, HPLC), assay (HPLC), uniformity of dosage units by content uniformity (Ph. Eur.), dissolution (BP monograph), related substances (HPLC), and microbiology (Ph. Eur.).

The proposed specification for the finished product is in line with ICH Q6A and BP monograph for furosemide tablets and it is generally acceptable for this type of dosage form. The specification parameters and acceptance criteria were satisfactorily described and justified.

Release and shelf-life limits for impurities are set in line with the BP monograph for furosemide tablets and in line with the requirements of ICH Q3B based on the maximum daily dose.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach. The assessment has been performed according to option 2b considering the drug product composition and the content of each elemental impurity in the components. It was demonstrated that the total daily intake of elemental impurities (class 1 and 2A) is below 30 % of the ICH Q3D PDE. Based on the risk assessment, it can be concluded that it is not necessary to include any elemental impurity controls, therefore, no further control is needful.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed. Based on the assessment there is a possibility of formation of nitrosamine active substance impurity N-nitroso-furosemide. It has been demonstrated that the nitrosamine content was below the LOD/ LOQ in three active substance batches. A major objection (MO) was raised by the CHMP to request confirmatory batch data for the finished product and, in addition, to consider several impurities of active that contain a secondary amine group**.** As a response the applicant performed a confirmatory testing on the finished product to detect and quantify the presence of any N-nitroso-furosemide. It was found that across all 5 mg batches the level of N-Nitroso-furosemide detected was at levels below 10% of the specification limit. Since the levels detected were very low, much lower than the threshold of 10% of the acceptance limit, it was considered acceptable not to include a test for N-Nitroso-furosemide in the specification of the finished product in accordance with the current EMA guidelines. Therefore, MO was resolved.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for three validation batches of proposed batch size for 5 mg strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 3 validation/commercial batches of the proposed finished product for up to 12 months and 3 technical and clinical batches of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Technical and clinical batches were manufactured by a different manufacturer and are packed in different packaging as proposed for commercial batches.

Samples were tested for appearance, water content, assay, related substances, dissolution, disintegration, and microbiological contamination. The analytical procedures used are stability indicating.

Stability data has been provided on N-Nitroso-furosemide impurity after storage under long-term storage conditions but no data on this impurity after storage under accelerated conditions has been provided. Therefore, the CHMP recommended to carry out testing of N-nitroso-furosemide during a stability study under long-term, intermediate and accelerated condition for at least three future batches.

The related substances stability data confirms the rate of degradation (impurity formation) increases as the product is exposed to higher temperatures. Therefore, considering the increase in impurities observed at the intermediate storage conditions (30°C/65% R.H.), the applicant proposes the labelled storage condition of 'Do not store above 25°C'. The rest of parameters meet specification across all conditions and batches.

Bulk stability studies were performed on two batches. The batches were packed in a PE-bag placed in a container and stored in a temperature-controlled warehouse at 15 - 25°C. At the 3-month timepoint no significant changes are observed. The bulk stability study confirms that at 6 months bulk tablets remain stable under warehouse storage conditions (15 - 25°C).

Photostability studies were performed on one batch. Photostability studies show that the product is susceptible to photolytic degradation when not protected by light protective packaging. Therefore, the product information includes the statement: "Store in the original package in order to protect from light.

Forced degradation studies have been performed on one batch of the finished product to establish the stability indicating nature of the finished product analytical methods and to identify the degradation mechanisms. As furosemide is known to be susceptible to light and hydrolysis degradation, the lack of degradation for the solution exposed to light and heat could be indicative of under stressing of samples. However, this is compensated for in the photostability studies and long-term stability studies. Peak purity has been performed to prove the method for assay and related substances is stability indicating. The chromatograms for the stressed samples were comparable to the chromatograms for unstressed samples, and no peak distortion was observed confirming the validity of the method.

Based on available stability data, the proposed shelf-life of 1 year, do not store above 25°C, and store in the original package in order to protect from light as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

Two MOs were raised during the procedure for the finished product, relating to a proposed biowaiver for a 1 mg strength and the risk evaluation concerning the presence of nitrosamine impurities. In response, the 1 mg strength has been withdrawn from the application and confirmatory testing of the finished product to detect and quantify the presence of any N-nitroso-furosemide was performed. The level of N-Nitroso-furosemide detected was at levels below 10% of the specification limit. Satisfactory responses were provided for these issues, and the MOs were considered resolved.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there was a minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertains to carry out testing of N-nitroso-furosemide during a stability study under long-term, intermediate and accelerated condition for at least three future batches. This point is put forward and agreed as recommendations for future quality development.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- to carry out testing of N-nitroso-furosemide during a stability study under long-term, intermediate and accelerated condition for at least three future batches.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data.

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

The non-clinical sections of the SmPC are considered acceptable.

Excipients contained in this medicinal product are standard excipients used in pharmaceutical preparations. They raise no additional safety concerns for the paediatric population except for the strawberry flavour containing sulphites (present as sulphur dioxide) for which hypersensitivity reactions have been reported (Vally et al., 2009; Cuzzolin, 2018). Sodium is present in several excipients, i.e. croscarmellose sodium,

sodium stearyl fumarate, and as a component of the strawberry flavour. Overall, the maximum daily intake is less than 1 mmol sodium based on the worst-case scenario with the maximum daily dose of Bopediat 24 x 5 mg. Appropriate warnings are included in the product information.

The impurity profile has been discussed very briefly. Specifications are set based on the monograph for furosemide tablets in the British Pharmacopoeia. Furthermore, toxicological qualification of furosemide impurity C (2-amino-4-chloro-5-sulfamoylbenzoic acid) for the heightened specification limit was provided.

2.3.2. Ecotoxicity/environmental risk assessment

ERA data sharing did not take place therefore the applicant provided their own ERA summarised below.

Phase I risk assessment

Using the default values offered by the guideline, the calculation based on a maximum daily dose of 120 mg per day can be performed as follows:

$$PEC_{SW} = \frac{120\ mg(DOSE) \times\ 0.01\ (F_{PEN})}{200\ L\ (WASTEW_{INHAB}) \times 10(DILUTION)} = 0.0006\ mg/L = 0.6\ \mu g/L$$

As the predicted concentration in surface water is above the limit value of 0.01 µg/L, an adjustment of Fpen can be reasonable. However, furosemide is a widely used diuretic, thus an adjustment is not considered to drastically lower the PECSW. Therefore, Phase II Tier A assessment is triggered.

Phase II Tier A risk assessment

The applicant did not conduct any studies, but a targeted literature search was conducted. Some of the studies identified were evaluated on several criteria based on the CRED method. Available ecotoxicity and environmental fate data are summarised in the submitted ERA report.

- Surface water

  The PNEC for the aquatic compartment (surface water) is derived from the lowest available chronic NOEC from the base set (algae, daphnia, fish). Lowest chronic NOEC = 0.156 mg/L (Crustacea, ISO 20665).

  $$RQ_{SW} = \frac{PEC_{SW}}{PNEC_{SW}} = \frac{0.6\ \mu g/L}{15.6\ \mu g/L} = 0.038$$

  As the RQ is well below 1, no Phase II Tier B risk assessment is required according to the applicant.

- Sewage treatment plant (STP)

  The PNEC for microorganisms in STPs was not determined. The lowest NOEC tested (Crustacea, 0.156 mg/L) is used.

  $$RQ_{Microorganism} = \frac{PEC_{STP}}{PNEC_{Microorganism}} = \frac{6\ \mu g/L}{15.6\ \mu g/L} = 0.385$$

  As the RQ is well below 1, no Phase II Tier B risk assessment is required according to the applicant.

- Sediment

Limited specific effect data are available for furosemide in sediments. However, Villa et al. investigated the impact of furosemide on *Diamesa zernyi* larvae, which inhabit both aquatic environments and sediments. Although recalculating the reported aquatic concentrations to sediment concentrations (mg/kg dry weight) is not feasible due to insufficient data, the study used a concentration of 500 mg/L, proposed as the Lowest Observed Effect Concentration based on a previously conducted master thesis. This concentration is substantially higher than the predicted environmental concentration in sediment, which is 0.003174 mg/kg dry weight. Hence, it is highly unlikely that the predicted concentration would pose significant risk to sediment-dwelling organisms.

- Groundwater (via bank filtration)

  The assessment of groundwater is based on the PEC_{SW} as calculated in Phase I.

  $$RQ_{GW} = \frac{PEC_{GW}}{PNEC_{GW}} = \frac{0.15\ \mu g/L}{1.56\ \mu g/L} = 0.096$$

  As the RQ is well below 1, no Phase II Tier B risk assessment is required according to the applicant.

- Soil

  $K_{foc,\ SLUDGE}$ was not evaluated, but Kd_{Sludge} was assessed for five different sludges with a maximum of 127 L/kg. As it has been shown that the adsorption of Furosemide to sludge is low, the risk is considered negligible. In addition, direct contamination of soil is unlikely given the hospital-only use setting. Indirect contamination via sludge application is possible but depends on wastewater treatment plant sludge disposal practices. Given the low overall environmental load predicted, significant risk to the soil compartment is not expected. Hence, no soil assessment is considered necessary according to the applicant.

- Secondary poisoning

  As the log K_{ow} and log D_{ow} for furosemide are both below 3, no secondary poisoning assessment is considered necessary according to the applicant.

PBT/vPvB screening

Furosemide is a weak acid with an acidic pKa value of 3.8 (carboxylic acid), log Kow for furosemide has been reported in literature. In a study by Berthod et al. (1999), octanol-water partition coefficients (Po/w) were determined for 23 diuretic drugs at various pH levels using countercurrent chromatography (CCC). Using this technique, logP values for furosemide were -1.20 at pH 7.39, 0.14 at pH 5.86, and 1.79 at pH 2.58. The logP from literature was reported to be 2.29. In the available study, logP was measured at three different pH values; however, a basic pH was not included. Nevertheless, pH values of 5.86 and 7.39 are particularly relevant as they reflect physiological conditions both in animals, humans and most environmental compartments. Since both measurements yielded logP values well below 4.5, the associated environmental risk is considered acceptable according to the applicant.

In addition, the applicant performed a literature search regarding the ecotoxicity of furosemide and identified no new toxicological hazard that would trigger a further risk assessment.

The applicant committed to provide the missing studies in line with the ERA guideline (EMEA/CHMP/SWP/4447/00 Rev.1-Corr.) within 2 years from the end of this procedure.

2.3.3. Discussion on non-clinical aspects

No new non-clinical studies have been conducted with furosemide in this application, and this is considered acceptable. Non-clinical sections of the SmPC are considered acceptable.

Environmental risk assessment

Phase I risk assessment

MDD of 120 mg/day furosemide was used (based on worst-case 2 mg/kg/day from the SmPC and 60 kg body weight of a 17-year-old), which is also in accordance with the quality part of the dossier. Unrefined PEC_{SW} exceeded 0.01 µg/L and the applicant did not refine the F_{PEN}, which is considered acceptable in this case.

Phase II Tier A risk assessment

- Physico-chemical and fate properties

The experimental methods used in the publications cited by the applicant to establish water solubility and dissociation in water of furosemide are unknown. Water solubility should be determined in line with OECD 105 and performed at pH 5, 7 and 9 for dissociating compounds. Dissociation in water (pKa) should be conducted in line with OECD 112. Furthermore, the ready biodegradability test (OECD 301/310) was not provided. Even though a study by Radke et al. (2014) claimed to determine DT_{50} generally based on OECD 308, it is not considered relevant or reliable as it does not adhere to the basic principles of the method and only DT_{50} for water phase is reported; thus, it cannot substitute the OECD 301 study. For sorption to soil and sludge, please see the soil assessment. The applicant should perform the missing Phase II Tier A studies of physico-chemical and fate properties as indicated in Table 2 of the ERA guideline (i.e. at least water solubility (OECD 105), dissociation in water (OECD 112), ready biodegradability test (OECD 301/310), adsorption using a batch equilibrium method with 3 soils and 2 sludges (OECD 106)).

- Surface water

The applicant identified aquatic toxicity studies from three trophic levels (algae, invertebrates and fish). However, none of them were conducted according to the OECD TG required by the ERA guideline. Firstly, the test in algae (*P. subcapitata*, now *Raphidocelis subcapitata*) measured growth inhibition by furosemide over 72 hours and adhered to the ISO 8692 method, which is highly similar to OECD 201 and could therefore be considered relevant. Algae do not seem to be the most sensitive organism based on the high measured EC_{50} (70 mg/L). Secondly, a chronic reproduction study in the crustacean *C. dubia* (ISO 20665) is also deemed as highly relevant and reliable. Although the test covered only a period of 7 days (in contrast to 21 days in *D. magna*, OECD 211), it encompassed a complete reproductive cycle of *C. dubia* and multiple brood releases, therefore it provides pertinent information on long-term invertebrate reproduction toxicity of furosemide. In addition, available OECD 211 results in *D. magna* (FASS database) show less conservative EC_{10}/NOEC values than the *C. dubia* study. Conducting an additional OECD 211 study would hence duplicate existing information without significantly modifying the risk characterisation, which would be against the principles of 3Rs. Lastly, no chronic fish study was identified in the public literature; however, available acute fish toxicity data indicates very low sensitivity, with reported effect concentrations in the hundreds of mg/L. Thus, fish most probably do not represent the most sensitive trophic level, and in line with the principles of the 3Rs, additional chronic fish testing is not considered necessary as it would not be expected to further refine the risk assessment or alter the

risk conclusion. As invertebrates (*C. dubia*) are clearly the most sensitive aquatic species based on the provided data, the calculation of RQ_{SW} is considered acceptable. No risk to the aquatic environment is identified.

- Sewage treatment plant (STP)

  The applicant calculated $PNEC_{microorganism}$ with aquatic toxicity data from *C. dubia* as an OECD 209 activated sludge respiration inhibition study was not found in literature. This is not considered acceptable. It is acknowledged that furosemide has no described antimicrobial mode of action, but evidence of some antimicrobial activity can be found in literature. Although monitoring data indicate that furosemide undergoes substantial removal (often > 70 %) in conventional wastewater treatment plants (Sandré et al., 2023, doi: 10.1016/j.chemosphere.2023.138212), no direct evidence that microbial respiration and STP performance are unaffected at relevant exposure levels is available. Therefore, the risk in terms of functioning of STPs cannot be evaluated. The applicant should perform an OECD 209 study.

- Sediment

  The available study by Villa et al. (2018) cannot be accepted in the Phase II Tier A sediment risk assessment. Although a benthic organism (*D. zernyi*) was used, the test was conducted in a water-only exposure system without sediment and therefore does not address sediment-associated exposure pathways. In addition, the study reports behavioural endpoints after exposure of 96 hours as opposed to population-relevant endpoints after prolonged exposure (OECD 218/219/233/225). Overall, the study is not considered relevant for sediment risk assessment and may only be used as supportive evidence indicating potential sensitivity of benthic invertebrates. At least one toxicity study with sediment-dwelling organisms should be conducted according to the OECD TG stated in Table 8 of the ERA guideline.

  Moreover, K_D for two types of soil (Spanish and Finnish) was investigated in a study by Dong et al. (2025). The higher of the two values (16.9 L/kg) was used in the PEC_{SED} ($K_{SUSP\text{-}WATER}$) calculation by the applicant instead of $K_{FOC,soil}$. The study applies a modified OECD 106 approach using relatively environmentally relevant soils and demonstrates high analytical and methodological quality. However, due to the use of only two soils, the absence of measured organic carbon content (only % organic matter is available), and intentional pH variability during adsorption, the study does not fully meet OECD 106 requirements. In addition, the authors chose to rely on K_D rather than K_F, although with scientific justification. Overall, the data are rather considered reliable with restrictions. Results from an OECD 106 study should be used instead (see *soil*).

- Soil

  Both identified studies (Jelić et al., 2012; Park et al., 2017) report $K_{D,sludge}$ values from wastewater treatment plants determined by non-standard methods ranging from 2.1 L/kg to 127 L/kg. Neither study provides organic carbon normalised sorption partition coefficient (K_{FOC}) or sufficient data to converse K_D to K_{FOC}. According to footnote 5 of the ERA guideline, only if it is impossible to determine K_F and K_{FOC}, the adsorption distribution coefficient (K_D) and K_{OC} may be used. No such justification was provided. Therefore, these studies are not sufficient to assess furosemide's risk to soil and can only be deemed as supportive. The applicant should perform an adsorption study – using a batch equilibrium method with 3 soils and 2 sludges (OECD 106) and determine further steps based on whether full soil assessment is triggered (Table 4 of the ERA guideline).

- Groundwater (via bank filtration)

  No risk to groundwater via bank filtration is indicated as $RQ_{GW} < 1$ based on $PNEC_{GW}$ derived from the aquatic toxicity study with *C. dubia* (see *surface water*). Regarding risk for groundwater via porewater, the need for assessment depends on the results of the OECD 106 study (see *soil*).

- Secondary poisoning

  Based on log K_{ow} of 1.81 (see *PBT/vPvB screening*), no risk to predators consuming contaminated prey is expected.

PBT/vPvB screening

The applicant provided data from public literature. Berthod et al. (1999) derive the octanol-water partitioning coefficient of furosemide experimentally using countercurrent chromatography, a direct liquid-liquid partitioning technique. Consequently, the method could be considered suitable as an alternative approach to the OECD 107/123 methods required by the ERA guideline. The study determines apparent partition coefficients (log Dow) at three pH values (1.78 at pH 2.58, -0.10 at pH 5.86 and -1.20 at pH 7.39), thus covering conditions under which furosemide is predominantly neutral (acidic pH) and ionised (neutral pH) as it is an acid with pKa1 ≈ 3.9. Then the authors derive the partition coefficient of the neutral molecule to be log P^0 = 1.81. Log P^0 (log Kow) does not exceed the trigger for further PBT/vPvB assessment (log Kow ≥ 4.5). Although no measurement was conducted at basic pH (9) as required in the guideline for dissociating substances, it is taken into consideration that furosemide is already ionised at pH ≥ 7 (pKa2 ≈ 7.5), therefore no significant increase in log Kow is expected at higher pH. No further PBT/vPvB assessment is required.

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of furosemide to the environment. The applicant committed to provide the missing studies in line with the ERA guideline (EMEA/CHMP/SWP/4447/00 Rev.1-Corr.) within 2 years from the end of this procedure.

2.3.4. Conclusion on the non-clinical aspects

The applicant committed to provide an ERA in line with the ERA guideline (EMEA/CHMP/SWP/4447/00 Rev.1-Corr.) within 2 years from the end of this procedure.

2.4. Clinical aspects

2.4.1. Introduction

The applicant submitted one bioequivalence study of furosemide orodispersible tablets (ODT) 5 mg administered as 4 x 5 mg tablets i.e, 20 mg (Proveca Pharma Limited) and compared the test product to Lasilix Faible 1 x 20 mg tablet as the reference medicinal product (Sanofi Winthrop Industrie). The study was conducted in normal, healthy, adult human subjects under fasting conditions. The study compared the pharmacokinetics and drug exposure of the new furosemide ODT to a licensed tablet formulation (Lasilix Faible 1 x 20 mg tablet). The bioequivalence study was to examine if the appropriate doses of furosemide are administered with the new ODT compared to the standard formulation, which is licensed for use in the paediatric population. Additionally, a biowaiver is requested for lower 1 mg strength.

Furthermore, PRO/FUR/002, an acceptability and palatability study has been conducted in paediatric participants.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

Relevant for the assessment are the Guideline on the Investigation of Bioequivalence, CPMP/EWP/QWP/ 1401/98 Rev. 1/ Corr **, the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev.1), the Guideline on the pharmacokinetic and clinical evaluation of modified-release dosage forms (EMA/CHMP/EWP/280/96 Rev.1), ICH M13A Guideline on bioequivalence for immediate-release solid oral dosage forms" (EMA/CHMP/ICH/953493/2022), and one of the questions of the Questions & Answers: Positions on specific questions addressed to the Pharmacokinetics Working Party (EMA/618604/2008).

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of furosemide based on published literature. The SmPC is in line with the SmPC of the reference product.

GCP aspect

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

For 1 mg strength

A strength biowaiver for furosemide 1 mg ODT was proposed according to the following grounds:

This proposal was reflective of previous furosemide tablets on the market that have been granted biowaivers for the lower strength based on a bioequivalence study performed with the higher strength tablets against the reference medicinal product. Absence of studies for the additional strengths were deemed acceptable due to furosemide's linear pharmacokinetics (Furosemide Medical Valley Public Assessment Report: SE/H/2109/01-02/DC).

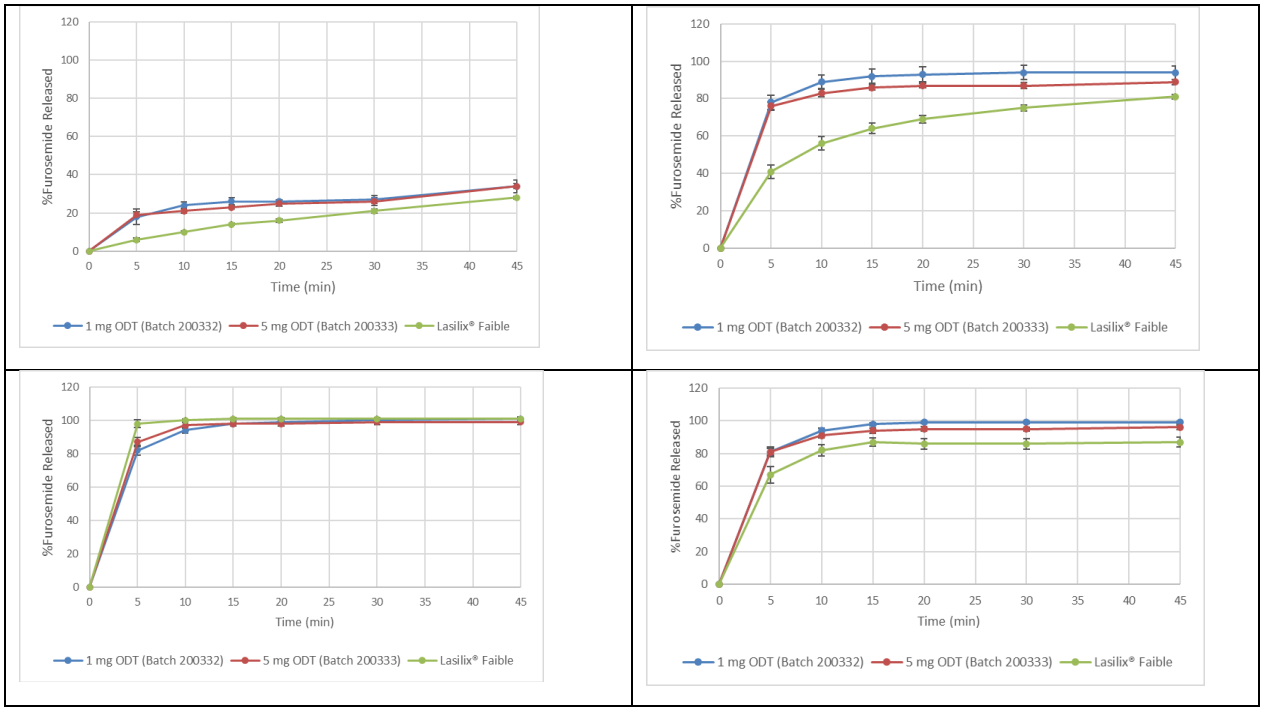
The 1 mg and 5 mg ODTs that Proveca Pharma Limited has been developing are both manufactured using the same excipients through an aqueous wet granulation process. The granule is dried, and extra granular excipients are added followed by blending and tablet compression. The only difference in the extra granular excipients between the two strengths is the addition of red iron oxide to the 5 mg strength which is used as a differentiator. The process generates 5.7mm tablets of similar excipient composition, each strength being differentiated by the colourant used.

An *in vitro* study was performed to explore the release characteristics of furosemide from both the 1 mg and 5 mg furosemide ODTs as well as from a commercially available furosemide product (Lasilix Faible 20 mg tablets, Sanofi Winthrop Industrie; for more information see quality part of the document, chapter 3.1.3.1). The 1 mg and 5 mg furosemide ODTs were rapidly dissolving (>85 % in 15 minutes) at pH 4.5, 5.8 and 6.8 and were considered similar to Lasilix Faible at pH 5.8 and 6.8. Due to the solubility profile of furosemide at pH 1.2, both the ODTs and commercially available product show slow release and dissolution of furosemide. Direct comparison between the ODT's and the reference medicinal product was difficult in this particular case,

as ODTs are being compared to a conventional tablet and the ODTs have been designed specifically to disintegrate as quickly as possible in the mouth.

The products were comparable in that they all show rapid release and dissolution of furosemide in the higher pH QC media and at pH 6.8, whereas a slower release and dissolution is observed at pH 1.2 and 4.5 (See the dissolution curves below).

Figure 1 Dissolution curves



Based on the submitted data, the criteria for the biowaiver for 1 mg ODT were not met, since the composition of the strengths (Bopediat 1 mg ODT and Bopediat 5 mg ODT) is not proportional and the dissolution data at pH 1.2 showed incomplete dissolution. Therefore, the lower strength (1 mg ODT) was withdrawn from this marketing authorisation application by the applicant.

Tabular overview of clinical studies

To support the application, the applicant has submitted 2 studies:

Table 8 Overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Comparative bioavailability	PRO/FUR/001	Clinical Study Report & PK Report, Adverse Event Listing and Individual Subject Listings, CRFs 5.3.1.2 Bio-Analytical Report & Method validation Report 5.3.1.4	**Efficacy:** To compare the bioavailability and characterize the pharmacokinetic profile of the sponsor's test product relative to that of reference product after single oral dose administration in normal, healthy, adult, human subjects under fasting condition and to assess the bioequivalence. **Safety:** To monitor the adverse events and to ensure the safety of the subjects.	**Study Design:** An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, comparative bioavailability study in normal, healthy, adult human subjects under fasting condition. **Type of Control:** No control groups	**Test Product-T** Furosemide Orodispersible Tablets 5 mg Dosage Regimen: 20 mg (administered as (4 Tablets x 5 mg) Route of administration: Oral **Reference Product-R** Lasilix Faible (Furosemide) 20 mg tablet Dosage Regimen: 20 mg Route of administration: Oral	Planned-42 Checked-in-45 Dosed-42 Completed-41 Analysed-42 (In which, 01 withdrawn subject was also analysed as per protocol requirement). Withdrawn-01	Healthy subjects	Single dose	Complete; Full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Acceptability and Palatability	PRO/FUR/002	Clinical Study Report, Adverse Event Listing and Individual Subject Listings 5.3.5.4	**Acceptability and Palatability:** To evaluate the acceptability of the new oral formulation, using an adapted version of the composite endpoint method which comprised of two scoring systems: one for swallowability and one for palatability.	**Study Design:** An open label study where the intervention was a single replacement dose exposure of the new orodispersible tablet formulation of furosemide (dose was given as per current prescription). **Type of Control:** No control groups	**Test Product-T** Furosemide Orodispersible Tablets 1 mg And/Or Furosemide Orodispersible Tablets 5 mg Dose given as per current prescription. Route of administration: Oral **Reference Product:** No reference product	Planned – 10 Dosed – 10 Completed – 10 Analysed – 10 Withdrawn - 0	Participants currently taking an oral formulation of furosemide and have completed at least 48 hours of oral treatment, with no dose alterations planned.	Single dose	Complete; Full

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study PRO/FUR/001: An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, comparative bioavailability study of Furosemide Orodispersible Tablets S mg administered as (4 tablets x *5* mg i.e., 20 mg) of Proveca Pharma Limited, Ireland, with Lasilix Faible (furosemide) 20 mg tablet of Sanofi Winthrop Industrie in normal healthy, adult human subjects under fasting condition.

Methods

Study design

The primary objective of this study was to compare the bioavailability and characterize the pharmacokinetic profile of the test product relative to that of reference medicinal product after a single oral dose administration and assess the bioequivalence. Secondary endpoints were monitoring adverse events to ensure safety.

The study was an open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, comparative bioavailability study in normal, healthy, adult human subjects under fasting condition, with a screening period of 28 days prior to IMP administration in Period-I. In each study period, 24 blood samples, including one pre-dose blood sample, were collected from each subject (except for the withdrawn subject) to analyse the pharmacokinetic profile of the test product as well as the reference medicinal product.

The screening phase was carried out within 28 days prior to the scheduled dosing day of Period-I. The subjects were administered the study drug in each period except for the withdrawn subject (Subject No. 1024). The sequence of administration was determined by the randomization schedule. The duration of the clinical part of the study was about 10 days (11 hours prior to the IMP administration in Period-I until the last pharmacokinetic sample collection in Period-II).

The IMP administration was performed as per the randomization schedule and under open label conditions. Period I commenced on 23 March 2024, with a washout period of 07 days prior to Period-II dosing on 30 March 2024.

After an overnight fast for at least 10 hours, a single oral dose [20 mg (administered as (4 Tablets x 5 mg)] of the test product was administered orally at scheduled dosing time in sitting posture.

The venous blood samples were withdrawn at pre-dose (0.000 hour) and at 0.250, 0.500, 0.750, 1.000, 1.250, 1.500, 1.750, 2.000, 2.333, 2.667, 3.000, 3.333, 3.667, 4.000, 4.500, 5.000, 6.000, 8.000, 10.00, 12.000, 16.000, 20.000 and 24.000 hours post-dose following drug administration in each period.

Table 9 Test and reference products

Product Characteristics	Test product	Reference product
Name	Furosemide 5 mg, orodispersible tablet	Lasilix Faible 20 mg
Strength	5 mg	20 mg
Dosage form	Orodispersible tablet	Tablet
Manufacturer/Supplier/MA holder	Proveca Pharma Limited	Sanofi Winthrop Industrie
Batch number	200333 (Bulk) and 500001 (Packed)	Lot No.: 3K02E
Batch size	8kg	
Expiry date/retest date	October 2024	December 2025
Location of Certificate of Analysis	PRO/FUR/001, Appendix 16.5	PRO/FUR/001, Appendix 16.5
Member State where the reference product was purchased from		France
This product was used in the following trials	PRO/FUR/001	PRO/FUR/001

Population studied

Non-smoking, normal, healthy, adult, human subjects between 18 and 45 years of age (both inclusive), having a Body Mass Index (BMI) between 18.5 and 30.0 (both inclusive), calculated as weight in kg / height in m1, were able to understand and comply with the study procedures and having given then- written informed consent for participation in the study were checked in for the study. They did not have any significant diseases or clinically significant abnormal findings during screening, medical history, clinical examination, laboratory evaluations, 12-lead ECG and chest X-ray recordings. Volunteers who complied with all the inclusion criteria were checked in for the study.

Analytical methods

The bioanalytical phase of the study was conducted as per the 'bioanalytical study plan'. The purpose of the study was to measure furosemide in the subject samples. The concentrations of furosemide in human plasma were determined using a selective, reproducible, precise and accurate LC-MS/MS method using furosemide D5 as an internal standard. The bioanalytical method was validated according to in-house SOP No. AHM/BA/0030-4.

The concentrations of furosemide in human plasma were measured using a 08-point calibration curve. The concentrations of subject samples were calculated using linear regression analysis with a weighting factor of 1/concentration2.

The analytical method is summarised below:

Table 10 analytical method

Applicable Method validation SOP No.:	AHM/BA/0030-4		
Analyte to be quantified:	Furosemide		
Internal Standard:	Furosemide-d5		
Method SOP No.:	MS-1867-D-00		
Quantification Method:	LC-MS/MS method		
Biological Matrix	Human plasma		
Anticoagulant	K_2EDTA		
Sample Processing Method:	**liquid-liquid extraction** using Ethyl acetate. The plasma layer was flash-frozen and the organic layer was transferred in to pre-labelled tubes. The contents were evaporated to dryness at around 40 ± 2°C under nitrogen gas stream. The contents were reconstituted with reconstitution solution. The final contents were used for analysis.		
MRM transitions (m/z)	329.100 → 204.900 for Furosemide		
	334.100 → 205.900 for Furosemide-d5 (ISTD)		
Column Type	Kinetex 2.6µm Biphenyl 100 A° 100 X 4.6 mm		
Mobile Phase	Binary mode	A: (50%)	Methanol
		B: (50%)	2 mM Ammonium Acetate buffer (pH 5.0)
Injection Volume	10 µL		
Run time	3.5 minutes		
Polarity	Negative		
Curve Type	Linear		
Equation Type	y = ax + b Where, x = concentration of analyte y = peak area ratio of analyte / ISTD a = slope of the calibration curve b = intercept of the calibration curve		
Weighting Factor	1/concentration2		
Aliquoting volume	100 µL		
Quantification Range:	10.001 ng/mL to 2506.950 ng/mL		
Lower Limit of Quantification:	10.001 ng/mL		
Dilution Quality control:	7518.788 ng/mL		

Pharmacokinetic Variables

The pharmacokinetic parameters were calculated from the Plasma concentration vs. time profile by non-compartmental model using Phoenix® WinNonlin® Version 8.3 (Certara L.P.) for Furosemide. Statistical comparison of the pharmacokinetic parameters of the two formulations was carried out using PROC GLM of SAS® Version 9.4 (SAS Institute Inc., USA) to assess the bioequivalence between test and reference formulations.

Primary pharmacokinetic parameters:

Cmax and AUC0-t

Secondary pharmacokinetic parameters:

Tmax, AUC0-∞, AUC_%Extrap_obs, λz and t1/2

Statistical methods

Descriptive statistics are calculated and reported. for the pharmacokinetic parameters of Furosemide.

ANOVA, power, intra-subject variability and ratio analyses for ln-transformed pharmacokinetic parameters Cmax, AUC0-t, and AUC0-∞ are computed and reported for Furosemide.

90% confidence intervals for the ratio of the geometric least squares means between drug formulations are calculated and reported for ln-transformed pharmacokinetic parameters Cmax. AUCo-t, and AUC0-∞ for Furosemide.

Criteria for conclusion of bioequivalence are as follows:

Bioequivalence of Test Product-T vs. Reference Product-R is concluded, if the 90% confidence interval for the ratio of the geometric least squares means falls within the acceptance range as defined below for In-transformed pharmacokinetic parameters for Furosemide.

Results

Based on the data analysed from 41 subjects for Furosemide, the pharmacokinetics were assessed for the comparison of Test Product-T vs. Reference Product-R. The pharmacokinetic data were analysed as per the statistical method defined in the protocol. As per approach specified in the protocol, the data of 41 subjects were analysed using ANOVA model with the terms Sequence, Subject (Sequence), Formulation and Period as fixed effects.

Table 11 Descriptive Statistics of Formulation Means for Furosemide (N = 41)

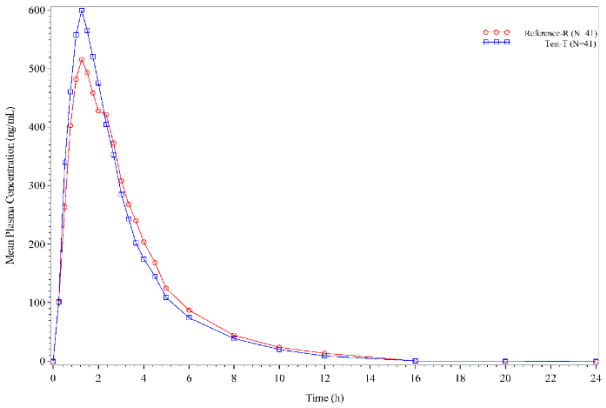
Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product – T	Reference Product – R
T_{max} (h)#	1.250 (0.500 - 3.000)	1.500 (0.500 - 3.667)
C_{max} (ng/mL)	788.033 ± 301.4228	747.816 ± 282.9009
AUC_{0-t} (ng.h/mL)	1884.066 ± 485.9437	1884.822 ± 512.3409
AUC0-∞ (ng.h/mL)	1935.377 ± 490.7834	1944.872 ± 515.4072
λ_z (1/h)	0.329 ± 0.0990	0.283 ± 0.0736
$t_{½}$ (h)	2.308 ± 0.7722	2.696 ± 1.1825
AUC $_{\%Extrap\_obs\ (\%)}$	2.765 ± 0.9717	3.254 ± 1.5876

Table 12 Relative Bioavailability Results for Furosemide (log transformed) (N = 41)

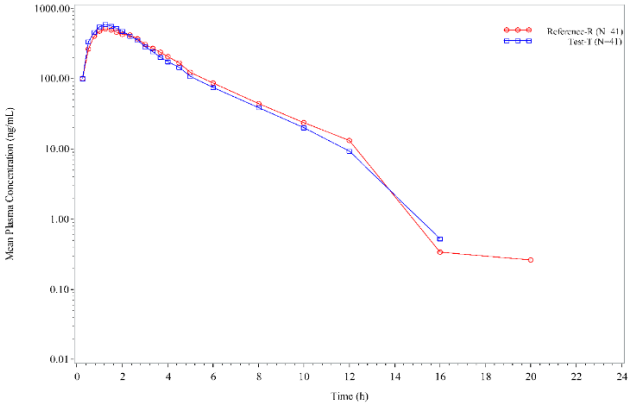
Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product - T	Reference Product - R	Ratio (T/R) %			
lnCmax	728.042	699.463	104.1	92.04-117.71	34.0	91.1
lnAUC0-t	1819.544	1819.003	100.0	95.36-104.93	12.9	100.0
lnAUC0-∞	1871.286	1880.490	99.5	95.13-104.09	12.1	100.0

Figure 2

Linear time versus mean furosemide concentration profile of treatment R and T.



Semilogarithmic time versus mean furosemide concentration profile of treatment R and T.



Safety data

See, clinical safety part for further information.

2.4.2.2. Pharmacokinetic discussion

In general, the design of this BE study is appropriate. Statistical analysis demonstrated bioequivalence between test product Bopediat (5 mg ODT) and reference product Lasilix Faible 20 mg.

Based on the submitted data, the criteria for the biowaiver for 1 mg ODT were not met, since the composition of the strengths (Bopediat 1 mg ODT and Bopediat 5 mg ODT) is not proportional and the dissolution data at pH 1.2 showed incomplete dissolution. Thus, the results of bioequivalence study (PRO/FUR/001) with 5 mg ODT formulation cannot be extrapolated to other strengths 1 mg, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1.

2.4.2.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.3. Conclusion on clinical pharmacology

To support this application for marketing authorisation, Applicant submitted review of clinical data as well as one bioequivalence study in healthy volunteers and one acceptability/palatability study conducted in paediatric patients. In this application, the essential similarity is claimed to the reference medicinal product Lasilix Faible 20 mg.

Submitted bioequivalence study is an open label, randomized, two-treatment, two-sequence, two-period, single oral dose, crossover, bioequivalence study in healthy, adult, human subjects comparing Bopediat 5 mg ODT to Lasilix Faible 20 mg tablet under fasting conditions.

In general, the design of this BE study is appropriate. Statistical analysis demonstrated bioequivalence between test product Bopediat (5 mg ODT) and reference product Lasilix Faible 20 mg.

The submitted bioequivalence study was performed with 5 mg strength, and the Applicant sought an exemption for lower strength (1 mg ODT). From the clinical point of view if criteria for a biowaiver are not met, clinical data on efficacy and safety of the reference medicinal product (Lasilix Faible 20 mg) cannot be extrapolated to the new formulation. The criteria for the biowaiver for 1 mg ODT were not met, since the composition of the strengths (Bopediat 1 mg ODT and Bopediat 5 mg ODT) is not proportional and the dissolution data at pH 1.2 showed incomplete dissolution. Therefore, the lower strength (1 mg ODT) was withdrawn from this marketing authorisation by the applicant.

2.4.4. Clinical efficacy

Not applicable.

2.4.5. Clinical safety

PRO/FUR/001

In the bioequivalence study PRO/FUR/001 in healthy adult volunteers, safety was assessed from the screening period to the end of the study. Safety was assessed through clinical examination, vital signs assessment, body temperature, 12-lead electrocardiogram (ECG), chest X-ray (posteroanterior view) recording, clinical laboratory parameters [e.g., haematology, biochemistry (including serum electrolyte Na+, K+, Mg 2+, Ca 2+ and Cl+), immunology and urine analysis], and subjective symptomatology.

The investigational products were well tolerated by healthy subjects, as a single dose administration. There were no clinically significant findings in the vital signs assessment, ECG or the laboratory tests in any of the subjects in the study.

PRO/FUR/002

PRO/FUR/002 was an acceptability study conducted in paediatric participants. It was classed as not a Clinical Trial of an Investigational Medicinal Product (non-CTIMP). The study involved a single visit, with no follow-up appointments planned. The study team actively monitored and reported on Adverse Events (AEs) including those classified as serious related or serious unexpected events as appropriate. An adverse event was considered to be any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment.

In the PRO/FUR/002 study, 100% of paediatric participants who took the furosemide ODTs swallowed their whole dose with zero refusals/spit-outs and 100% of parents (and participants who could respond) said they would give/take this formulation again.

2.4.5.1. Adverse events

Two adverse events occurred as displayed in Table 13 and were reported to the Chief Investigator; however, they were not considered to be related to the study intervention.

Table 13 Overview of ADRs

Study ID	Date of Birth	AE/ AR	Description of Event	Onset Date	Date Resolved	Date Reported
CHAF-GI-13	10/09/2024	AE	Coughing episodes during the administration of ODT{s) in CHAFfinch study visit on 30.11.2024. Reported to Chief Investigator (CI). Deemed to be not related to study drug / non-clinically significant event.	02.11.2024	02.11.2024	13.12.2024
CHAF-NEO-14	02/11/2024	AE	Hiccups/ gagging episode with elevated heart rate during the administration of ODT(s) in CHAFfinch study visit on 03.12.2024. Reported to Chief Investigator (Cl). Deemed to be not related to study drug / non-clinically significant event.	30.11.2024	30.11.2024	10.01.2025

2.4.5.2. Serious adverse event/deaths/other significant events

None

2.4.5.3. Laboratory findings

None

2.4.5.4. In vitro biomarker test for patient selection for safety

Not applicable

2.4.5.5. Safety in special populations

Furosemide is already licenced in all paediatric age ranges and has well established use in this population. The Interactive Drug Analysis Profile (iDAP) displays an overview of all UK spontaneous suspected Adverse Drug Reactions (ADRs) reported through the Yellow Card Scheme (MHRA, 2025). Table 2.5-15 lists the 124 adverse drug reactions for furosemide products in the UK in paediatrics reported via the Yellow Card Scheme since 1963.

A pilot study of 42 female children aged 8 to 18 years evaluating if low dose furosemide plus IV fluid administration resulted in faster bladder filling time in comparison to IV fluid administration alone in females with suspected ovarian torsion noted no adverse events (Jersey et al., 2024).

Infants

Furosemide is the most used diuretic in neonatal intensive care units (Pediatric Trials Network, 2024). The safety of furosemide in 80 pre-term infants at risk of bronchopulmonary dysplasia was evaluated in a randomized controlled trial in 17 centres (American Pediatric Society, 2022) and found that in preterm infants

at high risk for bronchopulmonary dysplasia, adverse events occurred in nearly all infants regardless of treatment group. Furosemide increased the risk of electrolyte adverse events. There was no difference in hearing loss, nephrocalcinosis, or bronchopulmonary dysplasia/death. The data from this study has informed a FDA label change for furosemide which now includes recommendations for dosing premature infants with the diuretic (Pediatric Trials Network, 2024).

Nephrocalcinosis, a consequence of the high urinary calcium excretion rate and an alkaline urine pH caused by furosemide, is a well-known risk of long-term therapy, particularly in infants. Saarela and colleagues (1999) compared the rate of nephrocalcinosis in 36 term infants (mean age 2.9 months) with cardiac failure receiving furosemide versus an age-matched control group. Patients were followed for up to 2 years or until resolution of the calcifications was established by ultrasound. Nephrocalcinosis was observed in 5/36 (14%) of the furosemide group, but none of the controls (p=0.03). Within the furosemide group, the patients with nephrocalcinosis had received a higher average daily dose than those who did not develop calcifications (1.3±0.4 mg/kg/day versus 1.0±0.6 mg/kg/day, p=0.01). As anticipated, urinary calcium was significantly higher in the furosemide group, 1.56 mmol/L compared to 0.82 mmol/L in the controls (p=0.005). Nephrocalcinosis resolved in three of the patients by the end of the study, but two had persistent calcifications at 2 years of age. The authors recommend renal ultrasonography to evaluate for nephrocalcinosis within the first several months of long-term furosemide therapy in infants and consideration of alternative diuretic regimens in those with evidence of calcifications.

Luciani et al. (1997) assessed and compared the safety and efficacy of continuous versus intermittent intravenous furosemide in patients less than 6 months of age. The study concluded that commonly used doses of both intermittent and continuous intravenous furosemide infusion can be safely administered to critically ill neonates and infants as early as 6 hours after operation.

Other Special Patient Populations

As written in the reference product SmPC, careful monitoring of furosemide is also required in:

- Hypotensive patients
- Patients who are at particular risk of a pronounced decrease in blood pressure, for example patients with significant stenoses of the coronary arteries or the blood vessels supplying the brain.
- Patients with manifest or latent diabetes mellitus.
- Patients with gout.
- Patients with hepatorenal syndrome, i.e., with functional renal failure associated with severe liver disease.
- Patients with hypoproteinaemia, associated for example with nephrotic syndrome (the effect of furosemide may be weakened and its ototoxicity potentiated). Careful dose titration is required.
- Premature infants (possible development of nephrocalcinosis/nephrolithiasis; renal function must be monitored and a renal ultrasound must be performed).

Symptomatic hypotension resulting in dizziness, fainting or unconsciousness may occur in patients treated with furosemide, particularly in the elderly, patients taking other medications that may cause hypotension and patients with other medical conditions that pose a risk of hypotension.

Table 14 Furosemide ADRs reported via the Yellow Card Scheme between 1963-2024 in patients aged 0-19 years (MHRA, 2025)

System Organ Class	Single active constituent		Multiple active constituents		Total reactions	
	All	Fatal	All	Fatal	All	Fatal
Blood and lymphatic system disorders	8	0	0	0	8	0
Cardiac disorders	4	0	0	0	4	0
Congenital, familial and genetic disorders	0	0	0	0	0	0
Ear and labyrinth disorders	0	0	0	0	0	0
Endocrine disorders	0	0	0	0	0	0
Eye disorders	0	0	0	0	0	0
Gastrointestinal disorders	9	0	0	0	9	0
General disorders and administration site conditions	16	1	0	0	16	1
Hepatobiliary disorders	3	1	0	0	3	1
Immune system disorders	1	0	0	0	1	0
Infections and infestations	1	0	0	0	1	0
Injury, poisoning and procedural complications	11	1	0	0	11	1
Investigations	10	0	0	0	10	0
Metabolism and nutrition disorders	14	0	0	0	14	0
Musculoskeletal and connective tissue disorders	0	0	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	0	0
Nervous system disorders	13	1	0	0	13	1
Pregnancy, puerperium and perinatal conditions	0	0	0	0	0	0
Product issues	0	0	0	0	0	0
Psychiatric disorders	6	0	0	0	6	0
Renal and urinary disorders	3	0	0	0	3	0
Reproductive system and breast disorders	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	8	0	0	0	8	0
Skin and subcutaneous tissue disorders	14	0	0	0	14	0
Social circumstances	0	0	0	0	0	0
Surgical and medical procedures	0	0	0	0	0	0
Vascular disorders	3	0	0	0	3	0
Total reactions	124	4	0	0	124	4

2.4.5.6. Immunological events

None

2.4.5.7. Safety related to drug-drug interactions and other interactions

None

2.4.5.8. Discontinuation due to adverse events

None

2.4.6. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.7. Discussion on clinical safety

The data provided as review of published literature clearly show that furosemide is well-known active substance and thus the safety profile of Bopediat should be mainly viewed in the context of the new pharmaceutical formulation-ODT. According to the PRO/FUR/002 study, the swallowability and palatability is not as positive as the acceptability (analysed in the patient and care-giver questionnaire), however, the concerns regarding the overall compliance to this new formulation were resolved by the Applicant.

Overall, the new pharmaceutical formulation has potential to improve current low availability of paediatric appropriate medicinal products containing furosemide. Currently, only oral solution (containing ethanol, liquid maltitol and ethylengylcol as colourant) and immediate release tablets are available to the paediatric population in the EU. Furthermore, off-label use of inappropriate pharmaceutical formulations is frequent in paediatric population who is treated with furosemide due to cardiovascular conditions (as per the indication wording of the 4.1 section of the SmPC of reference medicinal product Lasilix Faible 20 mg) (Pasquali SK, 2008, Jobe AH, 2019).

The two strengths 1 mg ODT and 5 mg ODT (as originally proposed) might cover the dosing requirements for the youngest paediatric patients (under the age of 2 years and preschool children below the age of 6 years) as required, i.e. 1-2 mg/kg. The method of administration (SmPC Section 4.2) was described and method of administration for neonates was included as well. However, as the MAA for 1 mg strength has been withdrawn, the applicant amended the posology to reflect the availability of 5 mg strength only.

2.4.8. Conclusions on clinical aspects

The results of study PRO/FUR/001 with 5 mg ODT formulation cannot be extrapolated to other strengths 1 mg ODT, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1 and ICH M13A Guideline on bioequivalence for immediate-release solid oral dosage forms", (EMA/CHMP/ICH/953493/2022).

To conclude, from the clinical point of view if criteria for a biowaiver are not met, the clinical data on efficacy and safety of the reference medicinal product (Lasilix Faible 20 mg) can be extrapolated to the Bopediat 5 mg ODT strength only. Bopediat 5 mg ODT is approvable from the clinical point of view.

2.5. Risk Management Plan

2.5.1. Safety concerns

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP version 0.4, signed 25.02.2026:

The Applicant has removed all proposed safety concerns from the Summary of safety concerns, i.e. the Summary of safety concerns was left empty.

Considering the well-established profile of furosemide, empty summary of safety concerns is considered adequate.

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

2.5.2. Pharmacovigilance plan

Routine pharmacovigilance activities will be performed. The potential risks are described both in the summary of product characteristics and in the patient information leaflet of Bopediat 5 mg orodispersible tablets.

The reference product has not imposed additional pharmacovigilance activities. Thus, the applicant did not propose any additional pharmacovigilance activities.

Furosemide has a well-established benefit-risk profile. The clinical and post marketing experience with medicinal products containing furosemide is considered to have demonstrated the therapeutic value in the proposed indications, with an acceptable safety profile in a wide range of populations, including the paediatric. The safety concerns associated with furosemide use are well characterised. In this setting, provided that bioequivalence with the reference medicinal product is demonstrated, routine pharmacovigilance activities are considered sufficient.

The PRAC, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

2.5.3. Risk minimisation measures

The reference product does not have additional risk minimisation activities. In the setting of a hybrid product application, provided that bioequivalence with the reference medicinal product is demonstrated, no additional risk minimisation activities are warranted.

The PRAC having considered the data submitted was of the opinion that:

In line with the reference product the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 0.4 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.6.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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.

3. Benefit-risk balance

This application concerns a hybrid version of furosemide orodispersible tablet. The reference medicinal product Lasilix Faible 20 mg tablets is indicated for oedema of cardiac or renal origin, oedema of hepatic origin (most often in combination with a potassium-sparing diuretic), hypertension in patients with chronic kidney disease, if thiazide diuretics are contraindicated (where the creatinine clearance is less than 30 mL/min).

No non-clinical studies have been provided for this application and except for ERA, for which a post-authorisation commitment was provided. The non-clinical dossier is considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety (apart from the acceptability study PRO/FUR/002) of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature and reference medicinal product Lasilix Faible 20 mg tablets was considered sufficient.

The bioequivalence study forms the pivotal basis with an open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, comparative bioavailability design. There was Bopediat (Proveca Pharma Limited, Ireland) containing furosemide 5 mg administered as 4 x 5 mg ODT tablets compared to 20 mg Lasilix Faible 20 mg (Sanofi Winthrop Industrie) containing furosemide 20 mg administered as 1 tablet to normal, healthy, adult human subjects under fasting conditions.

The study design is considered adequate to evaluate the bioequivalence of 5 mg strength of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The details of the analytical and validation method were provided. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Bopediat (4x5 mg ODT) met the protocol-defined criteria for bioequivalence when compared with the Lasilix Faible 20 mg tablet. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-∞, and Cmax were all contained within the protocol-defined acceptance range of the range, e.g. 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated in the bioequivalence study PRO/FUR/001.

Overall, the new pharmaceutical formulation 5 mg ODT has potential to improve current low availability of paediatric appropriate medicinal products containing furosemide. Currently, only oral solution (containing ethanol, liquid maltitol and ethylene glycol as colourant) and immediate release tablets are available to the paediatric population in the EU. Furthermore, off-label use of inappropriate pharmaceutical formulations is frequent in paediatric population who is treated with furosemide due to cardiovascular conditions (as per the indication wording of the 4.1 section of the SmPC of reference medicinal product Lasilix Faible 20 mg) (Pasquali SK, 2008, Jobe AH, 2019).

The application for Bopediat 5 mg orodispersible tablets is approvable.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Bopediat is favourable in the following indication:

Bopediat is indicated in children from birth to less than 18 years of age for the treatment of oedema of cardiac or renal origin, oedema of hepatic origin, and hypertension in patients with chronic kidney disease.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- ***Periodic Safety Update Reports***

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- 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.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P-03I5-2023 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.