EU Risk Management Plan for BOPEDIAT 5mg orodispersible tablets (Furosemide)

RMP version to be assessed as part of this application:

RMP Version number: 0.4

Data lock point for this RMP: 20-Feb-2026

Date of final sign-off: 25-Feb-2026

Rationale for submitting an updated RMP: Not applicable

Summary of significant changes in this RMP: Not applicable

[redacted]

[redacted]

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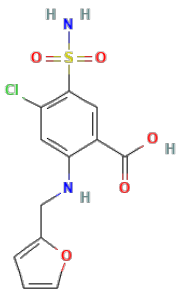
Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Furosemide
Pharmacotherapeutic group(s) (ATC Code)	This group comprises high-ceiling diuretics (loop-diuretics) ATC Code: C03C A01
Marketing Authorisation <Holder> <Applicant>	Proveca Pharma Ltd.
Medicinal products to which this RMP refers	BOPEDIAT 5 mg orodispersible tablets
Invented name(s) in the European Economic Area (EEA)	BOPEDIAT
Marketing authorisation procedure	Centralised (PUMA)
Brief description of the product	Chemical class This compound belongs to the sulphonamide-derived loop diuretics class from a chemical perspective. Furosemide is a chlorobenzoic acid that is 4-chlorobenzoic acid substituted by a (furan-2-ylmethyl)amino and a sulfamoyl group at position 2 and 5 respectively. *Chemical Formula* *C12H11ClN2O5S* *Structure* 
	Summary of mode of action Saluretic activity: At usual therapeutic doses, the main effect of furosemide is on the ascending limb of the loop of Henle, where it inhibits chloride then sodium reabsorption. It has a secondary effect on the proximal tubule and dilution segment. Furosemide increases renal blood flow to the renal cortex. This property is of particular value when

	furosemide is used in combination with beta-blockers, which can have the opposite effect. Furosemide does not affect glomerular filtration (though increased glomerular filtration has been observed under certain circumstances). The saluretic activity increases dose-dependently and persists in patients with renal failure. <u>Antihypertensive activity and other effects</u> Furosemide has a haemodynamic effect characterized by reduced pulmonary capillary pressure even before any diuresis begins, and increases the storage capacity of the venous vascular bed as shown by plethysmography (these properties have been studied particularly via the intravenous route). Furosemide acts on all forms of water/sodium retention with a dose-dependent response. It has an antihypertensive effect resulting from both sodium depletion and its haemodynamic activity.
	<u>Important information about its composition</u> Not applicable
Hyperlink to the Product Information	1.3.1.
Indication(s) in the EEA	Current: 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.
	Proposed (if applicable): N/A
Dosage in the EEA	Current: The recommended daily dose of furosemide is 1 to 2 mg/kg of body weight, in 1 dose or 2 divided doses. Dose should be adjusted according to the indication and severity of the disease. Other pharmaceutical forms are available for administration to patients who cannot receive the relevant dose with a suitable number of tablets.
	Proposed (if applicable): N/A
Pharmaceutical form(s) and strengths	Current (if applicable): 5 mg orodispersible tablets
	Proposed (if applicable):

Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

This application concerns an initial marketing authorisation for Furosemide 5 mg orodispersible tablets, involving a hybrid medicinal product, containing the active substance Furosemide, claiming essential similarity with the reference product, containing the same active substance - Lasilix Faible ® (furosemide) 20 mg Tablets, Sanofi-Aventis, France.

The report follows the general format and content described in the Guideline on Good Pharmacovigilance Practices (GVP) Module V – Risk management systems Rev. 2 (31 March 2017) and the Guidance on the format of the risk management plan (RMP) in the EU – in integrated format (EMA/164014/2018 Rev.2.0.1) accompanying GVP Module V Rev.2, from 31 October 2018.

According to the latest above cited guideline, in the Risk management plan in regards of initial marketing authorisation application involving a hybrid medicinal product, the applicant has followed the 1st scenario provided in section V.C.1.1.3. New applications under Article 10(3), i.e. "hybrid", of the GVP – Module V, according to, the RMP elements for a "hybrid" product are the same as for a generic product. Therefore, the applicant has omitted modules SI, SII, SIV, SV, SVI-SVII, while, has aligned requirements based on risk proportionality principle, addressing new data generated or differences with the "originator" product in modules SIII. The applicant has taken into consideration different pharmaceutical form of the reference product and has provided additional elaboration of bioequivalence and pharmacokinetic studies. Nevertheless, despite the pharmaceutical form of the medicinal product differs from that of the reference medicinal product, the applicant considers that this matter does not change safety concerns identified for the reference medicinal product.

Furthermore, the applicant bears in mind the Harmonisation of RMP Project (HaRP) and its proposed additional algorithm in the methodology of harmonising RMPs (CMDh/402/2019, June 2019). According to a Domain 2 (situation when there is no published RMP for the reference medicinal product, the safety concerns for the active substance should be aligned with the published ones in the List of safety concerns from the approved RMPs of active substances (CMDh_330_2015_Rev34_2021_06), last update in June 2021). The listed safety concerns for the active substance in the latest published CMDh list do not have ongoing additional pharmacovigilance activity, ongoing additional risk minimisation measure, or have essential targeted questionnaires in place.

Therefore, the applicant has decided to remove all other safety concerns so it could support the HaRP project and has additionally omitted the module SVII.

The active substance of Furosemide, is a well-known active substance with well-established efficacy and tolerability, based on a scientific literature and elaborated in details in the submitted Clinical Overview of the Dossier.

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Not applicable.

Part II: Module SII - Non-clinical part of the safety specification

Not applicable.

Part II: Module SIII - Clinical trial exposure

For this hybrid application, the applicant has submitted the results of one Bioequivalence study and one palatability study.

PRO/FUR/001 study*: Relative Bioavailability of Furosemide Administered as Orodispersible Tablets in Healthy Adults (42 healthy adult volunteers).*

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, comparative bioavailability study of furosemide ODTs 5 mg administered as 4 x 5 mg tablets i.e., 20 mg (Proveca Ltd., UK) vs Lasilix Faible 1 x 20 mg tablet (Sanofi) was 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 of paramount importance for ensuring that 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.

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

42 subjects were enrolled, with 41 being considered for statistical analysis as one subject did not complete dosing in period-II. After an overnight fast of at least 10 hours, a single oral dose of either test (20 mg administered as 4 Tablets x 5 mg) or Reference Product (20 mg administered as 1 tablet x 20 mg) was administered to the subjects in sitting posture by the trained study personnel. 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.

Plasma concentration profiles and pharmacokinetic results
Mean plasma concentration-time profiles of furosemide following treatment with furosemide 20 mg administered as Sanofi (R) 1 x 20 mg tablet and Proveca (T) 4 x 5 mg ODT are presented in Figure 2.5-1 and Figure 2.5-2. Subject (Sequence) effect was found to be statistically significant (i.e. p-value < 0.05) for ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ for Furosemide. All the other ANOVA effects were found to be statistically insignificant (i.e. p-value > 0.05) for Furosemide.

Table 2.5-1 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

[#]Tmax is represented as median (min-max) value.

Table 2.5-2 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 2.5-1 Linear time versus mean furosemide concentration profile of treatment R and T.

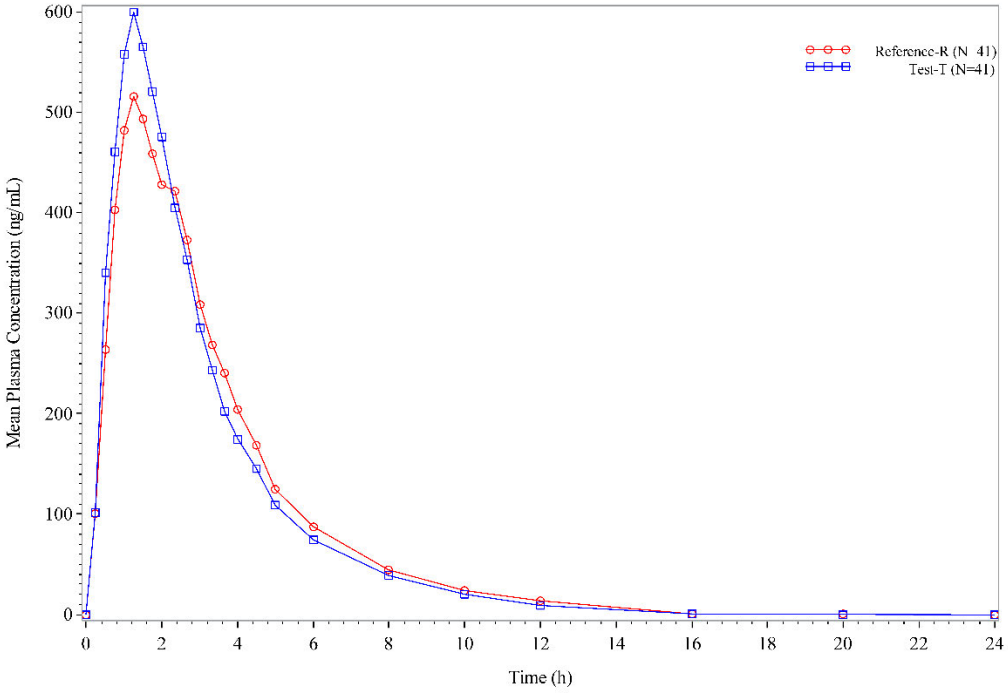
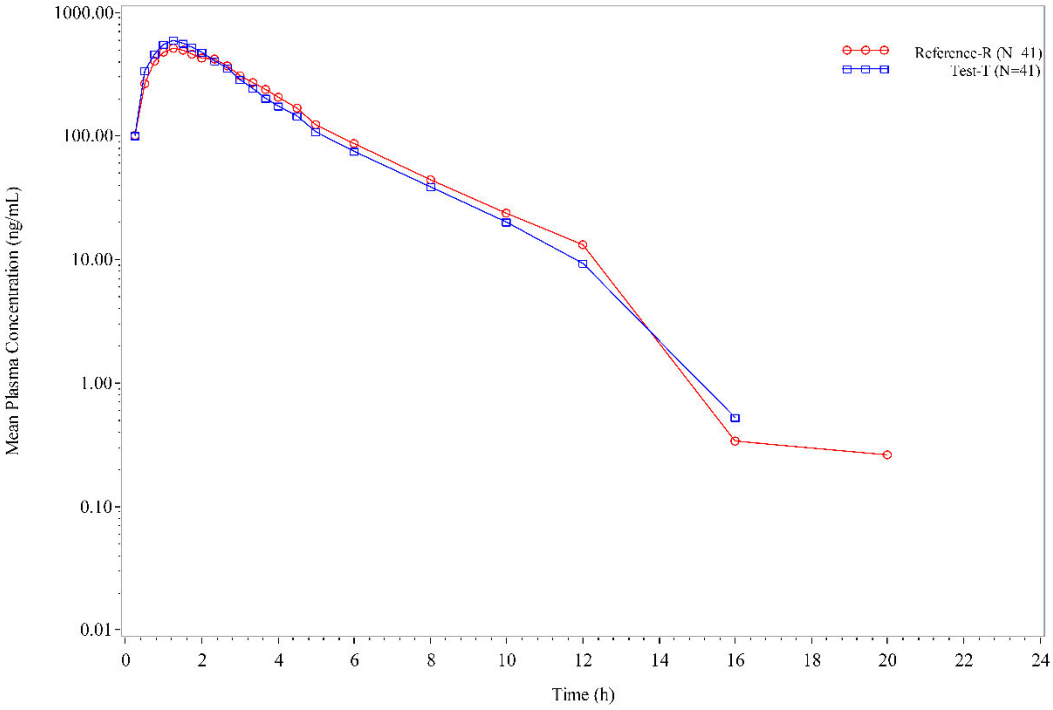


Figure 2.5-2 Semilogarithmic time versus mean furosemide concentration profile of treatment R and T.



Bridging with reference product:

The results from this study indicated that 4 x 5 mg Test Product-T when compared with 1 x 20 mg Reference Product-R meet the bioequivalence criteria (80-125%, 90% CI) with respect to Cmax and AUC0-t for Furosemide under fasting condition. The data from this study demonstrated that the test and the reference products were well tolerated. There were no adverse events reported during the conduct of the study. There were no clinically significant findings in the vital signs assessment, ECG or the laboratory tests in any of the subjects in the study.

Based on these results, it can be expected that the means by which the ODTs are administered i.e., dispersed in the mouth, will not significantly affect the bioavailability of furosemide in children.

PRO/FUR/002: *Children's Acceptability of Furosemide (CHAFfinch) Study in 10 paediatric participants.*

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.

The primary outcome measure of this study was 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. The palatability assessment was done retrospectively by two independent researchers using video footage of the participants being dosed.

The secondary outcome measure of this study was to record the number of participants who would be willing to take this new medication in the future. Parents and participants (where possible) gave feedback on whether they would be willing to give or take the medication again in the future via a questionnaire.

The exploratory outcome measure of this study was to record any participant/parent feedback received regarding the acceptability of the new ODT formulation. Parents provided additional feedback via a

questionnaire which included their opinion on the participant's willingness to take the study medication again. Participants also had the option to provide feedback if willing and able via an appropriate separate questionnaire.

100% of patients scored 1 (completely swallowed) in the swallowability assessment; there were no refusals or spit-outs. In the palatability assessment, more patients scored low (6) than neutral (4), none scored pleasant. However, despite this, in the secondary endpoint, 100% of parents said they would be willing to administer the drug to their child in the future, only one parent felt their child preferred their usual medication. Despite the low palatability scores in the primary endpoint, 90% of parents thought their child either preferred the ODT or were neutral. In the exploratory endpoint, two participants, who were old enough to complete the questionnaire themselves, also indicated that they would be happy to take the medicine in the future.

Part II: Module SIV - Populations not studied in clinical trials

Not applicable.

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Not applicable.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Not applicable.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Not applicable.

Part II: Module SV - Post-authorisation experience

Not applicable.

SV.1 Post-authorisation exposure

Not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable.

Part II: Module SVII - Identified and potential risks

The safety concerns are identified based on the list of safety concerns published on CMDh website (Doc. Ref: CMDh/330/2015, Rev.36, October 2023) for product containing Furosemide as an active substance.

The applicant considers that different pharmaceutical form of the hybrid medicinal product does not change safety concerns identified for the reference medicinal product.

SVII.1 Identification of safety concerns in the initial RMP submission

The applicant considers the following harmonised list of safety concerns as most appropriate to reflect the safety specification for the active substance Furosemide:

Summary of safety concerns	
Important identified risks	• Hypovolaemia and dehydration • Hypokalaemia and hyponatraemia • Hepatotoxicity • Blood disorders (agranulocytosis, haemolytic anaemia, thrombocytopaenia) • Severe renal disorders including renal failure • Tubulointerstitial nephritis • Severe cutaneous reaction (including Stevens-Johnson syndrome, toxic epidermal necrolysis, DRESS and AGEP) • Ototoxicity including deafness • Metabolic acidosis
Important potential risks	• Medication errors • Lack of efficacy
Missing information	• Use in pregnant and lactating women • Off-label use

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

- Hypovolaemia and dehydration
- Hypokalaemia and hyponatraemia
- Hepatotoxicity
- Blood disorders (agranulocytosis, haemolytic anaemia, thrombocytopaenia)
- Severe renal disorders including renal failure
- Tubulointerstitial nephritis
- Severe cutaneous reaction (including Stevens-Johnson syndrome toxic epidermal necrolysis, DRESS and AGEP)
- Ototoxicity including deafness
- Medication errors
- Lack of efficacy
- Use in pregnant and lactating women

- Off label use

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Not applicable.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Not applicable.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

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

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

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 for BOPEDIAT 5 mg orodispersible tablets.

The reference product has not imposed additional pharmacovigilance activities. Thus, no additional pharmacovigilance activities will be performed.

III.2 Additional pharmacovigilance activities

Not Applicable.

III.3 Summary Table of additional Pharmacovigilance activities

Not Applicable.

Part IV: Plans for post-authorisation efficacy studies

Not Applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

Not applicable.

V.2. Additional Risk Minimisation Measures

Not applicable.

V.3 Summary of risk minimisation measures

Not applicable.

Part VI: Summary of the risk management plan

Summary of risk management plan for BOPEDIAT 5 mg orodispersible tablets (Furosemide)

This summary of the RMP for BOPEDIAT 5 mg orodispersible tablets should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of BOPEDIAT 5 mg orodispersible tablets RMP.

I. The medicine and what it is used for

BOPEDIAT 5 mg orodispersible tablets is authorised for the treatment of oedema of cardiac or renal origin, oedema of hepatic origin, and hypertension in patients with chronic kidney disease in children from birth to less than 18 years.

It contains furosemide as the active substance and it is given by oral administration to be placed on the tongue or buccal cavity and allowed to disperse.

Further information about the evaluation of BOPEDIAT 5 mg orodispersible tablets benefits can be found in the BOPEDIAT 5 mg orodispersible tablets EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of BOPEDIAT 5 mg orodispersible tablets, together with measures to minimise such risks and the proposed studies for learning more about BOPEDIAT 5 mg orodispersible tablets risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so as to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of BOPEDIAT 5 mg orodispersible tablets is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of BOPEDIAT 5 mg orodispersible tablets are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of BOPEDIAT 5 mg orodispersible tablets. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

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

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of BOPEDIAT 5 mg orodispersible tablets.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for BOPEDIAT 5 mg orodispersible tablets.

Part VII: Annexes

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[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

[redacted]

[redacted]

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

[redacted]

[redacted]

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[redacted]	[redacted]	[redacted]
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