Medicines Evaluation Board

Public Assessment Report
Scientific discussion

Furosemide Teva 125 mg, 250 mg and 500 mg, tablets (furosemide)

NL/H/6050/001-003/DC

Date: 25 September 2026

This module reflects the scientific discussion for the approval of Furosemide Teva 125 mg, 250 mg and 500 mg, tablets. The procedure was finalised on 22 October 2025. For information on changes after this date, please refer to section 'steps taken after finalisation' at the end of this PAR.

Table of contents

I. INTRODUCTION 4
II. EXECUTIVE SUMMARY 4
II.1. Rationale for the product 4
II.2. About the product 4
II.3. General comments on the application 4
II.4. General comments on compliance with GMP, GLP, GCP and agreed ethical principles. 4
III. QUALITY ASPECTS 5
III.1. Introduction 5
III.2. Active Substance 6
III.3. Medicinal Product 6
III.4. Discussion on chemical, pharmaceutical and biological aspects 8
IV. NON-CLINICAL ASPECTS 8
IV.1. Introduction 8
IV.2. Ecotoxicity/environmental risk assessment (ERA) 8
IV.3. Discussion on the non-clinical aspects 8
V. CLINICAL ASPECTS 8
V.1. Introduction 8
V.2. Pharmacokinetics 8
V.3. Pharmacodynamics 11
V.4. Clinical efficacy 12
V.5. Clinical safety 13
V.6. Summary Pharmacovigilance system 13
V.7. Risk Management Plan 13
V.8. Discussion on the clinical aspects 14
VI. USER CONSULTATION 14
VII. POST-APPROVAL COMMITMENTS (PAC's) 14
VIII. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION 14
IX. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION 15
IX.1. List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC 15
IX.2. List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC 15

List of abbreviations

AE	Adverse Event
AI	Acceptable Intake
ANOVA	Analysis of Variance
BCS	Biopharmaceutics Classification System (-based biowaiver)
BE	Bioequivalence
CBG /MEB	College ter Beoordeling van Geneesmiddelen / The Medicines Evaluation Board
CEP	Certificate of Suitability of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State(s)
DCP	Decentralised Procedure
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ERP	European Reference Product
GFR	Glomerular Filtration Rate
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
LALA	Locally applied, locally acting products
MAH	Marketing Authorisation Holder
PAR	Public Assessment Report
PD	Pharmacodynamics
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PL	Package Leaflet
PSURs	Periodic safety update reports
QC	Quality control
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
USP/NF	United States Pharmacopoeia/National Formulary

Note: *Not all abbreviations may apply for this PAR.*

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Furosemide Teva 125 mg, 250 mg and 500 mg, tablets, from Teva B.V.

The product is indicated in adult patients with oedema and severely reduced glomerular filtration (glomerular filtration rate (GFR) < 20 ml/min).

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1. Rationale for the product

The marketing authorisation application concerns a mixed Article 10(1) generic and 10(3) hybrid application of Directive 2001/83/EC. The generic application involves the 500 mg strength. The hybrid application involves both the 125 mg and 250 mg strengths as the reference product is only registered in the 500 mg strength.

To demonstrate bioequivalence with the reference medicinal product, the MAH has submitted data on two bioequivalence studies and has requested a biowaiver. See Section V. Clinical aspects.

In this decentralised procedure the reference medicinal product is the European Reference Product (ERP) Lasix 500, 500 mg tablets, which has been authorised by Sanofi B.V. in The Netherlands via a national procedure, NL License number RVG 15018, since 20 November 1991.

This application has been assessed with The Netherlands as Reference Member State (RMS) and Bulgaria (125 mg and 250 mg), Czechia (125 mg and 250 mg), Denmark (250 mg and 500 mg), Germany (all strengths), France (500 mg), Italy (500 mg), Slovakia (125 mg and 250 mg) and Sweden (500 mg) as concerned Member States (CMS).

II.2. About the product

Pharmaco-therapeutic group (ATC Code): C03CA01
Dispensing status: Prescription only

II.3. General comments on the application

N.A.

II.4. General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

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

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

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the medicinal product and batch release situated in the EU.

GCP
Based on the data and documents submitted, the RMS has been assured that the studies were conducted and reported in compliance with GCP: a GCP statement and audit certificate(s) were provided; monitoring report(s) and recent inspection(s) by competent authorities identified no concerns relevant to the study; and, where conducted outside the EU, compliance with the ethical requirements of EU legislation (Directive 2001/20/EC or Regulation EU No. 536/2014, as relevant) was confirmed.

III. QUALITY ASPECTS

III.1. Introduction

Furosemide Teva is a tablet. Each tablet contains 125 mg, 250 mg or 500 mg of furosemide as active substance. The tablets of the different strengths can be distinguished by their size and break lines and are as follows:

125 mg strength
White or almost white, round, biconvex tablets, with a break line on one side, the other side is plain. Diameter: approx. 9 mm.

250 mg strength
White or almost white, round, biconvex tablets, with two crossed break lines on one side of the tablet, the other side is plain. Diameter: approx. 11 mm.

500 mg strength
White or almost white, round, biconvex tablets, with two crossed break lines on one side of the tablet, the other side is plain. Diameter: approx. 14 mm.

The tablet can be divided into equal doses.

The excipients are: microcrystalline cellulose (E460), lactose monohydrate, povidone K90 (E1201), sodium starch glycolate Type A and magnesium stearate (E470b).

The three tablet strengths are dose proportional.

The tablets are either packed in (unit dose) blisters made of polyvinyl chloride and aluminium (PVC-Alu), or in high-density polyethylene (HDPE) bottles with a polypropylene (PP) cap and aluminium seal.

III.2. Active Substance

The structure of the active substance, furosemide, has been adequately proven and its physico-chemical properties are sufficiently described. Furosemide is an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white crystalline powder, practically insoluble in water, soluble in acetone, sparingly soluble in ethanol (96%) and practically insoluble in methylene chloride. It dissolves in dilute solutions of alkali hydroxides. Furosemide exhibits polymorphism; for this product, polymorphic form I is consistently produced.

Manufacturing process
The manufacture of the active substance has been adequately described. The used starting materials, solvents and reagents are considered acceptable. Adequate tests and acceptable specifications have been adopted for these.

Quality control of the active substance
The active substance specification includes relevant tests and the limits for impurities and degradation products have been justified in accordance with the applicable ICH Guidelines for impurities in new Drug Substances. The analytical methods applied are suitably described and non-compendial methods have adequately been validated. The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur., with an additional EDTA-requirement according to the CEP and an additional in-house particle size distribution. Batch analytical data demonstrating compliance with this specification have been provided for three batches by the drug product manufacturer and three batches by the substance manufacturer.

Stability of the active substance
The active substance is stable for 60 months when stored under the stated conditions. This aspect has been evaluated within the scope of the CEP procedure by the EDQM and the conclusion is taken from the CEP.

III.3. Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of the excipients is justified, and their functions are explained. Relevant development data have been provided, including formulation and manufacturing process studies addressing binder and disintegrant effects, scale-up, and compression parameters. Risks related to critical process steps have been identified and mostly mitigated. Further verification will be performed during pivotal batches. The pharmaceutical development of the product has been adequately performed.

Comparative dissolution studies in support of the BE study have been performed at three pHs (0.1N HCl, acetate buffer pH 4.5, and phosphate buffer pH 6.8). Supporting data have been provided to demonstrate that the tablets can be split into equal halves and quarters.

Manufacturing process
The manufacturing process has been sufficiently described and critical steps identified. The manufacturing process has been validated according to relevant European/ICH guidelines.
The product is manufactured using conventional manufacturing techniques.

Process validation data on the product have been presented for two minimum commercial scale batches in accordance with the relevant European guidelines. Process validation for full scale batches will be performed post authorisation.

Control of excipients
The excipients comply with the current version of the Ph.Eur. monograph. Additional critical functionality-related characteristics have been controlled. These specifications are acceptable.

Quality control of the medicinal product
The medicinal product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity, uniformity of dosage units, dissolution, assay, impurities and microbiological quality. The release and shelf-life tests and limits are identical for all test parameters. Limits in the specification have been justified and are considered appropriate for the adequate quality control of the product.

An adequate risk evaluation report on nitrosamines has been submitted. Appropriate routine control with acceptable limits for nitrosamine impurities are performed on the medicinal product.

Satisfactory validation data for the non-compendial analytical methods have been provided. Batch analytical data on two pilot scale batches per strength from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability of the medicinal product
Stability data on the product have been provided for two production scaled batches of 125 mg and 250 mg and eight production scaled batches of 500 mg stored at 25°C/ 60% RH (36 months) and 40°C/75% RH (6 months). The stability was tested in accordance with the ICH stability guideline. Photostability studies were performed in accordance with ICH recommendations. The results showed that the product is not stable when exposed to light. Based on the data submitted, a shelf life of three years was granted. The labelled storage conditions are: '*Store in the original package in order to protect from light. Keep blisters in the outer carton*."

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM for lactose monohydrate have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

III.4. Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the Member States consider that Furosemide Teva has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and medicinal product.

IV. NON-CLINICAL ASPECTS

IV.1. Introduction

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

IV.2. Ecotoxicity/environmental risk assessment (ERA)

At the time of start of this application, before 1 September 2024, the revised ERA guideline (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*) was not yet applicable. Then the conclusion for this medicinal product was: since Furosemide Teva is intended for (generic/hybrid) substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

IV.3. Discussion on the non-clinical aspects

This product is a mixed generic/hybrid formulation of Lasix 500 which is available on the European market. Reference was made to the preclinical data obtained with the reference medicinal product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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. Therefore, the Member States agreed that no further non-clinical studies are required.

V. CLINICAL ASPECTS

V.1. Introduction

Furosemide is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The Member States agreed that no further clinical studies are required, besides the two bioequivalence studies discussed below. Bioequivalence has been investigated in line with the EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**).

V.2. Pharmacokinetics

To support the application, the MAH has submitted two bioequivalence studies comparing the pharmacokinetic profiles of the test product Furosemide Teva 500 mg tablets (Teva B.V., the

Netherlands) and the reference medicinal product Lasix 500 mg tablets (Sanofi S.R.I), obtained from the German market. A biowaiver was requested for the lower strengths of 125 mg and 250 mg. The formula and manufacturing process of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

According to the EMA bioequivalence guideline, the following general requirements must be met where a waiver for additional strength is claimed:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The requirements a-d were met. Comparative *in vitro* dissolution data of the 125 mg and 250 mg strengths versus the 500 mg biobatch were provided in 0.1N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8 and similarity was demonstrated.

The lower limit of the 90% confidence interval of the expected f_2 was at least 50 in all media. An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar. However, as the relative standard deviations were above 20% at early time points (up to 10 minutes) and/or above 10% at later time points, the preconditions for the f_2 calculation were not fulfilled and similarity was assessed by bootstrapping. The reported bootstrap results for the 250 mg and 125 mg strengths versus the 500 mg strength were all above 50 in all media.

Based on these data, a biowaiver was granted for the 125 mg and 250 mg strengths.

Bioequivalence pivotal studies FMS-BESD-04-TVP/22 and FMS-BESD-06-RPM/23

Study 1: FMS-BESD-04-TVP/22 (fasted, pivotal)

Design

A single-dose, randomised, open label, two-treatment, two-period, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 60 healthy male subjects, aged 18-45 years. Each subject received a single dose (500 mg) of one of the two furosemide formulations. The tablet was orally administered with 240 mL water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 7 days.

The plasma concentration time curve was used to assess the rate and extent of absorption. Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 7, 8, 10, 12 and 16 hours after administration of the products.

The SmPC recommends administering the product orally. The tablets should be swallowed without chewing with plenty of liquid and on an empty stomach. In line with this recommendation, both bioequivalence studies were performed under fasting conditions.

The design of the study was considered acceptable as according to the SmPC furosemide may be administered without reference to food intake. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** Note for Guidance on the investigation of bioavailability and bioequivalence.

Bioanalytical/statistical methods
The bioanalytical method has been adequately validated according to current guidelines (ICH M10 and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
60 Subjects enrolled in the study. Four subjects discontinued the study: two for personal reasons, one due to a positive alcohol test at check-in for Period II, and one due to an adverse event (vomiting) after dosing in Period I. A total of 56 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of furosemide, 500 mg under fasted conditions.

Treatment N=56	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	18611.734 ± 7606.179	19858.350 ± 7717.192	6504.218 ± 3308.641	1.67 (0.50 - 5.00)
Reference	20401.813 ± 8051.461	21721.063 ± 8012.226	7204.418 ± 3759.070	1.71 (0.50 – 4.00)
***Ratio (90% CI)**	91.46 (83.22 - 100.51)	91.49 (83.59 - 100.14)	90.28 (79.25 - 102.84)	--

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 16 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval
*	Back-transformed from ln-transformed least-squares mean values

Study 2: FMS-BESD-06-RPM/23 (fasted, pivotal repeat)
Design
A single-dose, randomised, open label, two-treatment, four-period, two-sequence, fully replicated crossover bioequivalence study was carried out under fasted conditions in 50 healthy male subjects, aged number from 18-45 years. Each subject received a single dose (500 mg) of one of the two furosemide formulations. The tablet was orally administered with 240 mL water after a fasting period of at least 10 hours. There were four dosing periods, separated by a washout period of 7 days.

The plasma concentration time curve was used to assess the rate and extent of absorption. Blood samples were collected pre-dose and at 0.25, 0.50, 0.75, 1, 1.25, 1.50, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 7, 8, 10, 12 and 16 hours after administration of the products.

The SmPC recommends administering the product orally. The tablets should be swallowed without chewing with plenty of liquid and on an empty stomach. In line with this recommendation, both bioequivalence studies were performed under fasting conditions.

The design of the study was considered acceptable as according to the SmPC furosemide may be administered without reference to food intake. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** Note for Guidance on the investigation of bioavailability and bioequivalence.

Bioanalytical/statistical methods
The bioanalytical method has been adequately validated according to current guidelines (ICH M10 and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Three subjects discontinued the study: two for personal reasons and one who received counteractive medication due to an adverse event. A total of 49 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of furosemide, 500 mg under fasted conditions.

Treatment N=49	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	30139.7 ± 11718.3	31704.7 ± 11656.7	9259.2 ± 4374.2	1.50 (0.75 - 4.00)
Reference	29962.6 ± 11407.3	31649.2 ± 11415.2	9625.0 ± 4333.7	1.50 (0.50 - 6.00)
***Ratio (90% CI)**	97.64 (90.35 - 105.52)	97.54 (90.69 - 104.92)	92.92 (85.68 - 100.77)	--

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 16 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval
*	Back-transformed from ln-transformed least-squares mean values

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated for C_{max} in study 1 marginally failed to meet the bioequivalence criteria due to high intra-subject variability. In addition, a fully replicate repeat bioequivalence study 2 has been conducted in which the AUC_{0-t} and C_{max} ratios (90% CI) were within the acceptance range of 80.00-125.00%. Based on the totality of evidence, Furosemide Teva is considered bioequivalent with Lasix 500 under fasted conditions.

As a biowaiver has been granted, the results of the 500 mg formulation strength can be extrapolated to the 125 mg and 250 mg strengths, in accordance with the conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **.

V.3. Pharmacodynamics

Furosemide is a potent, short- and rapid-acting loop diuretic. It inhibits sodium, chloride and potassium re-absorption in the ascending limb of the loop of Henle by blocking the Na+/2Cl/K+ transporter. Fractional sodium excretion may thus reach 35% of glomerular sodium filtration. As a result of the increased sodium excretion, urine secretion and distal tubular potassium secretion are augmented secondary to osmotic water movement. Calcium and magnesium excretion are similarly increased. Uric acid excretion may be reduced and the acid base balance disrupted towards metabolic alkalosis in parallel with these electrolyte losses.

The MAH provided published scientific literature on clinical pharmacodynamics (publication years 1984 to 2004); no new clinical pharmacodynamic data were submitted. The provided literature supports the pharmacodynamic data proposed in section 5.1 of the SmPC.

V.4. Clinical efficacy

No new efficacy studies were performed. The MAH provided a clinical overview of several published scientific papers on open label clinical studies and placebo-controlled randomised clinical studies to support the efficacy of Furosemide Teva tablets 125 mg, 250 mg and 500 mg.

Regarding nephrotic syndrome, congestive heart failure and renal insufficiency (glomerular filtration rate (GFR) < 20 ml/min with residual diuresis still present), the MAH provided several studies, supporting the use of furosemide in high doses within these therapeutic indications.
Although the presented data support remains marginal, since the papers show generally small studies, mainly not placebo-controlled, and mostly from earlier times and from studies without survival data on furosemide use, these data can support inclusion of the indication ”the use in patients with severely reduced glomerular filtration, which can be in nephrotic syndrome and insufficient elimination of oedema fluid at doses up to 120 mg furosemide per day, which can be in in congestive heart failure and insufficient response to the usual dose of standard medicines, to eliminate oedema fluid, and which can be in renal insufficiency (glomerular filtration rate (GFR) < 20 ml/min), with residual diuresis still present” with doses of 125 up to 500 mg.

Further, data in peritoneal dialysis and haemodialysis patients showed a positive impact of high doses furosemide. A pharmacodynamic study of Leclerc, et al (2019) of a 250 mg and a 500 mg dose of oral furosemide in peritoneal dialysis patients showed an increase in urinary volume significantly after the 500-mg dose, whilst the difference did not reach statistical significance after the 250 mg dose. Furthermore, the higher dose was associated with a greater increase in diuresis than the lower dose (226 ml (250 mg) vs. 522 ml (500 mg), p=0.04). The paper concluded that furosemide could be used at oral single doses reaching 500 mg in peritoneal dialysis patients requiring greater volume control.
The early paper of Van Olden, et al (1992) looked into the effects of daily administration of 250-2.000 mg furosemide in patients on haemodialysis who still had residual renal function. In the short study, the authors observed an increase in the 24-hour volume excretion with a median of 109% ($p<0.005$). In the long-term study (year), a marked initial rise in diuresis and electrolyte excretion was found.
In an open label, single-arm, 18-week, dose titration pilot study (Flythe, et al (2022)) of oral furosemide (maximum dose 320 mg/day) among patients receiving maintenance haemodialysis who reported at least 1 cup of urine output per day, furosemide was generally safe and well tolerated, but only one-third of participants met the efficacy definition at week 5. The clinical importance of the efficacy findings is uncertain, which is not supportive for the indication.
Moreover, four studies on patients receiving peritoneal dialysis showed a positive effect on diuresis with the use of furosemide. It should be noted that the studies were small, not recent and did not show important survival data supporting the effect of furosemide within these indications.

In conclusion, although marginal, the efficacy data in the clinical overview is generally adequate and supports, in principle, the therapeutic indication in section 4.1 of the SmPC with the new 125 mg and 250 mg tablets:

[Product name] tablets are indicated in adult patients with oedema and severely reduced glomerular filtration (glomerular filtration rate (GFR) < 20 ml/min).

Further, the MAH has sufficiently justified the use of the 125 mg and 250 mg doses within the scientific literature in the Clinical Overview, supporting the application of the 125 and 250 mg strengths of the Furosemide Teva tablets (for example as a starting dose) within the therapeutic indication. Therefore, as these dose strengths are also used within clinical practice, and based on the provided scientific literature, the application of all the three strengths of the Furosemide Teva tablets within the claimed therapeutic indication can be supported.

The rest of the efficacy data in the SmPC is in accordance with the SmPC of ERP Lasix 500 and with the Dutch SmPC of Furosemide 500 mg Teva and the Clinical Overview.

V.5. Clinical safety

The safety data in the clinical overview is generally adequate and the provided data on adverse events (AEs), special populations and overdose is acceptable. The safety data in the SmPC is in accordance with the SmPC of Lasix and the Dutch SmPC of Furosemide 500 mg Teva.
In the bioequivalence studies, nine adverse events occurred in seven subjects in study 1 (FMS-BESD-04-TVP/22) and 79 adverse events occurred in 32 subjects in the replicate study 2 (FMS-BESD-06-RPM/23). In both studies, none of the adverse events were serious, and the subjects who experienced adverse events recovered completely before the end of the study.

V.6. Summary Pharmacovigilance system

The MAH has submitted a signed Summary of the MAH's and/or Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

V.7. Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Furosemide Teva. At the time of approval, the accepted version of the RMP was version 1.2 with sign-off date 27 August 2025.

Table 3. Summary table of safety concerns as approved in the RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The Member States agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

V.8. Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the reference medicinal Lasix 500 mg. Apart from the two bioequivalence studies, no new clinical studies were conducted. The MAH demonstrated through two pivotal bioequivalence studies that the pharmacokinetic profile of Furosemide Teva is similar to the pharmacokinetic profile of the reference product.
Risk management is adequately addressed. This current medicinal product can be used instead of the medicinal reference product. The clinical aspects of this product are approvable.

VI. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.

The test consisted of two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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.

VII. POST-APPROVAL COMMITMENTS (PACs)

Post-approval commitments: not applicable.

VIII. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Furosemide Teva 125 mg, 250 mg and 500 mg, tablets have a proven chemical-pharmaceutical quality and are mixed generic/hybrid forms of Lasix 500, 500 mg tablets. Lasix 500 is a well-known medicinal product with an established favourable efficacy and safety profile. This application is partially based on published data on the pharmacology, efficacy and safety of Lasix 500, 500 mg tablets. Bridging of the data in the literature to the current product has been adequately performed. Based on the review of the data on quality, safety and efficacy, the Benefit/Risk ratio of Furosemide Teva is considered positive.

Bioequivalence has been shown between the test and reference medicinal products, in line with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between Member States was reached during a written procedure. The Member States, based on the data submitted, considered that essential similarity has been demonstrated for Furosemide Teva with the reference medicinal product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 22 October 2025.

IX. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

IX.1. List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

N.A.

IX.2. List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

N.A

LITERATURE REFERENCES

- Flythe, J. E., Assimon, M. M., Tugman, M. J., Narendra, J. H., Singh, S. K., Jin, W., Li, Q., Bansal, N., Hostetter, T. H., & Dember, L. M. (2022). Efficacy, safety, and tolerability of oral furosemide among patients receiving hemodialysis: A pilot study. *Kidney International Reports, 7*(10), 2186–2195. https://doi.org/10.1016/j.ekir.2022.07.003
- Leclerc, S., Laurin, L.-P., Lafrance, J.-P., Lamarche, C., Ouimet, D., Paquette, F., Pichette, V., & Nadeau-Fredette, A.-C. (2019). Pharmacodynamics of 250 mg and 500 mg oral furosemide in peritoneal dialysis. *International Journal of Clinical Pharmacology and Therapeutics, 57*, 603–606. https://doi.org/10.5414/CP203594
- van Olden, R. W., van Meyel, J. J. M., & Gerlag, P. G. G. (1992). Acute and long-term effects of therapy with high-dose furosemide in chronic hemodialysis patients. *American Journal of Nephrology, 12*(5), 351–356. https://doi.org/10.1159/000168471

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
N.A.	N.A.	N.A.	N.A.	N.A.	N.A.