COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Foragen 100 mg hard modified-release capsules (nitrofurantoin)

NL/H/5601/001/DC

Date: 29 April 2025

This module reflects the scientific discussion for the approval of Foragen 100 mg modified-release capsule, hard. The procedure was finalised on 27 September 2023. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs 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
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
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Foragen 100 mg hard modified-release capsules from CNX Therapeutics Ireland Limited.

The product is indicated for: use in adults and children aged 12 years and older for treatment of acute uncomplicated lower urinary tract infections caused by nitrofurantoin sensitive microorganisms.

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

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Furabid 100 mg capsules met gereguleerde afgifte, which has been registered in the Netherlands via national procedure (RVG 15290) since 25 January 1994.

The concerned member states (CMS) involved in this procedure were Denmark, Finland, Luxembourg, Norway and Sweden.

II. QUALITY ASPECTS

II.1 Introduction

Foragen is a hard modified-release capsule with a blue opaque cap with “NTRF” debossed in white ink and a yellow opaque body.

Each hard modified-release capsule contains as active substance 100 mg of nitrofurantoin.

The excipients are:
Capsule content - talc (E 553b), maize starch, carbomers, povidone (E 1201), lactose monohydrate, sucrose, and magnesium stearate (E 470b).
Capsule shell - iron oxide yellow (E 172), iron oxide black (E 172), titanium dioxide (E 171), gelatin, and indigo carmine (E 132)
Printing ink - shellac (E 904), propylene glycol (E 1520), strong ammonia solution (E 527), purified water, potassium hydroxide (E 525), and titanium dioxide (E 171)

The hard modified-release capsules are packed in polyvinyl chloride-polychlorotrifluoroethylene/aluminium (PVC-PCTFE/Alu) blisters in carton boxes.

II.2 Drug Substance

The active substance is nitrofurantoin, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Two forms of the active substance are used: nitrofurantoin macrocrystals and nitrofurantoin monohydrate. The active substance is very slightly soluble in water and in ethanol (96%), and soluble in dimethylformamide. The polymorph beta of nitrofurantoin monohydrate, and polymorphic form II of nitrofurantoin macrocrystals are used.

The Active Substance Master File (ASMF) procedure is used for the active substance nitrofurantoin monohydrate. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

The CEP procedure is used for the active substance nitrofurantoin macrocrystals. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

Nitrofurantoin monohydrate

The manufacturing process consists of four steps starting from two starting materials. No class 1 solvents or heavy metal catalysts are used in the manufacturing process. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Nitrofurantoin macrocrystals

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

Nitrofurantoin monohydrate

The specification for the nitrofurantoin monohydrate is identical to the specification of the Ph. Eur. monograph for nitrofurantoin, with additional tests for limit of impurities, related substances, residual solvent and particle size distribution.

Nitrofurantoin macrocrystals
The specification for the nitrofurantoin macrocrystals is in line with the specification of the Ph. Eur. monograph for nitrofurantoin with additional tests mentioned by the CEP.

Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches per active substance form.

Stability of drug substance
Nitrofurantoin monohydrate
Stability data on the active substance have been provided for 12 batches in accordance with applicable European. Based on the data submitted, a retest period could be granted of 5 years when stored under the stated conditions.

Nitrofurantoin macrocrystals
The active substance has a retest period of 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

II.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 development of the product has been described, the choice of excipients is justified and their functions explained. The development of the nitrofurantoin microcrystal and of the nitrofurantoin monohydrate tablets used in the capsules has been described in detail. The choices of the packaging and manufacturing process are adequately justified. The manufacture and composition of the bio-batches used in BE studies is identical to the commercial product. Acceptable dissolution profiles (pH 2, 4.5 and 7.5) supportive to the BE study have been provided. The QC dissolution test method is adequately justified and its discriminatory power demonstrated.

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines. The nitrofurantoin monohydrate tablets are manufactured by a wet granulation process which consists of weighing, blending, granulation, drying and milling, final blending, and compression. The manufacturing process of the drug substance nitrofurantoin macrocrystals consists of weighing and blending. The nitrofurantoin macrocrystals final and the compressed nitrofurantoin monohydrate tablets are encapsulated using a suitable capsule filling machine. Process validation data on the product have been presented for three full scale batches in accordance with the relevant European guidelines.

Control of excipients
The same excipients are used as in the reference product. The excipients comply with the Ph.Eur. or with USP/NF except for the colourants of the capsule which comply with in-house requirements. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, uniformity of dosage units, dissolution, assay, related substances, limit of impurity, residual solvents, water content and microbial limits. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf life limits are identical, except for the limit for water content, which is tighter at release. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data three bulk batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three commercial batches stored at 25°C/ 60% RH (24 months), 30°C/ 75% RH (12 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European. Photostability studies were performed and it was concluded that the drug product is not sensitive to light. On basis of the data submitted, a shelf life was granted of 2 years. The labelled storage condition is “Do not store above 25°C”.

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 and gelatin 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.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Foragen has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Foragen is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Furabid which is available on the European market. Reference was made to the preclinical data obtained with the innovator 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

Nitrofurantoin 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, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Foragen 100 mg modified-release capsule, hard (CNX Therapeutics Ireland Limited, United States) was compared with the pharmacokinetic profile of the reference product Furabid controlled release capsules 100 mg (Amdipharm Limited, Ireland).

The choice of the reference product in the bioequivalence studies have been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Bioequivalence studies

Study 1: Nitrofurantoin 100 mg capsules under fasting conditions

Design

A single-dose, randomised, four-period, two-treatment, two-sequence, crossover, open label, four-way fully replicated bioequivalence study was carried out under fasted conditions in 60 healthy male (43) and female (17) subjects, aged 20-44 years. Each subject received a single dose (100 mg) of one of the two nitrofurantoin formulations. The tablet was orally

administered with 240 mL water after an overnight fast of at least 10 hours. There were four dosing periods, separated by a washout period washout period of 14 days between period I and period II, 7 days between period II and period III, and 9 days between period III and period IV.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 7, 8, 10, 12, 16 and 24 hours after administration of the products.

The design of the study is acceptable.

Analytical/statistical methods
The analytical method has been adequately validated 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 were enrolled in the study. One subject was discontinued in period I due to an adverse event (vomiting) Three subjects dropped out in period II only, due to personal reasons. Six subjects dropped out for period III due to personal reasons. Four subjects dropped out of period IV only, due to personal reasons. 59 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of nitrofurantoin 100 mg under fasted conditions.

Treatment N=59	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	3020.37 ± 1063.83	3047.30 ±1065.44	1109.53 ± 382.28	4.00 (1.67 – 6.00)
Reference	3034.41 ± 1205.18	3039.76 ± 1204.82	1103.15 ± 416.83	3.84 (1.00 – 5.00)
***Ratio (90% CI)**	1.03 (0.97 – 1.10)	1.03 (0.97 – 1.10)	1.04 (0.97 – 1.12)	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 2: Nitrofurantoin 100 mg capsules under fed conditions
Design
A single-dose, randomised, four-period, two-treatment, two-sequence, crossover, open label, balanced, four-way fully replicated bioequivalence study was carried out under fed conditions in 60 healthy male subjects, aged 19-43 years. Each subject received a single dose (100 mg) of one of the two nitrofurantoin formulations. The tablet was orally administered with 240 mL water after a high fat high calorie breakfast (981 total kcal, 25% carbohydrates, 15% protein

and 60% fat) after an overnight fast of at least 10.00 hours. There were four dosing periods, separated by a washout period of at least 7 days.

Blood samples were collected pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22, 24, 28 and 32 hours after administration of the products.

The design of the study is acceptable.

Nitrofurantoin is rapidly absorbed in the upper gastrointestinal tract. Intake with food or milk increases absorption. Plasma concentrations are low at therapeutic doses with peak levels usually less than 1 µg/mL.

Analytical/statistical methods
The analytical method has been adequately validated 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. One subject was discontinued in period II due to a positive urine test indicative of drug abuse. One subject did not report for check in in periods II, III and IV and was therefore discontinued. 58 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of nitrofurantoin, 100 mg under fed conditions.

Treatment N=58	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	3420.04 ± 775.01	3423.50 ± 776.59	854.09 ± 337.98	6.00 (2.00 – 22.00)
Reference	3098.94 ±760.61	3155.86 ± 740.48	732.16 ± 241.53	8.00 (2.00 – 24.00)
***Ratio (90% CI)**	1.13 (1.08 – 1.19)	1.14 (1.09 – 1.19)	1.18 (1.10 – 1.26)	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Foragen is considered bioequivalent with Furabid.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 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 Foragen.

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

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Furabid. No new clinical studies were conducted. The MAH demonstrated through two bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. 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.

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Nitrofurantoin 25mg/5ml oral suspension, UK/H/7006/001/DC. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Foragen 100 mg modified-release capsule, hard has a proven chemical-pharmaceutical quality and is a generic form of Furabid 100 mg capsules met gereguleerde afgifte. Furabid is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance 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, on the basis of the data submitted, considered that essential similarity has been demonstrated for Foragen with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 27 September 2023.

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
NL/H/5601/001/IA/003	Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location	No	14-05-2024	Approved	N/A
NL/H/5601/II/002/G	Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier • Introduction of a manufacturer of the active substance supported by an ASMF (x2)	No	15-11-2024	Approved	N/A
NL/H/5601/II/001/G	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: for an active substance, or for a starting material/reagent/intermediate used in the manufacturing process of the active substance, or for an excipient • European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/reagent/ intermediate/or excipient ○ New certificate for a starting material/reagent/ intermediate/or excipient from a new or an already approved manufacturer Change in the batch size (including batch size ranges) of the finished product • The change relates to all other pharmaceutical forms	No No	15-11-2024	Approved	N/A

	manufactured by complex manufacturing processes				
	Widening of the control limit for moisture content.; Change to in-process tests or limits applied during the manufacture of the finished product • Widening of the approved IPC limits, which may have a significant effect on overall quality of the finished product	No			
	Change to importer, batch release arrangements and quality control testing of the finished product • Replacement or addition of a manufacturer responsible for importation and/or batch release ○ Not including batch control/testing	Yes			
	Change to importer, batch release arrangements and quality control testing of the finished product • Replacement or addition of a site where batch control/testing takes place	No			
	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product • Secondary packaging site	No			
	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product • Primary packaging site	No			
	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product • Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/ immunological medicinal products, or for pharmaceutical forms	Yes			

	manufactured by complex manufacturing processes				
NL/H/5601/001/IA/004	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product • Secondary packaging site	No	17-3-2025	Approved	N/A