COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Nitrofurantoïne 50 mg and 100 mg Focus Care, hard capsules
(nitrofurantoin as macrocrystals)

NL Licence RVG: 127575

Date: 29 December 2022

This module reflects the scientific discussion for the approval of Nitrofurantoïne 50 mg and 100 mg Focus Care, hard capsules. The procedure was finalised on 4 April 2022. 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
ERA	Environmental Risk Assessment
EMA	European Medicines Agency
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Nitrofurantoïne 50 mg and 100 mg Focus Care, hard capsules, from Focus Care Pharmaceuticals B.V.

The product is indicated for diseases of the urinary tract that are caused by micro-organisms sensitive to nitrofurantoin,

- in acute uncomplicated lower urinary tract infections;
- for short-term prophylaxis in surgical procedures, transurethral interventions, catheterisation, cystoscopy and indwelling catheter;
- for long-term treatment of urinary tract infections up to 6 months; longer than 6 months only if the benefits clearly exceed the possible risks. Given the side effects, long-term therapy should be used only if no suitable alternative is available (see section 4.4 of the SmPC).

Consideration should be given to official local guidelines for the proper use of antibiotics.

A comprehensive description of the indications and posology is given in the SmPC.

This national procedure concerns a generic application claiming essential similarity with the innovator product Furadantine MC 50 mg, capsules which has been registered in the Netherlands trough a national application (NL License RVG 05748) by Amdipharm Limited, Ireland since 28 May 1969.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Nitrofurantoïne 50 mg and 100 mg Focus Care, are hard gelatin capsules. Each capsule contains as active substance 50 mg or 100 mg nitrofurantoin (in the macrocrystalline form).

The 50 mg strength is a hard gelatin capsule of size “2” with white opaque cap marked “NF 50” with red colour and white opaque body marked “NF 50” with red colour and 360 degree red colour band on cap and body containing pale yellow to yellow granular powder.

The 100 mg strength is a hard gelatin capsule of size “2” with white opaque cap marked “NF 100” with black colour and white opaque body marked “NF 100” with black colour and 360 degree black colour band on cap and body containing pale yellow to yellow granular powder.

The capsules are packet in Aluminium/PVC-PVdC blisters (10 or 20 capsules) or in white opaque round cylindrical screw type high density polyethylene (HDPE) bottles with neck and white opaque polypropylene continuous threaded closure, with a wad having an induction sealing liner (500 or 1000 capsules).

The excipients are:
Hard capsule shell and content - maize starch, talc, lactose monohydrate, titanium dioxide (E171), gelatin, water and sodium lauryl ether sulphate.
Red ink (50 mg) - shellac (E904), dehydrated alcohol (E1510), isopropyl alcohol, butyl alcohol, propylene glycol (E1520), strong ammonia solution (E527) and red iron oxide (E172).
Black ink (100 mg) - shellac (E904), dehydrated alcohol (E1510), isopropyl alcohol, butyl alcohol, propylene glycol (E1520), strong ammonia solution (E527), potassium hydroxide (E525), purified water and black iron oxide (E172).

The composition of both strengths are qualitatively the same and quantitatively dose proportional.

II.2 Drug Substance

The active substance is nitrofurantoin, an established active substance described in the European Pharmacopoeia (Ph.Eur.) and United States Pharmacopoeia (USP). The active substance are yellow crystals, very slightly soluble in water and in ethanol (96 per cent), soluble in dimethylformamide. Anhydrous nitrofurantoin polymorphs are defined form α and form β, for this product the nitrofurantoin macrocrystals (β-form) is used.

The Active Substance Master File (ASMF) procedure is used for the active substance. 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.

Manufacturing process
For the production of the active substance, nitrofurantoin normal powder is synthetised and then converted to nitrofurantoin macrocrystals through a recrystallisation step. The manufacturing process of nitrofurantoin is described and general information regarding chemicals and reaction conditions is provided. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and USP. Additional to the tests described

in the Ph.Eur. and USP, the manufacturer has included tests for a residual compound, related substances and residual solvents. Furthermore, for nitrofurantoin macrocrystals, adequate specifications were set based on batch data for the tests particle size distribution, bulk density and appearance.

Batch analytical data demonstrating compliance with this specification have been provided for several batches.

Stability of drug substance

Stability studies on nitrofurantoin have been performed by the ASMF-holder since 1991, gaining a lot of stability data and experience. Since then, the specification for active substance has been improved, e.g., additional tests for related substances and polymorphic form have been introduced. All stability data are within specification, no out of specifications results (OOS) or trends have been observed. Additionally, forced degradation studies have been performed. No stability data of nitrofurantoin (normal and macrocrystals) have been provided to confirm the re-test period of 5 years. However, taking into account the large experience with the manufacturing of nitrofurantoin and the fact that no OOS or trends have been observed, the proposed retest period of 5 years can be granted without any special storage conditions.

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. General properties of the drug substance have been described satisfactorily. Excipients have been chosen to resemble those of the originator product.

Manufacturing process

The manufacturing process of the product is a standard manufacturing process for hard capsules and it consists of sieving, blending of ingredients, encapsulation and packaging. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients

The quality of the excipients is adequately controlled and certificates of analysis were provided. Furthermore, compliance of the printing inks with EU Regulation No. 231/2012 has been confirmed.

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 (two methods), average fill mass, average mass of filled capsules, uniformity of filled capsules, disintegration time, dissolution, uniformity of dosage unit, related substances, assay, microbial

enumeration tests and water content. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life limits per strength are identical except for water content.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three batches per strength from the proposed production sites have been provided, demonstrating compliance with the specification.

The risk assessment on elemental impurities indicate that no additional monitoring is required. An acceptable risk evaluation on the presence of nitrosamine impurities in the drug product has been provided. No risk mitigation is deemed necessary.

Stability of drug product

Stability data on the product have been provided for three batches in accordance with the ICH guidelines. The batches were stored in the proposed final packing (Alu/ PVC-PVdC blister and HDPE bottle) at 25°C ± 2°C / 60% RH ± 5% RH (24 months) and 40°C ± 2°C / 75% RH ± 5% RH (6 months). All results are well within the stated shelf-life acceptance criteria. Based on the submitted stability data, a shelf life of 3 years was granted for both packaging materials, with no special storage conditions.

In-use stability studies were performed for the product packed in HDPE bottles. The same three batches packed in the HDPE bottles were stored at 25°C ± 2°C / 60% RH ± 5% RH. The results show that the product remains stable up to 90 days after first opening the bottle.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

For the excipient lactose monohydrate, scientific data and/or certificates of suitability issued by the EDQM 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 MEB considers that Nitrofurantoïne Focus Care 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 Nitrofurantoïne Focus Care is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Furadantine MC which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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. Therefore, the MEB finds 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 overview justifies why there is no need to generate additional clinical data. Therefore, the MEB finds that no further clinical studies are required.

For this generic application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Nitrofurantoïne 100 mg Focus Care, hard capsules (Focus Care Pharmaceuticals B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Furadantine MC 50 mg, capsules (Amdipharm Limited, Ireland).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing. The bioequivalence study was performed with the highest strength (100 mg) under fed conditions. A justification for a biowaiver for the additional lower strength (50 mg) was submitted and approved.

Biowaiver

Based on the acceptable bioequivalence study with the 100 mg product strength of the test and reference product, a biowaiver for additional strengths was requested for the 50 mg test product.

The biowaiver is granted according to the criteria described in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**). The submitted data show that the following criteria were met:

- Nitrofurantoïne 50 mg and 100 mg hard capsules are manufactured using the same manufacturing process
- the qualitative and quantitative composition of the Nitrofurantoïne 50 mg and 100 mg hard capsules are the same, i.e. quantitatively proportional
- the generated *in vitro* dissolution data showed that the rate and extent of drug release for test products Nitrofurantoïne 50 mg and 100 mg capsules are similar to reference product Furadantine MC 50 mg capsules in pH 1.2 HCl buffer, pH 4.5 acetate buffer, pH 6.8 and pH 7.2 phosphate buffer.

Bioequivalence studies

Design

A single-dose, randomised, balanced, two-period, two-treatment, two-sequence, crossover oral bioequivalence study was carried out under fed conditions in 35 healthy male subjects, aged 19-44 years. Each subject received a single dose (100 mg) of one of the two nitrofurantoin formulations. An overnight fasting of at least ten hours was followed by a high fat, high calorie breakfast (cheese sandwich, whole milk, plain egg omelette, chicken fry, potato fry and tomato chutney) which was consumed within the 30 minutes before dosing. The subjects were dosed with a single oral dose (1x capsule 100 mg) with 240 ± 2 mL water at room temperature. The subjects were instructed not to chew or open the capsule but to consume it whole.

There were two dosing periods, separated by a washout period of eight days.

Blood samples were collected pre-dosed (within one hour before dosing), at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 11, 12, 13, 14 and 16 hours after administration of the products in each period.

The design of the study is acceptable. Dosing under fed conditions is justified as, according to the SmPC, the product should be administered during or just after food consumption in order to improve the tolerance and bioavailability of nitrofurantoin.

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

For this study, 42 subjects were enrolled. A total of seven subjects were withdrawn, consequently 35 subjects were eligible for pharmacokinetic analysis. Three subjects were withdrawn before dosing of period 1 (one subject did not complete the breakfast before dosing and two subjects withdrew their consent), hence not dosed in any period. Four subjects were withdrawn after dosing of period 1 due to adverse events (vomiting) hence not dosed in period 02.

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

Treatment N=35	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)
Test	2413 ± 444	2467± 463	505 ± 143	4.50 (1.00 - 6.50)	1.41 ± 0.7522
Reference	2301 ± 417	2338 ± 433	447 ± 115	5.00 (2.50 - 8.00)	1.244 ± 0.4186
***Ratio (90% CI)**	1.05 (1.02 - 1.08)	--	1.12 (1.04 - 1.20)	--	--
CV (%)	7.3	--	18.7	--	--

$AUC_{0-\infty}$ 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 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study:

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Nitrofurantoïne 100 mg Focus Care is considered bioequivalent with Furadantine MC 100 mg, capsules. For Nitrofurantoïne 50 mg a biowaiver is granted according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**).

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 Nitrofurantoïne 50 mg and 100 mg Focus Care.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Hypersensitivity • Use in patients with renal impairment • Use in pregnancy and lactation • Use in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency • Use in patients with acute porphyria • Pulmonary disorders • Hepatic impairment including cholestatic jaundice and chronic active hepatitis • Peripheral neuropathy and neurological disorders • Use in patients with diabetes mellitus • Use in patients with electrolyte imbalance • Haematological disorders including anaemia • Use in patients with debilitating conditions • Use in patients with vitamin B (particularly folate) deficiency • Gastrointestinal disturbances • Drug interactions with quinolone anti-infectives, oestrogen-containing contraceptives and oral typhoid vaccine
Important potential risks	None
Missing information	None

The MEB 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 Furadantine MC 50 mg, capsules. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study 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

A user consultation with target patient groups on the package leaflet (PL) has been performed for both strengths on the basis of a bridging report making reference to Furadantine MC 50 mg, capsules, NL Licence RVG 05748 for design, layout and content. 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

Nitrofurantoïne 50 mg and 100 mg Focus Care, hard capsules have a proven chemical-pharmaceutical quality and are generic forms of Furadantine MC 50 mg and 100 mg, capsules. Furadantine 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.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Nitrofurantoïne 50 mg and 100 mg Focus Care with the reference product, and have therefore granted a marketing authorisation. Nitrofurantoïne 50 mg and 100 mg Focus Care were authorised in the Netherlands on 4 April 2022.

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
B.III.1.a.3	European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. – New certificate from a new manufacturer (replacement or addition).	No	31-5-22	Approved	N/A