COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Nitrofurantoin MC Mylan 50 mg and 100 mg, hard capsules (nitrofurantoin)

## NL/H/4849/001-002/DC

## Date: 9 March 2022

**This module reflects the scientific discussion for the approval of Nitrofurantoin MC Mylan 50 mg and 100 mg, hard capsules. The procedure was finalised on 30 April 2021. 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 |
| ICH | International Conference of Harmonisation |
| MAH | Marketing Authorisation Holder |
| OOS | Out of Specification |
| Ph.Eur. | European Pharmacopoeia |
| PL | Package Leaflet |
| RH | Relative Humidity |
| RMP | Risk Management Plan |
| SmPC | Summary of Product Characteristics |
| TSE | Transmissible Spongiform Encephalopathy |
| USP | United States Pharmacopoeia |

# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Nitrofurantoin MC Mylan 50 mg and 100 mg, hard capsules, from Mylan B.V.

The products are indicated in diseases of the urinary tract that are caused by micro-organisms sensitive to nitrofurantoin (see section 5.1 of the SmPC):

- In acute uncomplicated lower urinary tract infections;
- For short-term prophylaxis after surgical procedures, transurethral interventions, catheterization, 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 outweigh the potential risks. In view of the side effects, long-term therapy should only be used if no suitable alternative is available (see section 4.4 of the SmPC).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Furadantine MC 50 mg and 100 mg capsules which has been registered in the Netherlands (RVG 05748) by Amdipharm Limited since 28 May 1969.

The concerned member states (CMS) involved in this procedure were Croatia (50 mg strength only), Italy and the United Kingdom (Northern Ireland).

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

# II. QUALITY ASPECTS

## II.1 Introduction

Nitrofurantoin MC Mylan 50 mg is a hard gelatine capsule with a yellow cap and white body.
Nitrofurantoin MC Mylan 100 mg is a hard gelatine capsule with a yellow cap and yellow body.

Each 50 mg capsule contains 50 mg of nitrofurantoin (in macrocrystalline form).
Each 100 mg capsule contains 100 mg of nitrofurantoin (in macrocrystalline form).

The capsules are packed in PVC/aluminium foil blister packs.

The excipients are:
*Capsule content* - maize starch, lactose monohydrate and talc.
*Capsule shell* - titanium dioxide (E171), gelatine and yellow iron oxide (E172).

The two tablet strengths are dose proportional.

## II.2 Drug Substance

The active substance is nitrofurantoin, an established active substance described in the European (Ph.Eur.) and US Pharmacopoeia (USP). The active substance is a yellow crystal, very slightly soluble in water and ethanol (96%) and soluble in dimethylformamide. Nitrofurantoin macrocrystals exhibit polymorphism.

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
The manufacturing process of nitrofurantoin is described and general information regarding chemicals and reaction conditions is provided. Comprehensive descriptions of the manufacturing processes are provided, which includes a sequential procedural narrative of the process. Details of reprocessing, milling/micronisation/sifting are 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 monograph of nitrofurantoin. Additionally, tests for residual solvents, particle size and tapped density have been included in the specification of the active substance by the active substance manufacturer. Control of known, unknown and total impurities have been included in the specification of the active substance. The limits are according to the USP.

The stability studies have been performed by the MAH since several decades, and the batch analytical data are within the specifications.

Stability of drug substance

Stability data for nitrofurantoin have been provided for three batches stored at 40°C/75% RH (6 months) and five batches stored at 25°C /60% RH (60 months). Stability data for nitrofurantoin macrocrystals have been provided for three batches stored at 40°C/75% RH (6 months) and five batches stored at 25°C /60% RH (60 months). Based on the data submitted, and the large experience of the MAH with the manufacturing of the drug substance, a retest period could be granted of five years without any specific storage conditions.

## II.3 Medicinal Products

Pharmaceutical development

The products are established pharmaceutical forms and their 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. Two bioequivalence studies have been performed with the highest strength of the medicinal product. The batch size of the test product bio-batch is considered acceptable and in line with provisions of the *Guideline on the Investigation of Bioequivalence*. Comparative dissolution tests in all media have been provided and could be considered as acceptable.

Manufacturing process

The manufacturing process of Nitrofurantoin Mylan consists of sieving, blending of ingredients, encapsulation and packaging. It is a common manufacturing process for hard capsules. It is considered to be a standard process. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the products have been presented for three batches of each strength in accordance with the relevant European guidelines.

Control of excipients

All excipients are well recognised for their role in this pharmaceutical formulation. The quality of the excipients is adequately controlled. Certificates of analysis were provided for the excipients by respective supplier/manufacturer and drug product manufacturer. These specifications are acceptable.

Quality control of drug products

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, disintegration, weight of content, uniformity of dosage units, identification, assay, related substances, dissolution and microbial quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification. The MAH provided a risk evaluation for the possible presence of nitrosamines, and no risk has been identified.

Stability of drug products

Stability data on the products have been provided for three batches of each strength stored at 25°C ± 2°C/60% RH (36 months) and 30°C ± 2°C/65% RH (12 months) in accordance with applicable European guidelines. A forced degradation study was performed according to the ICH guideline, and showed no out-of-specification results. A photostability study showed that the products are not sensitive to light.

On basis of the data submitted, a shelf life was granted of three years. The labelled storage condition is: "This medicinal product does not require any special storage conditions."

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

Scientific data and/or certificates of suitability issued by the EDQM have been provided for the used lactose monohydrate 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 Nitrofurantoin MC Mylan have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished products.

No post-approval commitments were made.

## III. NON-CLINICAL ASPECTS

### III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Nitrofurantoin MC Mylan are 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

These products are generic formulations of Furadantine MC 50 and 100 mg, capsules which are available on the European market. Reference is made to the preclinical data obtained with the innovator products. 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 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 overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted 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 Nitrofurantoin MC Mylan 100 mg capsules (Mylan B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Nitrofurantoin 100 mg capsules (Mercury Pharmaceuticals Limited, United Kingdom).

The choice of the reference product in the bioequivalence studies has been justified by comparison of dissolution results and compositions of reference products in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

A waiver for the additional 50 mg strength is granted and the MAH provided the following requirements of the *Guideline on the Investigation of Bioequivalence* have been met:

- Both pharmaceutical product strengths are manufactured by the same manufacturing process.
- The qualitative composition of the two strengths is the same.
- The composition of the two strengths is quantitatively proportional.
- Appropriate *in vitro* dissolution data confirmed the adequacy of waiving additional *in vivo* bioequivalence testing.

Therefore, a waiver for the additional 50 mg strength is granted.

Bioequivalence studies

**Pharmacokinetic study I**

*Design*

A randomised, single dose, blinded, two-way crossover bioequivalence study was carried out under fasting conditions in 32 healthy subjects, aged 19-50 years. Each subject received a single dose (100 mg) of one of the two nitrofurantoin formulations. The capsule was orally

administered after an overnight fast of at least eight hours. There were two dosing periods, separated by a washout period of six days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1,1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12 and 16 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*
Three subjects were withdrawn before pre-dose period one: one subject due to medical reasons and two subjects withdrew consent. 29 subjects were eligible for pharmacokinetic analysis.

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

| **Treatment N=29** | **$AUC_{0-t}$ (ng/ml/h)** | **$AUC_{0-\infty}$ (ng/ml/h)** | **$C_{max}$ (ng/ml)** | **$t_{max}$ (h)** |
|---|---|---|---|---|
| **Test** | 1428 ± 548 | 1448 ± 564 | 432 ± 138 | 2.67 (0.75, 5.00) |
| **Reference** | 1368 ± 504 | 1378 ± 508 | 443 ± 138 | 2.33 (1.00, 5.50) |
| ***Ratio (90% CI)** | 1.04 (0.94 – 1.16) | 1.05 (0.95 – 1.16) | 0.98 (0.90 – 1.07) | - |

**$AUC_{0-\infty}$** 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

**ln-transformed values*

**Pharmacokinetic study II**
*Design*
A randomised, single dose, blinded, two-way crossover bioequivalence study was carried out under fed conditions (151 kcal protein, 530 kcal fat and 266 kcal carbohydrates, total 948 kcal) in 32 healthy subjects, aged 19-50 years. Taking Nitrofurantoin MC Mylan with a meal improves absorption and is important for optimal efficacy. Each subject received a single dose (100 mg) of one of the two nitrofurantoin formulations. The capsule was orally administered. There were two dosing periods, separated by a washout period of six days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1,1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12 and 16 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*
One subject was withdrawn after drug administration during period one due to adverse events (i.e. headache, nausea and vomiting). 31 subjects were eligible for pharmacokinetic analysis.

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

| **Treatment N=31** | **$AUC_{0-t}$ (ng/ml/h)** | **$AUC_{0-\infty}$ (ng/ml/h)** | **$C_{max}$ (ng/ml)** | **$t_{max}$ (h)** |
|---|---|---|---|---|
| **Test** | 1787 ± 315 | 1823 ± 315 | 504 ± 138 | 4.50 (1.00 – 7.00) |
| **Reference** | 1778 ± 372 | 1801 ± 373 | 498 ± 129 | 4.50 (1.67 – 5.50) |
| ***Ratio (90% CI)** | 1.01 (0.98 – 1.05) | 1.02 (0.98 – 1.06) | 1.01 (0.95 – 1.07) | - |

**$AUC_{0-\infty}$** 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

**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, Nitrofurantoin MC Mylan is considered bioequivalent with Furadantine MC.

The MEB has been assured that the bioequivalence studies have 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 Nitrofurantoin MC Mylan.

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

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|---|---|
| Important identified risks | • Haematological disorders including anaemia<br>• Use in patients with acute porphyria<br>• Concomitant use with quinolone anti-infectives and typhoid vaccine<br>• Effect on ability to drive and use machines<br>• Use in neonates (less than three months of age)<br>• Use in patients with debilitating conditions<br>• Hepatic impairment minus including<br>• Hypersensitivity<br>• Use in patients with diabetes mellitus<br>• Use in patients with electrolyte imbalance<br>• Use in patients with glucose-6-phosphate dehydrogenase deficiency<br>• Use in patients with vitamin B (particularly folate) deficiency<br>• Peripheral neuropathy and neurological disorders<br>• Use in pregnancy and lactation<br>• Use in patients with renal impairment<br>• Pulmonary disorders |
| 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 products Furadantine MC. No new clinical studies were conducted. The MAH demonstrated through two bioequivalence studies that the pharmacokinetic profile of the 100 mg product is similar to the pharmacokinetic profile of the respective reference product strength. A biowaiver has been granted for the lower (50 mg) product strength. Risk management is adequately addressed. These generic medicinal products can be used instead of the reference products.

# V. USER CONSULTATION

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 Levoflaxin, 250 mg, 500 mg film-coated tablets, NL/H/1129-1134/01-002/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

Nitrofurantoin MC Mylan 50 mg and 100 mg, hard capsules have a proven chemical-pharmaceutical quality and are generic forms of Furadantine MC 50 mg and 100 mg, capsules. Furadantine MC are well-known medicinal products with established favourable efficacy and safety profiles. 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 Nitrofurantoin MC Mylan with the reference products, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 30 April 2021.

## 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/4849 /001/G | Type IB – B.II.b): Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product:<br>• Secondary packaging site<br>• Primary packaging site<br>• Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products<br>• Replacement or addition of a site where batch control/ testing takes place<br>• Minor change in the manufacturing process<br>• Other variations | None | 30-06-2021 | Approval | - |
| NL/H/4849 /002/G | Type IB – B.II.e):<br>• Solid, semi-solid and non-sterile liquid pharmaceutical forms<br>• Change outside the range of the currently approved pack sizes | None | 30-06-2021 | Approval | |
| NL/H/4849 /003/G | Type IA – B.II b and e):Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product:<br>• Secondary packaging site<br>• Other variation | | 21-02-2022 | Approval | |
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