IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Nitrofurantoin 100 mg Capsules, hard
Nitrofurantoin
PA22871/024/002

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Nitrofurantoin 50 mg & 100 mg Capsule, hard from Azure Pharmaceuticals Ltd. on 3rd September 2021 for the treatment of and prophylaxis of acute of recurrent, uncomplicated lower urinary tract infections or pyelitis either spontaneous or following surgical procedures. Nitrofurantoin is specifically indicated for the treatment of infections due to susceptible strains of *Escherichia coli*, Enterococci, Staphylococci, Citrobacter, Klebsiella and Enterobacter.

This decentralised application concerns generic version of nitrofurantoin capsules. The reference product is Macrodantin 100 mg Capsules, MAH Mercury Pharmaceuticals (PL 12762/0048-0049), authorised on 31/03/2000.

This procedure initially started with UK as RMS. Post Brexit, at Day 120, IE became RMS. The UK (NI) remained in the procedure as CMS.

This product is subject to prescription that may be renewed. Supply is through pharmacies only.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website.

Name of the product	Nitrofurantoin 50 mg & 100 mg Capsule, hard
Name(s) of the active substance(s) (INN)	Nitrofurantoin
Pharmacotherapeutic classification (ATC code)	J01XE01
Pharmaceutical form and strength(s)	50 mg & 100 mg Capsule
Marketing Authorisation Number(s) in Ireland (PA)	PA22871/024/001-002
Marketing Authorisation Holder	Azure Pharmaceuticals Ltd.
MRP/DCP No.	IE/H/1123/001-002/DC
Reference Member State	IE
Concerned Member State	UK (NI)

II. QUALITY ASPECTS

II.1. Introduction

This application is for Nitrofurantoin 50 mg and 100 mg Capsules, Hard.

II.2 Drug substance

The active substance is nitrofurantoin, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for hard capsules, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site has been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Nitrofurantoin 50 mg and 100 mg Capsules, Hard.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Macrodantin 50 mg and 100 mg Capsules on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

Since Nitrofurantoin 50 mg and 100 mg Capsules are generic products, they will not lead to an increased exposure to the environment. Additional studies on environmental risk assessment are therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of nitrofurantoin are well known. As nitrofurantoin is a widely used, well-known active substance, the applicant has not provided additional nonclinical studies and further studies are not required. A nonclinical overview based on literature review was provided and is acceptable for this type of generic application. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

Nitrofurantoin is a well known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Nitrofurantoin 100mg Capsules, Hard (Mercury Pharmaceuticals Ltd).

For this generic application, the applicant has submitted 2 bioequivalence studies in which the pharmacokinetic profile of the test product Nitrofurantoin 100mg Capsules.
India is compared with the pharmacokinetic profile of the reference product Nitrofurantoin 100mg Capsules, Hard (Mercury Pharmaceuticals Ltd).

Study 17-VIN-02 A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Based on the pharmacokinetic parameters of active substance, the reference tablet Nitrofurantoin 100mg Capsules marketed by (Mercury Pharmaceuticals Ltd) and test tablet Nitrofurantoin 100mg Capsules were not bioequivalent with extent to the rate and extent of absorption and did not fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance. This was due to a single outlier.

Study 19-VIN-0214 02 A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Based on the pharmacokinetic parameters of active substance, the reference tablet Nitrofurantoin 100mg Capsules marketed by (Mercury Pharmaceuticals Ltd) and test tablet Nitrofurantoin 100mg Capsules were bioequivalent with extent to the rate and extent of absorption and did fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

As per CHMP guidance the results of both studies were combined. When the two studies are combined, and including the outlier patient which the applicant previously wished to exclude, it is agreed that the 90% CI for both AUC and Cmax are within in the required 80-125%. Considering the available evidence as a whole, it can be concluded that 100mg test product has been demonstrated to be bioequivalent to the reference product.

A biowaiver was requested for Nitrofurantoin 50mg capsules, hard.
The 50mg strength is dose proportional with the 100mg strength.

IV.2 Pharmacokinetics

The PK results for 77 subjects (after pooling of subjects) were considered for statistical analysis. After pooling the data of both the studies, the observed geometric least squares mean of Test Formulation (T) and Reference Formulation (R), its ratio (T/R)%, intra-subject variability, power and 90% confidence intervals for geometric least square mean ratio (T/R) of ln-transformed parameters Cmax and AUC0-t are summarized in the following table :

PK Parameters (Unit)	Geometric Least Square Means andIts Ratio (N=77)			Intra subject %CV	90% Confidence Interval	Power (%)
	Test Product (T)	Reference Product (R)	(T/R) (%)			
Cmax						

(ng/mL)	476.622	416.187	114.52	19.31	108.79% - 120.56%	100.00
AUC0-t (hr*ng/mL)	2336.134	2176.112	107.35	9.09	104.76% - 110.01%	100.00

Nitrofurantoin macrocrystals are specially formulated. The controlled crystal size is designed to control the speed of absorption and thus reduce the incidence of nausea. Clinical and animal studies indicate that nitrofurantoin therapy decreases the likelihood of nausea in patients who might experience these symptoms on nitrofurantoin therapy.
Orally administered nitrofurantoin (macrocrystalline) is readily absorbed in the upper gastrointestinal tract at a slower rate and to a reduced extent when compared to microcrystalline nitrofurantoin. Blood concentrations at therapeutic dosage are usually low with an elimination half-life of approximately 30 minutes or less.
Maximum urinary excretion usually occurs 4-5 hours after administration of macrocrystalline nitrofurantoin. Urinary drug dose recoveries of approximately 25-30% are obtained. Administration with food increases the absorption of nitrofurantoin.

IV.3 Pharmacodynamics

Nitrofurantoin is a urinary tract antibacterial whose molecular mechanism of action is not fully delineated. Nitrofurantoin at low concentrations has been reported to inhibit the inducible synthesis of both β-galactosidase and galactokinase in *Escherichia coli*. At higher concentrations, nitrofurantoin treatment inhibits enzymes of the citric acid cycle as well as DNA, RNA, and total protein synthesis in bacteria by a mechanism thought to involve the reaction of electrophiles generated following bacterial reduction of nitrofurantoin with nucleophilic sites on bacterial macromolecules.

It is bactericidal *in vitro* to most gram-positive and gram-negative urinary tract pathogens. The range of organisms sensitive to the bactericidal activity include: the majority of E*scherichia coli*, C*itrobacter* species, group B streptococci, enterococci, *Staphylococcus* species (eg. *S. aureus, S. epidermidis, S. saprophyticus), Klebsiella pneumoniae* and E*nterobacter* species.

IV.4 Clinical Efficacy

Multiple studies have demonstrated the efficacy of Nitrofurantoin for the treatment of and prophylaxis of acute of recurrent, uncomplicated lower urinary tract infections or pyelitis either spontaneous or following surgical procedures. Nitrofurantoin is specifically indicated for the treatment of infections due to susceptible strains of *Escherichia coli*, Enterococci, Staphylococci, Citrobacter, Klebsiella and Enterobacter.

Dosage
Adults:
Acute Uncomplicated Urinary Tract Infections: 50mg four times daily for seven days.
Severe Chronic Recurrence: 100 mg four times daily for seven days.
Long Term Suppression: 50-100 mg once a day.
Prophylaxis: 50 mg four times daily for the duration of the procedure and for the 3 days thereafter.

Children and Infants over three months of age:
Acute Urinary Tract Infections: 3mg/kg/day in four divided doses for seven days.
Suppressive therapy: 1mg/kg/day once a day.
For children under 25 kg body weight consideration should be given to the use of Nitrofurantoin oral suspension.

Elderly: Provided there is no significant renal impairment in which Nitrofurantoin is contraindicated, the dosage should be that for any normal adult.

IV.5 Clinical Safety

The submitted bioequivalence study demonstrates a reasonable safety profile with no serious adverse events. There was a similar number of adverse events between test and reference products.
The safety of this drug is well established and the SmPC clearly states relevant contraindications and potential adverse reactions.

IV.6 Discussion on the clinical aspects

Benefits

Nitrofurantoin 100mg capsules, hard has an established efficacy and safety profile.
It is indicated for the treatment and prophylaxis of acute, recurrent, uncomplicated lower urinary tract infections or pyelitis either spontaneous or following surgical procedures. Nitrofurantoin is specifically indicated for the treatment of infections due to susceptible strains of *Escherichia coli*, Enterococci, Staphylococci, Citrobacter, Klebsiella and Enterobacter.

The bioequivalence study submitted shows 90% confidence intervals within the range of 80.00% to 125.00% which complies with CPMP/EWP/QWP/1401/98 Rev

The SmPC is consistent with that of the reference product.

Risks:

Nitrofurantoin is contraindicated in patients suffering from renal dysfunction with an eGFR of less than 45 ml/minute and patients with G6PD deficiency. This is detailed in the SmPC.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

Risk Management Plan

The applicant 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 50mg and 100mg capsules.
The revised RMP (version 0.2, signed 1st April 2021) is acceptable. Routine pharmacovigilance and routine risk minimisation activities are considered sufficient.
The applicant is requested to ensure it maintains the RMP in line with the latest SmPC updates and maintains regular reviews.

Summary of Safety Concerns	
Important identified risks	• None
Important potential risks	• None
Missing Information	• None

Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

V. OVERALL CONCLUSIONS

The overall conclusion favours a positive risk benefit profile.

Nitrofurantoin 50 mg is a generic form of Nitrofurantoin 50 mg marketed by (Mercury Pharmaceuticals Ltd) in the UK and Amdipharm Ltd in Ireland and is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

The legal basis for the application is Article 10(1) of 2001/83/EC a generic application.

The product will be subject to medical prescription that may be renewed.

Based on the pharmacokinetic parameters of the reference product Nitrofurantoin 100 mg Capsules, Hard and the test product Nitrofurantoin 50 mg are bioequivalent with reference to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in by the EMA in CPMP/EWP/240/95 Rev 1.

The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product Nitrofurantoin 50 mg marketed by (Mercury Pharmaceuticals Ltd) in the UK and Amdipharm Ltd in Ireland

The HPRA, on the basis of the data submitted considered that Nitrofurantoin 100 mg demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

21.05.2026

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE