IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Nitrofurantoin 100 mg hard capsules
Nitrofurantoin, macrocrystalline
PA1567/004/002

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.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Nitrofurantoin 50mg & 100mg capsule, hard**,** from Activase Pharmaceuticals Limited, on 15th November 2024, for the treatment of and prophylaxis against acute or recurrent, uncomplicated lower urinary tract infections either spontaneous or following surgical procedures, caused by micro-organisms sensitive to nitrofurantoin.

This application for a marketing authorisation was submitted in accordance with Article 10(1) of Directive 2001/83/EC and is referred to as a generic application.

This decentralised application concerned a generic version of nitrofurantoin capsules. The reference product was Macrodantin 50 mg & 100 mg capsules by Amdipharm Limited registered since 01/Apr/1977. With IE as the Reference Member State in this procedure, Activase Pharmaceuticals Limited, Nicosia, Cyprus, applied for Marketing Authorisations for Nitrofurantoin 50 mg & 100 mg capsules in BE, NL, PT and SI.

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 at www.hpra.ie

Name of the product	Nitrofurantoin 100mg Capsule, hard
Name(s) of the active substance(s) (INN)	Nitrofurantoin, macrocrystalline
Pharmacotherapeutic classification (ATC code)	J01XE01
Pharmaceutical form and strength(s)	100mg Capsule, hard
Marketing Authorisation Number(s) in Ireland (PA)	PA1567/004/002
Marketing Authorisation Holder	Activase Pharmaceuticals Limited
MRP/DCP No.	IE/H/1278/002/DC
Reference Member State	IE
Concerned Member State	BE, NL, PT, SI

II. QUALITY ASPECTS

II.1. Introduction

This application is for Nitrofurantoin 50mg & 100mg Capsule, 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

Nitrofurantoin 50 mg hard capsules and Nitrofurantoin 100 mg hard capsules contain 50 mg and 100 mg of Nitrofurantoin respectively.

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 (hard capsules) 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 ICH guidelines and the process is considered to be sufficiently validated.

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

All ingredients comply with their respective Ph. Eur. monographs.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for 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(s) have 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- blister packs- is described in section 6.5 of the SmPC.

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

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU and ICH 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 hard capsules and Nitrofurantoin 100 mg hard capsules.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is the same as that present in Macrodantin on the European market since 1977. No new preclinical data have been submitted. This is acceptable for this type of application.

The pharmacodynamic, pharmacokinetic and toxicological properties of Nitrofurantoin are well known.

III.2 Ecotoxicity/environmental risk assessment

Since Nitrofurantoin 50mg & 100mg Capsule, hard is intended for generic substitution, this will not lead to an increased exposure to the environment. Additional studies on environmental risk assessment are therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

The 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 studies and further studies are not

required. A nonclinical overview based on literature review was provided and is acceptable. 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 broadly in accordance with that accepted for the reference product. Any deviations from that of the reference product were adequately substantiated during the procedure.

For this generic application, the applicant submitted data from three bioequivalence studies in which the pharmacokinetic profile of the generic 100 mg capsule was compared with the pharmacokinetic profile of the reference 100 mg capsule. These studies are outlined in Section IV.2

The generic 100 mg capsule is dose proportional with the generic 50 mg capsule. The pharmacokinetics of the active substance nitrofurantoin are linear within the relevant dose range. The results of the bioequivalence studies performed with the generic 100 mg capsule therefore apply to the generic 50 mg capsule.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

To support the application, data from three bioequivalence studies comparing the generic and reference products 100 mg capsules were submitted: One was conducted under fasting conditions (Study 16-VIN-0918) and two under fed conditions (Study 16-VIN-0919 and Study 19-VIN-0412).

The studies were of a randomised, single-dose, two-treatment, two-sequence, two period crossover design in healthy male subjects.

Studies 16-VIN-0918 and 16-VIN-0919 failed to demonstrate bioequivalence between the generic and reference products. In the fasted study (16-VIN-0918), the upper 90% confidence interval for extent of nitrofurantoin exposure (AUC0-t) was 125.07%. In the fed study (16-VIN-0919), the upper 90% confidence interval for rate of nitrofurantoin exposure (Cmax) was 126.22%.

Study 19-VIN-0412 was considered to have demonstrated bioequivalence between the 100 mg generic and reference products and its results are summarised below in Table 1.

Table 1. Bioequivalence evaluation [geometric least squares mean of Test Formulation (T) and Reference Formulation (R), its ratio (T/R) %, intra-subject variability, 90% confidence intervals the geometric least square mean ratio (T/R) and power obtained from the analysis of ln-transformed parameters Cmax and AUC0-t]

Parameters (Units)	Geometric Least Square Means and It's Ratio (N = 50)			Intra subject %CV	90% Confidence Interval	Power (%)
	Test Product (T)	Reference Product (R)	(T/R)%			
C_{max} (ng/mL)	481.565	498.316	96.64	18.26	90.94% - 102.69%	100.00
AUC_{0-t} (hr*ng/mL)	2630.809	2562.980	102.65	9.27	99.51% - 105.88%	100.00

As per regulatory guidance (CPMP/EWP/QWP/1401/98 Rev. 1), the existence of a study which demonstrates bioequivalence does not mean that those which did not can be ignored. However, based on the totality of data presented and the applicant's further substantiation of same, bioequivalence between the generic and reference 100 mg capsules was considered to have been adequately supported.

A proposed waiver for the generic 50 mg capsule was granted in accordance with criteria set out in regulatory guidance.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for this application and none were required.

IV.4 Clinical Efficacy

No new efficacy data have been submitted for this application and none were required.

IV.5 Clinical Safety

With the exception of safety data submitted from the reported bioequivalence studies, no new safety data were submitted.

Submitted data showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were identified.

Risk Management Plan

A Risk Management Plan, version 0.1, dated 28 April 2024 has been submitted, 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 50 mg and 100 mg Capsules. It is concluded that routine pharmacovigilance and risk minimisation measures are sufficient.

Summary table of safety concerns as approved in RMP:

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.

IV.6 Discussion on the clinical aspects

Based on the totality of data presented from the conducted bioequivalence studies and the applicant's further substantiation of same, the generic and reference 100 mg capsules were considered to be bioequivalent. A waiver for additional bioequivalence testing was granted for the generic 50 mg capsule. No further clinical studies were required to support authorisation.

V. OVERALL CONCLUSIONS

Nitrofurantoin 50mg & 100mg capsules are generic forms of Macrodantin 50 mg & 100 mg capsules. Macrodantin is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Based on the totality of data presented from the conducted bioequivalence studies and the applicant's further substantiation of same, the generic and reference 100 mg capsules were considered to be bioequivalent. A waiver for additional bioequivalence testing was grated for the generic 50 mg capsule. No further clinical studies were required to support authorisation.

The content of the SmPC, package leaflet and labelling approved during the procedure was broadly in accordance with that accepted for the reference product. Any deviations from that of the reference product were adequately substantiated during the procedure.

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

The HPRA, on the basis of the data submitted, considered that Nitrofurantoin 50mg & 100mg capsules were the same as the cited reference products and therefore granted marketing authorisation to both generics.

VI. REVISION DATE

25.10.2029