Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

UKPAR

Nitrofurantoin 25mg/5ml Oral Suspension

(nitrofurantoin monohydrate)

UK Licence Number: PL 33882/0058

Glenmark Pharmaceuticals s.r.o.

LAY SUMMARY

Nitrofurantoin 25mg/5ml Oral Suspension

This is a summary of the Public Assessment Report (PAR) for Nitrofurantoin 25mg/5ml Oral Suspension (PL 33882/0058). It explains how Nitrofurantoin 25mg/5ml Oral Suspension was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Nitrofurantoin 25mg/5ml Oral Suspension

The product will be referred to as Nitrofurantoin oral suspension throughout the remainder of this public assessment report (PAR).

For practical information about using Nitrofurantoin oral suspension, patients should read the package leaflet or contact their doctor or pharmacist.

What is Nitrofurantoin oral suspension and what is it used for?
Nitrofurantoin oral suspension is a 'generic medicine'. This means that Nitrofurantoin oral suspension is similar to a 'reference medicine' already authorised in the European Union (EU) called Furadantion 25mg/5ml oral suspension (Mercury Pharmaceuticals).

Nitrofurantoin oral suspension used to prevent and treat infections of the bladder, kidney and other parts of the urinary tract.

How does work?
The active substance in Nitrofurantoin 25mg/5ml oral suspension is nitrofurantoin an antibiotic—medicines used to treat infections caused by bacteria. Nitrofurantoin works by killing the bacteria that cause infections of the urinary tract.

How is Nitrofurantoin oral suspension used?
The pharmaceutical form of this medicine is an oral solution and the route of administration is oral (by mouth).

The doctor's instructions should be followed exactly, and the course of the treatment completed even if the patient feels better. If unsure the patient should check with their doctor or pharmacist.

This medicine should be taken at meal times with food or milk. This will help to avoid stomach upset and also help absorption of the medicine.

It is recommended to shake well before use, until complete resuspension.

It is recommended to use the plastic spoon or the plastic dosing syringe (see instructions below) provided to deliver the patient's specific dose.

Adults:
The normal dosage depends on the type of infection and instructions should be written on the label provided by the pharmacist. The patient should consult a pharmacist or doctor if these instructions are not clear.

The usual doses are:

- For the treatment of infections: two to four 5ml spoonfuls four times a day for seven days
- For prevention of further infections: two to four 5ml spoonfuls to be taken once a day
- For prevention of infections during surgery: two 5ml spoonfuls four times a day on the day of the operation and three days thereafter.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

For further information on how Nitrofurantoin oral suspension is used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

What benefits of Nitrofurantoin oral suspension have been shown in studies?
Because Nitrofurantoin oral suspension is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine Furadantin 25mg/5ml Oral Suspension (Mercury Pharmaceuticals Ltd). Two medicines are bioequivalent when they produce the same levels of active substance in the body.

What are the possible side effects of Nitrofurantoin oral suspension?
Because Nitrofurantoin oral suspension is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are taken as being the same as those of the reference medicine Furadantin 25mg/5ml Oral Suspension (Mercury Pharmaceuticals Ltd).

For a full list of all the side effects reported with Nitrofurantoin oral suspension see section 4 of the package leaflet, available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

For the full list of restrictions, see the package leaflet.

Why is Nitrofurantoin oral suspension approved?
It was concluded that, in accordance with EU requirements, Nitrofurantoin oral suspension has been shown to have comparable quality and to be bioequivalent to Furadantin 25mg/5ml Oral Suspension (Mercury Pharmaceuticals Ltd). The benefits are greater than the risks and it was recommended that Nitrofurantoin oral suspension can be approved for use.

What measures are being taken to ensure the safe and effective use of Nitrofurantoin oral suspension?
A risk management plan (RMP) has been developed to ensure that Nitrofurantoin oral suspension is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Nitrofurantoin oral suspension including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Nitrofurantoin oral suspension
A marketing authorisation was granted in the UK on 2 October 2018.

The full PAR for Nitrofurantoin oral suspension follows this summary.

For more information about treatment with Nitrofurantoin oral suspension, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in December 2018.

TABLE OF CONTENTS

I	INTRODUCTION	5
II	QUALITY ASPECTS	6
III	NON-CLINICAL ASPECTS	8
IV	CLINICAL ASPECTS	8
V	USER CONSULTATION	11
VI	OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION	11
TABLE OF CONTENT OF THE PAR UPDATE		14

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Glenmark Pharmaceuticals s.r.o., a marketing authorisation for the medicinal product Nitrofurantoin 25mg/5ml Oral Suspension (PL 33882/0058).

Nitrofurantoin oral suspension is indicated for the treatment of and prophylaxis against acute or recurrent, uncomplicated lower urinary tract infections either spontaneous or following surgical procedures when due to susceptible micro-organisms.

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

The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference product for this application is Furadantin 25mg/5ml Oral Suspension, initially authorised to Teva Pharma UK Limited since 1989. On 31 March 2000 the Marketing Authorisation underwent a change of ownership procedure to the current Marketing Authorisation Holder Mercury Pharmaceuticals Ltd (PL 12762/0055).

Nitrofurantoin, i.e. 1 -[(5-nitrofurfurylidene)amino] hydantoin, is a nitrofuran derivative with broad antimicrobial activity. Its spectrum of in vitro susceptibility includes the majority of *Escherichia coli*, *Citrobacter* species, group *B streptococci*, *enterococci*, *Staphylococcus aureus*, mS. *epidermidis*, *Klebsiella pneumoniae* and *Enterobacter* species.

Nitrofurantoin inhibits bacterial acetyl coenzyme A, thus disrupts carbohydrate mechanism of the microorganism. It may also break bacterial cell wall formation. Its antibacterial activity is dependent on acidity of urine. Even though it is usually bacteriostatic, it may show bactericidal effect in high doses and against certain microorganisms.

Two bioequivalence studies (one conducted under fasting conditions and one under fed conditions were submitted, the fasting condition study was considered pivotal to demonstrate bioequivalence. The applicant has stated that the bioequivalence studies were conducted in accordance with the study protocol and the guidelines for good laboratory practice (GLP).

With the exception of the bioequivalence studies no new clinical studies were submitted, which is acceptable given that the application was based on being a generic medicinal product of a reference product that has been in clinical use for over 10 years.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of the product.

For manufacturing sites within the Community, the MHRA has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

II QUALITY ASPECTS

II.1 Introduction

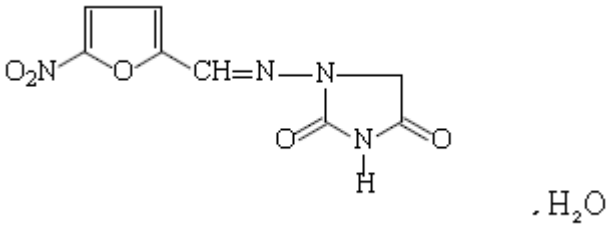
The finished product is an oral suspension each 5ml spoonful contains 25mg of Nitrofurantoin (as monohydrate). The other ingredients are methyl parahydroxybenzoate, propyl parahydroxybenzoate, polysorbate 20, glycerol, carbomer, sucralose, apricot flavour, and sodium hydroxide.

The finished product is packaged in 300ml amber glass bottles with LDPE, child-resistant and tamper evident screw cap packed in a cardboard box containing a 5 ml plastic oral dosing syringe (graduated every 0.1 ml) and an adaptor for the syringe or one double plastic 2.5/5.0 ml measuring spoon.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance

INN:	Nitrofurantoin Monohydrate
Chemical name:	*1-[(5-Nitrofurfurylidene)-amino]hydantoin monohydrate*
Structure:	



Molecular formula:	$C_8H_6N_4O_5 \cdot H_2O$
Molecular weight:	256.18
Appearance	Lemon-yellow crystalline powder
Solubility	Very slightly soluble in water and in ethanol (96%), soluble in dimethylformamide

Nitrofurantoin monohydrate is the subject of an active substance master file (ASMF).

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards used.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food. Appropriate stability will be generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to develop a safe, efficacious, oral solution containing 25 milligrams nitrofurantoin (as monohydrate) per 5 ml of solution that is a generic version of the reference product Furadantin 25mg/5ml Oral Suspension (Mercury Pharmaceuticals Ltd). The development of the product has been described, the choice of excipients is justified, and their functions explained.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and reference product.

All excipients comply with their respective European Pharmacopoeia or British Pharmacopoeia monographs, with the exception of the apricot flavour which is controlled to a suitable in-house specification.

Satisfactory specifications and Certificates of Analysis have been provided for the packaging components.

No materials of animal origin covered by the TSE guideline are contained or used in the manufacturing process of the medicinal product.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, together with an appropriate account of the manufacturing process. Process validation data on three pilot scale batches has been provided. The results are satisfactory.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data complying with the release specification have been provided. Certificates of Analysis have been provided for all working standards used.

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf life of 3 years, the product should be discarded 3 months after first opening. This medicinal product does not require any special storage conditions before opening, after first opening the special storage condition of “do not store above 25^{o}C and use within 3 months” is applied.

Suitable post approval stability commitments to continue stability testing on batches of finished product have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of this application from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of nitrofurantoin monohydrate are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

Impurities

The levels of residual solvents within the drug substance meet their respective limits as set out in ICH Q3C (R6). A genotoxic impurity is marginally above the Threshold of Toxicological Concern (TTC) within the ICH guidance, however, this is acceptable as nitrofurantoin monohydrate is a drug substance used for treatments of a few weeks duration and the guidance states that higher values are acceptable in the case of short-term exposure.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Nitrofurantoin 25mg/5ml Oral Suspension is intended for generic substitution, this will not lead to an increase in the environmental exposure. An environmental risk assessment is therefore not deemed necessary**.**

III.6 Discussion on the non-clinical aspects

There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of nitrofurantoin monohydrate is well-known. With the exception of data from the bioequivalence studies detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for the application.

A comprehensive review of the published literature has been provided by the applicant. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of nitrofurantoin monohydrate.

IV.2 Pharmacokinetics

In support of this application the applicant submitted two bioequivalence studies comparing the pharmacokinetics of the Nitrofurantoin 25mg/5ml Oral Suspension versus the reference product Nitrofurantoin 25mg/5ml oral suspension (Mercury Pharmaceuticals Limited) under fed and fasting conditions.

Study 1 (Fed conditions)
A randomised, single-dose, two-way, crossover bioequivalence study of the test product; Nitrofurantoin 25mg/5ml oral suspension (Glenmark Pharmaceuticals s.r.o.) versus with the reference product Nitrofurantoin 25mg/5ml oral suspension (Mercury Pharmaceuticals Limited) in healthy, adult, human subjects under fed conditions.

Following an overnight fast of at least 10 hours, subjects were served a high fat high calorific breakfast. A single dose (100 mg [20 ml oral suspension]) of the test or reference product drug was administered with 200 ml of water. Blood samples were collected for plasma levels before dosing and up to and including 16 hours after the drug administration. The washout period between treatment phases was 6 days.

The main summary of pharmacokinetic results are presented below:

Parameters	Test		Reference		Statistical analysis	
	Mean SD	CV%	Mean SD	CV%	Point estimate	90% CI
C_{max} (ng/mL)	7.88.30 ± 265.69	33.70	827.92 ± 257.42	31.09	94.73	0.851 - 1.054
AUC_{last} (ng*h/mL)	2344.31 ± 460.97	19.66	2526.29 ± 448.6	17.76	92.61	0.875 - 0980
AUC_{total} (ng*h/mL)	2394.88 ± 473.23	19.76	2570.34 ± 459.23	17.87	92.93	0.878 - 0.983
AUC_{extra} (%)	2.07 ±2.50	120.83	1.68 ± 1.83	108.91	–	
T_{max} (h)	2.18 ± 1.06	48.64	1.85 ± 0.98	53.08	***not significant difference	
T_{half}	1.02 ± 0.87	85.82	1.03 ± 0.54	52.18	***not significant difference	
K_{el} (h^{-1})	0.93 ± 0.35	37.49	0.82 ± 0.32	39.36	***not significant difference	

*Geometric means of Log values ***Kruskal-Wallis non-parametric test
** For Log values

Study 1 Conclusion
The 90% confidence intervals for study 1; single dose under fed conditions of the test/reference ratio for AUC and Cmax values for nitrofurantoin lie within the acceptable limits of 80.00% to 125.00%, in line with the 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**).Thus, the data support the claim that the test product Nitrofurantoin 25mg/5ml oral suspension (Glenmark Pharmaceuticals s.r.o.) is bioequivalent to the reference product Nitrofurantoin 25mg/5ml oral suspension (Mercury Pharmaceuticals Limited).

In each period of the study, after an overnight fast of at least 9 hours subjects received either the test or reference product in a single oral dose of 100 mg nitrofurantoin (20mL oral suspension). Blood samples were collected for plasma levels before dosing and up to and including 16 hours after the drug administration. The treatment phases were separated by a wash out period of 6 days.

Study 2 (Fasting conditions)
A randomised, single-dose, two-way crossover bioequivalence study of the test product; Nitrofurantoin 25mg/5ml oral suspension (Glenmark Pharmaceuticals s.r.o.) compared with the reference product Nitrofurantoin 25mg/5ml oral suspension (Mercury Pharmaceuticals Limited) in healthy, adult, human subjects under fasting conditions.

The main pharmacokinetic results are presented below:

	C_{max}	AUC_{last}	AUC_{total}
Point estimates (%)	94.42	96.70	96.71
90 % CI	0.84799 – 1.0513	0.92469 – 1.0112	0.92493 – 1.0112

Study 2 Conclusion

The 90% confidence intervals for study 2; single dose under fasting conditions of the test/reference ratio for AUC and Cmax values for nitrofurantoin lie within the acceptable limits of 80.00% to 125.00%, in line with the 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**).Thus, the data support the claim that the test product Nitrofurantoin 25mg/5ml oral suspension (Glenmark Pharmaceuticals s.r.o.) is bioequivalent to the reference product Nitrofurantoin 25mg/5ml oral suspension (Mercury Pharmaceuticals Limited).

Overall Bioequivalence Conclusion

The applicant conducted two bioequivalence studies to support this application, in fed and fasting conditions. As per bioequivalence guideline CPMP/EWP/QWP/1401/98 Rev 1/Corr**, bioequivalence studies should generally be conducted under fasting conditions for products with limited solubility and affects on gastric motility, as this is considered to be the most sensitive condition to detect a potential difference between formulations. This is deemed to be crucial for nitrofurantoin as it is only slightly soluble in water and in ethanol (96 per cent) and it is known that nitrofurantoin absorption may be affected by food/gastric emptying.

The data presented by the applicant for the fasting study shows that the 90% confidence intervals of the test/reference ratio for AUC and C_{max} values for nitrofurantoin lie within the acceptable limits of 80.00% to 125.00%, in line with the 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**). Bioequivalence is considered to be demonstrated after a single dose administration of two formulations of nitrofurantoin suspension under fasting conditions. The study under fasting conditions was pivitol for the demonstration of bioequivalence.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted, and none were required for an application of this type.

IV.4 Clinical efficacy

No new efficacy data were submitted, and none were required for an application of this type.

IV.5 Clinical safety

No new data on safety have been submitted and none are required for an application of this type.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended.

In line with the reference product, the applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns (labelling in the SmPC and the PIL), which is acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the competent authority;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a Periodic Safety Update Report and the update of an RMP coincide, they can be submitted at the same time, but via different procedures.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application from a clinical viewpoint.

V User consultation

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Nitrofurantoin 50mg/5ml oral suspension. The bridging report submitted by the applicant has been found acceptable

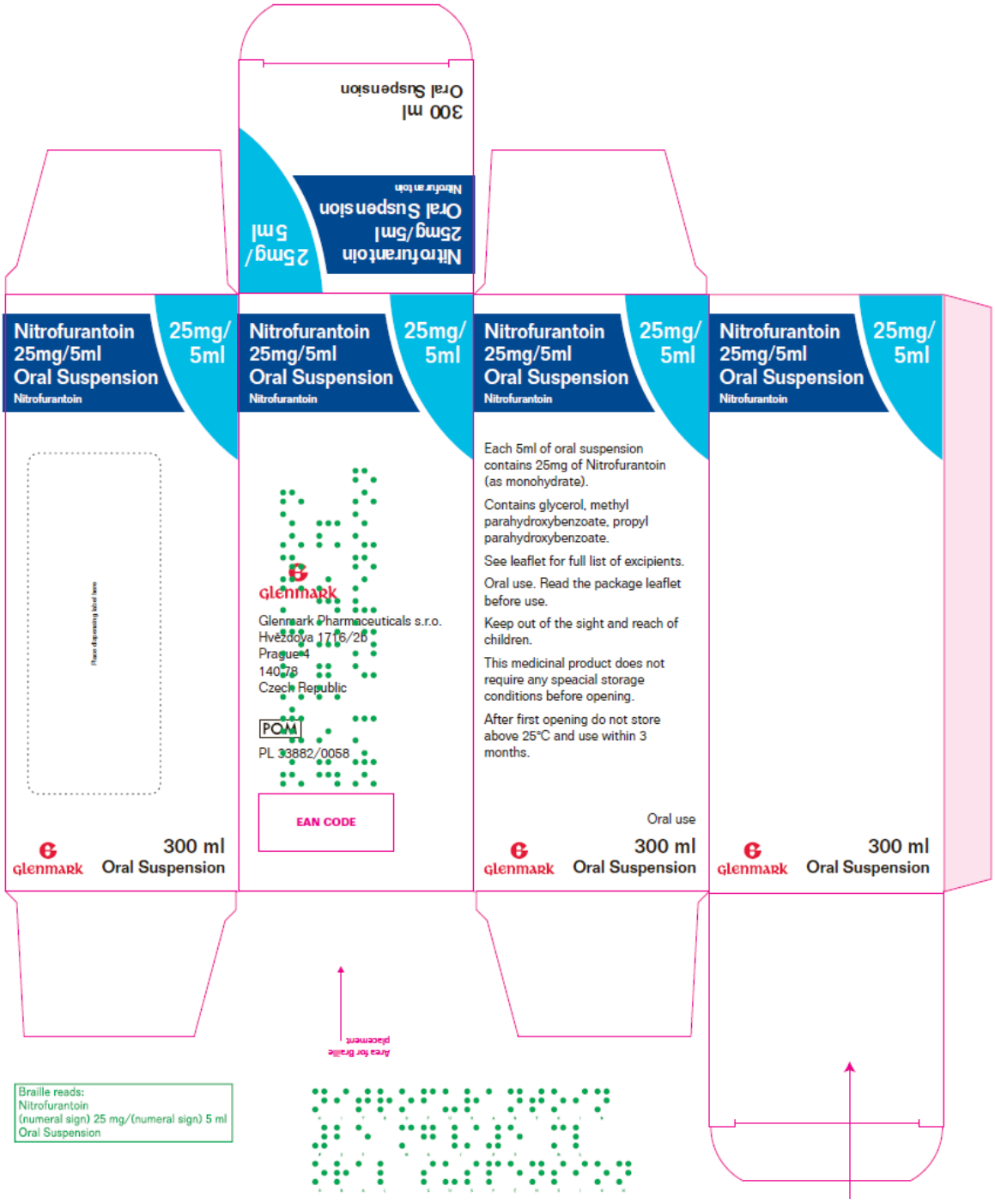
VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with nitrofurantoin monohydrate is considered to have demonstrated the therapeutic value of the compound, therefore, the benefit: risk balance is considered to be positive.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The MAH has submitted the following approved labelling for this medicine which is presented below:




Each 5ml of oral suspension contains 25mg of Nitrofurantoin (as monohydrate). Contains glycerol, methyl parahydroxybenzoate, propyl parahydroxybenzoate. See leaflet for full list of excipients. Oral use. Read the package leaflet before use. Keep out of the sight and reach of children. This medicinal product does not require any speacial storage conditions before opening. After first opening do not store above 25°C and use within 3 months.
Date of first opening: dd/mm/yyyy
PL 33882/0058
Nitrofurantoin 25mg/5ml Oral Suspension
Nitrofurantoin
25mg/ 5ml
Oral use
glenmark
300 ml
Oral Suspension
Glenmark Pharmaceuticals s.r.o.
Hvězdova 1716/2b, Prague 4, 140 78
Czech Republic
POM

Annex 1

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)