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LAY SUMMARY
Nitrofurantoin 50 mg Capsules
Nitrofurantoin 100mg Capsules
(nitrofurantoin macrocrystals)

This is a summary of the public assessment report (PAR) for Nitrofurantoin 50 mg Capsules (PL 20117/0226) and Nitrofurantoin 100mg Capsules (PL 20117/0227). It explains how Nitrofurantoin 50 mg and 100mg Capsules (PL 20117/0226-7) were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Nitrofurantoin 50 mg and 100mg Capsules.

For practical information about using Nitrofurantoin 50 mg and 100mg Capsules, patients should read the package leaflet or contact their doctor or pharmacist.

What are Nitrofurantoin 50 mg and 100mg Capsules and what are they used for?
Nitrofurantoin 50 mg and 100mg Capsules are ‘generic medicines’. This means that Nitrofurantoin 50 mg and 100mg Capsules are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Macrodantin Capsules 100 mg.

Nitrofurantoin 50 mg and 100mg Capsules are used to prevent and treat infections of the bladder, kidney and other parts of the urinary tract.

How are Nitrofurantoin 50 mg and 100mg Capsules used?
Nitrofurantoin 50 mg and 100mg Capsules should be taken at meal times with food or milk. This helps to avoid stomach upset and also helps absorption.

In adults the usual dose for the treatment of infections is either one 50 mg capsule or one 100 mg capsule, four times a day for seven days. The usual dose for the prevention of further infections is either one 50 mg capsule or one 100 mg capsule at bedtime. The usual dose for prevention of infections during surgery is one 50 mg capsule four times a day on the day of the operation and for three days thereafter.

In children and infants over three months of age the dose depends on the weight of the child. Children below three months of age should not take Nitrofurantoin 50 mg and 100mg Capsules.

These medicines can only be obtained with a prescription.

How do Nitrofurantoin 50 mg and 100mg Capsules work?
Nitrofurantoin 50 mg and 100mg Capsules contain an active ingredient called nitrofurantoin, which is an antibiotic. Antibiotics are used to treat infections caused by bacteria. Nitrofurantoin works by killing the bacteria that cause infections of the urinary tract.

How have Nitrofurantoin 50 mg and 100mg Capsules been studied?
Because Nitrofurantoin 50 mg and 100mg Capsules are generic medicines, studies in patients have been limited to tests to determine that the higher strength of the product Nitrofurantoin 100mg Capsules is bioequivalent to the reference medicine, Macrodantin Capsules 100 mg. Two medicines are bioequivalent when they produce the same levels of the active substance in the body. It was deduced from these tests that Nitrofurantoin 50 mg Capsules are comparable to an equivalent strength of the reference medicine.
What are the benefits and risks of Nitrofurantoin 50 mg and 100mg Capsules?
Because Nitrofurantoin 50 mg and 100mg Capsules are generic medicines that are bioequivalent to the reference medicines, their benefits and risks are taken as being the same as the reference medicines.

Why are Nitrofurantoin 50 mg and 100mg Capsules approved?
It was concluded that, in accordance with EU requirements Nitrofurantoin 50 mg and 100mg Capsules have been shown to have comparable quality and to be bioequivalent to Macrodantin Capsules 50 mg and Macrodantin Capsules 100 mg. Therefore, the view was that, as for Macrodantin Capsules 50 mg and Macrodantin Capsules 100 mg, the benefit outweighs the identified risk.

What measures are being taken to ensure the safe and effective use of Nitrofurantoin 50 mg and 100mg Capsules?
Safety information has been included in the Summary of Product Characteristics and the package leaflet for Nitrofurantoin 50 mg and 100mg Capsules, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Nitrofurantoin 50 mg and 100mg Capsules
The UK agreed to grant Marketing Authorisations for Nitrofurantoin 50 mg and 100mg Capsules on 20 January 2014.

The full PAR for Nitrofurantoin 50 mg and 100mg Capsules follows this summary. For more information about treatment with Nitrofurantoin 50 mg and 100mg Capsules, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in February 2014.
SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted Morningside Healthcare Limited Marketing Authorisations (licences) for the medicinal products Nitrofurantoin 50 mg and 100mg Capsules (PL 20117/0226-7) on 20 January 2014.

These are prescription-only medicines (POM) indicated for the treatment of and prophylaxis against acute or recurrent, uncomplicated lower urinary tract infections, when due to susceptible microorganisms.

The applications were submitted according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of the originator products Macrodantin Capsules 100 mg (PL 00364/0006; Warner Chilcott Pharmaceuticals UK Limited), which was initially granted a licence in the UK on 16 October 1989. The current Marketing Authorisation Holder of the reference products is Mercury Pharmaceuticals Limited (PL 12762/0049), following a change of ownership that was concluded on 31 March 2000.

These products contain the active ingredient nitrofurantoin, which is an antibacterial agent. Nitrofurantoin is bactericidal in urine at therapeutic doses. Nitrofurantoin is reduced by bacterial flavoproteins to reactive intermediates which inactivate or alter bacterial ribosomal proteins and other macromolecules. As a result of this inactivation, the vital biochemical processes of protein synthesis, aerobic energy metabolism, DNA synthesis, RNA synthesis, and cell wall synthesis are inhibited.

With the exception of the bioequivalence studies, no new non-clinical or clinical data were submitted, which is acceptable given that these applications were based on the products being generic medicinal products of originator products that have been licensed for over 10 years.

Bioequivalence studies were performed, which compared the pharmacokinetics of the applicant’s Nitrofurantoin 100mg Capsules with those of Macrodantin Capsules 100 mg (Mercury Pharmaceuticals Limited), under both fed and fasted conditions. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of these products.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Nitrofurantoin macrocrystals

INN: Nitrofurantoin
Chemical name: i) 1-[[5-Nitro-2-furanyl]methylene]amino]2,4-imidazolidinedione
       ii) N-(5-nitro-2-furfurylidene)-1-amino-hydantoin and 1-(5-Nitro-2-furfurylideneamino)hydantoin.

Structure:

Molecular formula: C₈H₆N₄O₅
Molecular weight: 238.16
Physical form: lemon-yellow crystals
Solubility: Very slightly soluble in water and in ethanol, soluble in dimethylformamide.

Active Substance Master Files (ASMFs) have been provided by the active substance manufacturer, covering the manufacture and control of the active substance nitrofurantoin macrocrystals.

Synthesis of the drug 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. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

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.
DRUG PRODUCT

Other ingredients
Other ingredients consist of the pharmaceutical excipients, as follows:
Capule core: lactose monohydrate, maize starch and purified talc.
Capsule shell: gelatin, sodium lauryl sulfate, titanium dioxide (E171) and yellow iron oxide (E172).

The capsule shell excipients comply with suitable in-house standards. All other excipients used comply with their respective British Pharmacopoeia monographs.

With the exception of lactose monohydrate and gelatin, none of the excipients used contain material of animal or human origin.

Suitable European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability have been provided by the suppliers of gelatin, showing that it is in compliance with current European regulations concerning the minimisation of transmission of TSE/BSE. The lactose monohydrate is produced from milk sourced from healthy animals, under the same conditions as milk collected for human consumption.

Pharmaceutical development
The objective of the pharmaceutical development programme was to produce safe, tolerable capsules that could be considered generic medicinal products of the reference product Macrodantin Capsules 100 mg (Mercury Pharmaceuticals Ltd). The applicant has provided a suitable product development rationale and data.

Comparative in vitro dissolution profiles have been provided for the applicant’s products versus the reference product.

Manufacture
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished products.

Process validation has been carried out on three pilot-scale batches of each strength of finished product. The results are satisfactory.

Finished product specification
The finished product specifications are satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container Closure System
The finished products are packaged in polyvinylchloride/aluminium blisters in pack sizes of 10, 14, 15, 20, 28, 30 and 100 capsules.

Not all pack sizes may be marketed, however the applicant has committed to submitting mock-ups for approval before marketing any pack size.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided.
Stability
Stability studies were performed, in accordance with current guidelines, on batches of finished product manufactured by the finished product manufacturer and packed in the packaging proposed for marketing. The results from these studies support a shelf-life of 30 months, with the storage conditions of “Store in the original container in order to protect from light”.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPCs, PIL and labels are pharmaceutically acceptable.

The results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC (as amended) for the package leaflet for Nitrofurantoin 50 mg and 100 mg Capsules, were provided. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report (Quality Overall Summary)
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.

NON-CLINICAL ASSESSMENT

As the pharmacodynamic, pharmacokinetic and toxicological properties of nitrofurantoin are well-known, no further non-clinical studies are required and none have been provided.

The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment. As these products are intended for generic substitution with products currently marketed, the environmental burden is not expected to increase. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

There are no objections to the approval of these products from a non-clinical viewpoint.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
In support of these applications, the Marketing Authorisation Holder has submitted the following bioequivalence studies:

Study 1: Fed conditions
A single-dose, randomised, open-label, balanced, two-treatment, two-sequence, two-period, crossover bioequivalence study to compare the pharmacokinetic profile of the applicant’s Nitrofurantoin 100mg Capsules with Macrodantin Capsules 100 mg (Mercury Pharmaceuticals Limited) in healthy adult subjects, under fed conditions.

Study participants were given each treatment after a high fat, high-calorie breakfast, which was consumed following an overnight fast of at least 10 hours. Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 24 hours post dose. Each treatment regimen was separated by a washout period of 7 days.

The main pharmacokinetic results are presented in the table below:

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>Geometric Least Squares Means and it’s ratio</th>
<th>Intra subject %CV</th>
<th>90% Confidence Interval</th>
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<tr>
<td></td>
<td>Test Product (T)</td>
<td>Reference Product (R)</td>
<td>(T/R)%</td>
</tr>
<tr>
<td>C_max (ng/mL)</td>
<td>450.287</td>
<td>455.616</td>
<td>98.83%</td>
</tr>
<tr>
<td>AUC_0-4 (ng.h/mL)</td>
<td>2258.251</td>
<td>2221.982</td>
<td>101.63%</td>
</tr>
<tr>
<td>AUC_0-inf (ng.h/mL)</td>
<td>2305.692</td>
<td>2262.667</td>
<td>101.90%</td>
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</table>

Compared with the reference product, the 90 % confidence intervals for the test product are within 80.00-125.00 % for AUC and Cmax. Nitrofurantoin 100mg Capsules can, therefore, be considered to be bioequivalent with Macrodantin Capsules 100 mg, under fed conditions.

Study 2: Fasting conditions
A single-dose, randomised, open-label, balanced, two-treatment, two-sequence, two-period, crossover bioequivalence study to compare the pharmacokinetic profile of the applicant’s Nitrofurantoin 100mg Capsules with Macrodantin Capsules 100 mg (Mercury Pharmaceuticals Limited) in healthy adult subjects, under fasting conditions.

Study participants were given each treatment after an overnight fast of at least 10 hours. Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 24 hours post dose. Each treatment regimen was separated by a washout period of 7 days.

The main pharmacokinetic results are presented in the table below:
Compared with the reference product, the 90% confidence intervals for the test product are within 80.00-125.00 % for AUC and Cmax. Nitrofurantoin 100mg Capsules can, therefore, be considered to be bioequivalent with Macrodantin Capsules 100 mg, under fasting conditions.

As these products meet the bio-waiver criteria specified in the *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), the results and conclusions of the bioequivalence study on the 100 mg strength can be extrapolated to the 50 mg strength capsules.

**Efficacy**
No new data on efficacy have been submitted and none are required for this type of application.

**Safety**
With the exception of the data submitted during the bioequivalence study, no new safety data were submitted and none were required. No new or unexpected safety issues were raised by the bioequivalence data.

**Pharmacovigilance System**
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a risk management plan for this product.

**Expert Report**
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Summary of Product Characteristics (SmPC)**
These are consistent with the SmPCs for the reference product and are satisfactory.

**Patient Information Leaflet (PIL)**
This is consistent with that for the reference products and is satisfactory.

**Labelling**
This is satisfactory.

**Application Forms (MAA)**
These are satisfactory.

**Conclusion**
The grant of marketing authorisations is recommended for these applications.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Nitrofurantoin 50 mg and 100 mg Capsules are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s product and Macrodantin Capsules 100 mg (Mercury Pharmaceuticals Limited). As these products meet the bio-waiver criteria specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), the results and conclusions of the bioequivalence study on the 100 mg strength can be extrapolated to the 50 mg capsules.

No new or unexpected safety concerns arose from these applications.

The SmPCs, PIL and labelling are satisfactory and consistent with that for the reference products.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Bioequivalence has been demonstrated between the applicant’s products and the reference products. Extensive clinical experience with nitrofurantoin is considered to have demonstrated the therapeutic value of the compound. The benefit/risk assessment is, therefore, considered to be positive.
## STEPS TAKEN FOR ASSESSMENT

<table>
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<th>Description</th>
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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 13 January 2012.</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 05 March 2012.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information on 12 June 2012, 18 December 2012, 16 October 2013 and 17 October 2013.</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 15 November 2012, 27 August 2013 and 22 October 2013.</td>
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<td>The applications were approved on 20 January 2014.</td>
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## STEPS TAKEN AFTER AUTHORISATION - SUMMARY

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<th>Application type</th>
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Summary of Product Characteristics and Patient Information Leaflet

In accordance with Directive 2010/84/EU, the current approved UK versions of the Summaries of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) for this product are available on the MHRA website.
Labelling

Carton for 50 mg capsules:

Each capsule contains 50 mg of Nitrofurantoin. Also contains lactose monohydrate. See leaflet for further information.
For oral use.
Read the package leaflet before use.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Store in the original container in order to protect from light.

Blister for 50 mg capsules:
Carton for 100 mg capsules:

Each capsule contains 100 mg of Nitrofurantoin. Also contains lactose monohydrate. See leaflet for further information. For oral use. Read the package leaflet before use. KEEP OUT OF THE REACH AND SIGHT OF CHILDREN. Store in the original container in order to protect from light.

Blister for 100 mg capsules: