Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Nitrofurantoin 50 mg capsules, hard
Nitrofurantoin 100 mg capsules, hard

(nitrofurantoin)

PRODUCT LICENCE NUMBERS:
PL 48468/0014-0015

Vivalabs Europe Limited

LAY SUMMARY

Nitrofurantoin 50 mg capsules, hard
Nitrofurantoin 100 mg capsules, hard

(nitrofurantoin)

This is a summary of the Public Assessment Report (PAR) for Nitrofurantoin 50 mg capsules, hard and Nitrofurantoin 100 mg capsules, hard. It explains how these products 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 these products.

These products will be referred to as Nitrofurantoin capsules in this lay summary for ease of reading.

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

What are Nitrofurantoin capsules and what are they used for?
These applications are for generic medicines. This means that these medicines are the same as, and considered interchangeable with, reference medicines already authorised in the European Union (EU) called Macrodantin 50mg and 100mg Capsules/Nitrofurantoin 50 mg and 100 mg capsules, hard.

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

How do Nitrofurantoin capsules work?
The active substance, nitrofurantoin (as nitrofurantoin macrocrystals) is an antibiotic.

How are Nitrofurantoin capsules used?
The pharmaceutical form of these medicines are hard capsules and the route of administration is oral (taken by mouth).

The recommended dose is:
Adults:
The normal dosage depends on the type of infection the patient has and instructions should be written on the label provided by the pharmacist. The patient should consult their pharmacist or doctor if these instructions are not clear.
The usual doses are:

- For treatment of infections: Either one 50 mg capsule or one 100 mg capsule four times a day for seven days
- For prevention of further infections: Either one 50 mg capsule or one 100 mg capsule at bedtime
- For prevention of infections during surgery: One 50 mg capsule four times a day on the day of the operation and three days thereafter.

Use in children and infants over three months of age:
The dose depends on the weight of the child and will be provided by the child's doctor. The caregiver should follow the child's doctor's instructions exactly.

Children below 3 months of age should not take nitrofurantoin. For children under the age of 6 years or weighing less than 25 kg, other, more suitable formulations should be used.

For further information on how Nitrofurantoin capsules are used, refer to the package leaflet and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take these medicines exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Nitrofurantoin capsules have been shown in studies?
Because Nitrofurantoin capsules are generic medicines, studies in healthy volunteers have been limited to tests to determine that these bioequivalent to the reference medicines. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Nitrofurantoin capsules?
Because Nitrofurantoin capsules are generic medicines and are bioequivalent to the reference medicines, the benefits and possible side effects are considered to be the same as the reference medicines.

For the full list of all side effects reported with these medicines, see Section 4 of the package leaflet or the SmPCs available on the MHRA website.

Why were Nitrofurantoin capsules approved?
It was concluded that, in accordance with EU requirements, Nitrofurantoin capsules have been shown to be bioequivalent to the reference medicines. Therefore, the MHRA decided that, as for the reference medicines, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Nitrofurantoin capsules?
A Risk Management Plan (RMP) has been developed to ensure that Nitrofurantoin capsules are used as safely as possible. Based on this plan, safety information has been included in the SmPCs and the package leaflet, 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 capsules
Marketing Authorisations for Nitrofurantoin capsules were granted in the UK on 09 November 2020.

The full PAR for Nitrofurantoin capsules follows this summary.

This summary was last updated in December 2020.

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Nitrofurantoin 50 mg capsules, hard (PL 48468/0014) and Nitrofurantoin 100 mg capsules, hard (PL 48468/0015) could be approved.

The products are approved for the following indications in in adults, children and infants over 3 months old:

- For the treatment of and prophylaxis against acute or recurrent, uncomplicated lower urinary tract infections or pyelitis either spontaneous or following surgical procedures. Nitrofurantoin is specifically indicated for the treatment of infections when due to susceptible strains of *Escherichia coli*, enterococci, staphylococci, *Citrobacter, Klebsiella* and *Enterobacter*.

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

The active substance, nitrofurantoin (as nitrofurantoin macrocrystals), 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.

These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic medicines of suitable originator medicinal products, Macrodantin 50mg and 100mg Capsules/Nitrofurantoin 50 mg and 100 mg capsules, hard that have been licensed within the EU for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the applications are based on being generic medicinal products of reference products that have been licensed for over 10 years.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications are based on being generic medicinal products of reference products that have been in clinical use for over 10 years. The bioequivalence study was conducted in line with current Good Clinical Practice (GCP).

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

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 13 September 2018 and 08-09 October 2020 because major objections were raised with respect to quality and clinical aspects of the dossier. The Committee provisionally concluded that further information on quality and clinical aspects should be requested before the products could be

approved. In response to the CHM advice, the applicant provided additional data, to address the points that had been raised. Following consideration of the responses and further data that were submitted, the approval of the Marketing Authorisations was recommended.

Marketing Authorisations were granted for these products on 09 November 2020.

II QUALITY ASPECTS

II.1 Introduction

These products contain 50 mg or 100 mg of nitrofurantoin (as nitrofurantoin macrocrystals) in each capsule.

In addition to nitrofurantoin, these products contain the excipients lactose monohydrate, pregelatinised maize starch, purified talc, magnesium stearate in the capsule fill, and iron oxide yellow (E172), titanium dioxide (E171) and gelatin in the capsule shell.

The finished products are packaged in aluminium-white opaque polyvinylchloride blisters, in pack sizes of 10, 14, 15, 20, 28, 30 and 100 capsules.

Not all pack sizes may be marketed.

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.

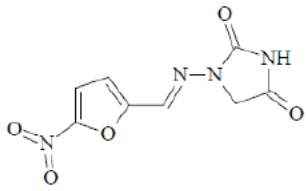
II.2 ACTIVE SUBSTANCE

rINN: Nitrofurantoin

Chemical Name: 1-[[(5-nitrofuran-2-yl)methylene]amino]imidazolidine-2,4-dione

Molecular Formula: $C_8H_6N_4O_5$

Chemical Structure:



Molecular Weight: 238.2 g/mol

Appearance: A yellow crystalline powder or yellow crystals, odourless or almost odourless

Solubility: Very slightly soluble in water and in ethanol (96 percent), soluble in dimethylformamide

Nitrofurantoin is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current European regulations concerning materials in contact with food.

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

II.3 DRUG PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

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

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate and gelatin, no excipients of animal or human origin are used in the final products. The suppliers of gelatin has provided Certificates of Suitability from the European Directorate for the Quality of Medicines and Healthcare (EDQM) to show that it is manufactured in line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).

The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the products

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

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

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years, with the storage conditions ‘Do not store above 25ºC.’ , is acceptable.

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

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of Marketing Authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of nitrofurantoin 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.

III.2 Pharmacology
No new pharmacology data were provided and none were required for these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of already authorised products, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects
The grant of Marketing Authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of nitrofurantoin are well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for applications of this type. An overview based on a literature review and a review of the study is, thus, satisfactory.

IV. 2 Pharmacokinetics
In support of the applications, the applicant submitted the following bioequivalence study.

Study (under fed conditions)
The study was an open-label, randomised, single-dose, two-treatment, two period, two-sequence, oral, cross-over bioequivalence study comparing the test product Nitrofurantoin Capsules 100 mg versus the reference product Nitrofurantoin 100 mg Capsules, hard in healthy, adult, human, subjects under fed conditions.

After an overnight fast of at least 10 hours, subjects were administered a single dose (1 x 100 mg capsule) of either treatment with approximately 240 ml of water 30 minutes after a high fat, high calorie breakfast. Blood samples were taken pre-dose and up to 28 hours post dose, with a washout period of eight days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Table 1 Statistical analysis for nitrofurantoin

PK Parameters (Unit)	Geometric Least Square Means and It"s Ratio (N=51)			ISCV (%)	90% CI
	Test Product (T)	Reference Product (R)	(T/R) (%)		
C_{max} (ng/mL)	452.880	466.771	97.02	22.92	89.99% - 104.61%
AUC_{0-t} (hr*ng/mL)	2426.823	2436.611	99.60	10.22	96.28% - 103.03%

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
ISCV Intra-subject coefficient of variation
CI confidence intervals

In line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

As the strengths of the product applied for (50 mg and 100 mg) meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the 100 mg product strength can be extrapolated to the 50 mg strength.

IV.3 Pharmacodynamics
No new pharmacodynamic data have been submitted for these applications and none were required.

IV.4 Clinical efficacy
No new efficacy data were submitted with these applications and none were required.

IV.5 Clinical safety
With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from

IV.6 Risk Management Plan (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects
The grant of Marketing Authorisations is recommended for these applications.

V USER CONSULTATION
The Patient Information Leaflet (PIL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the PIL meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

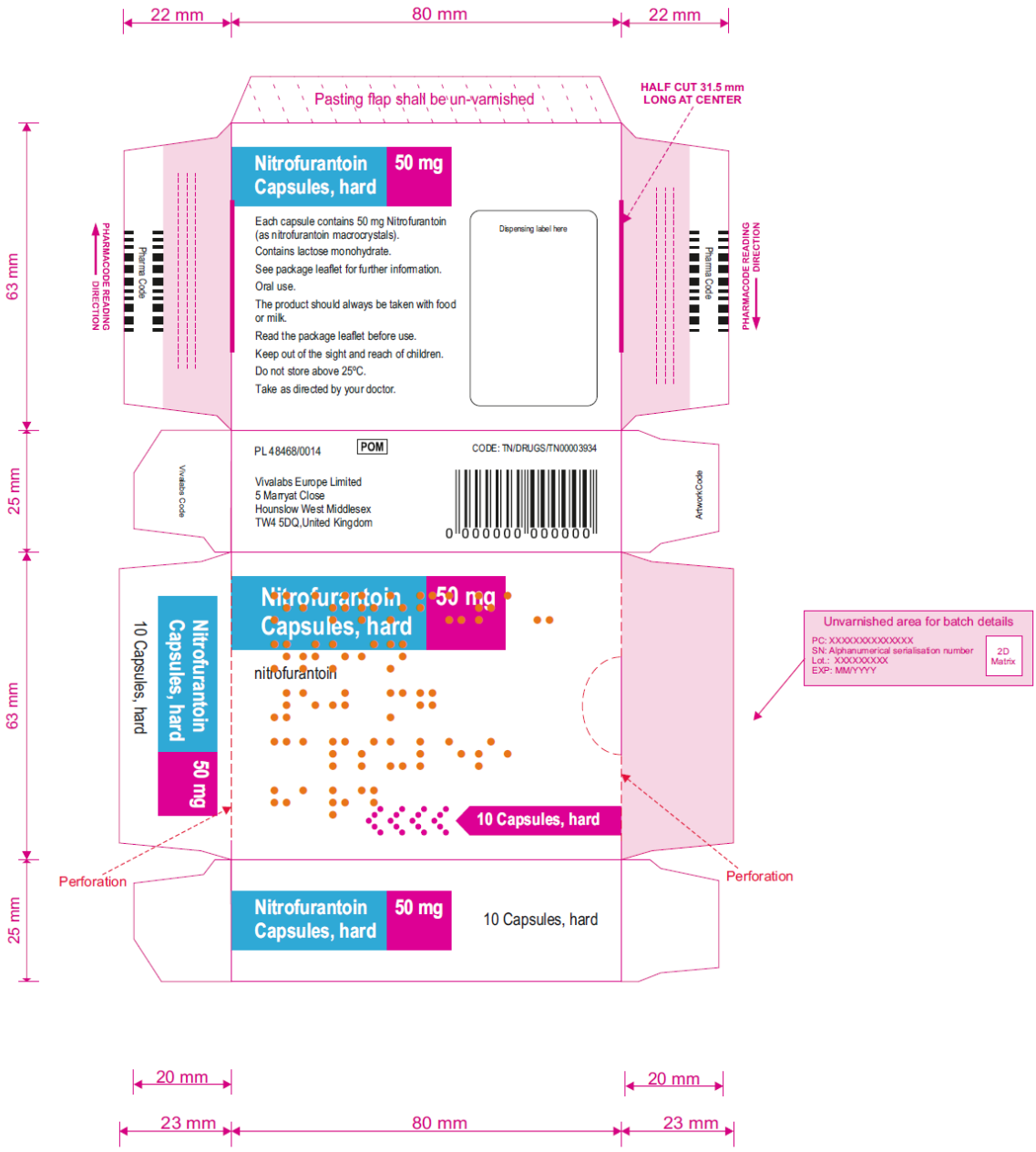
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with nitrofurantoin is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

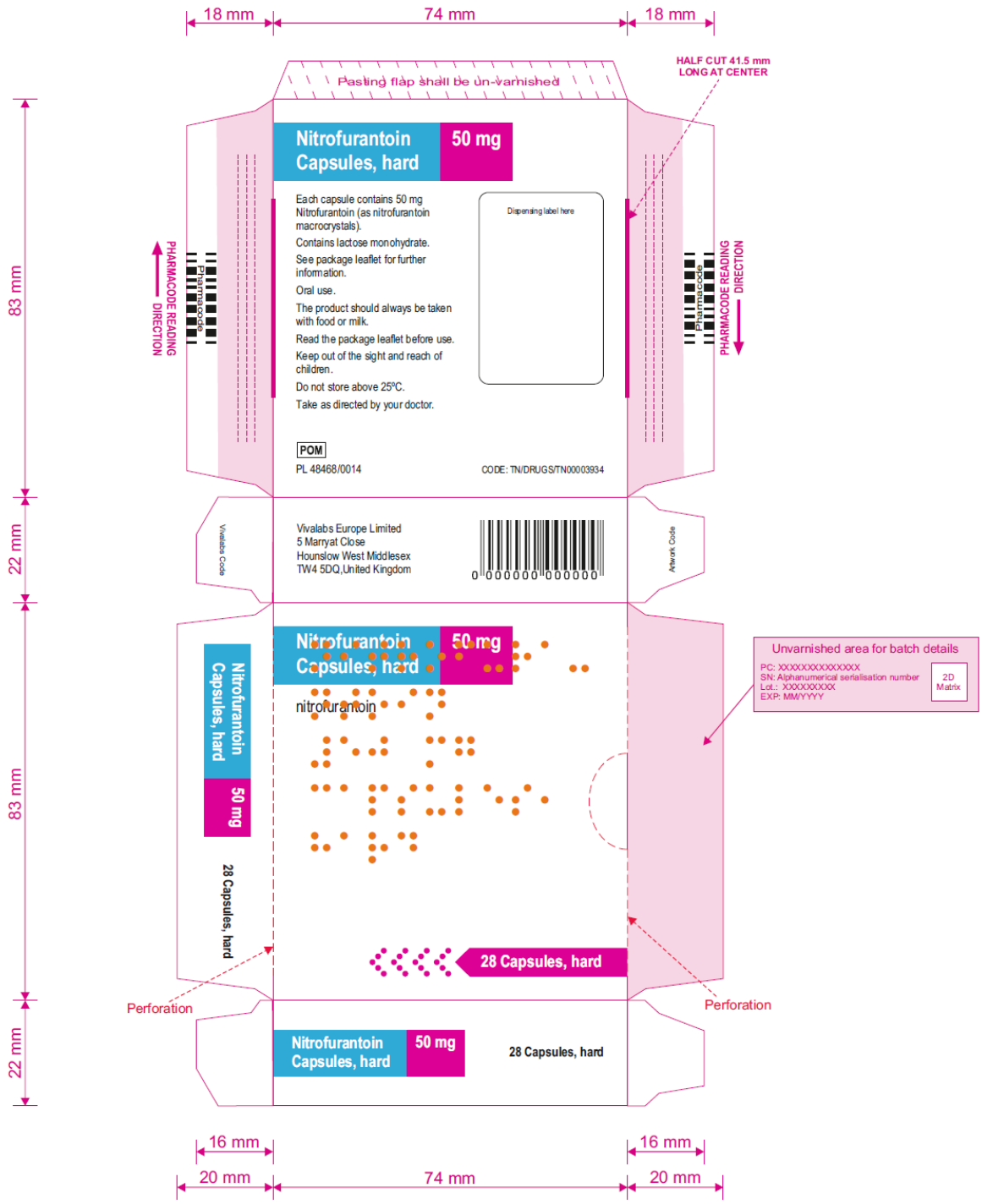
The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product(s).

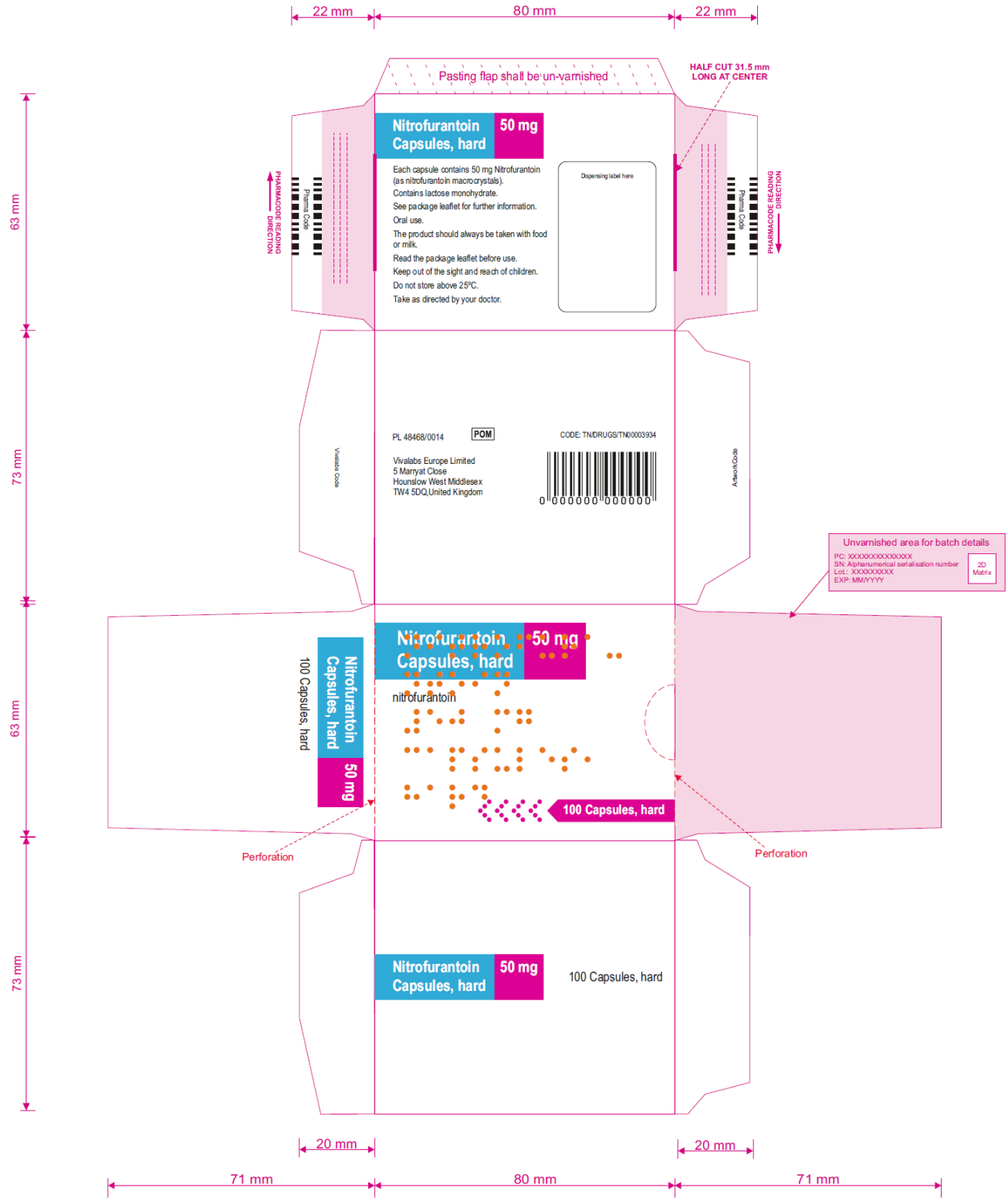
In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

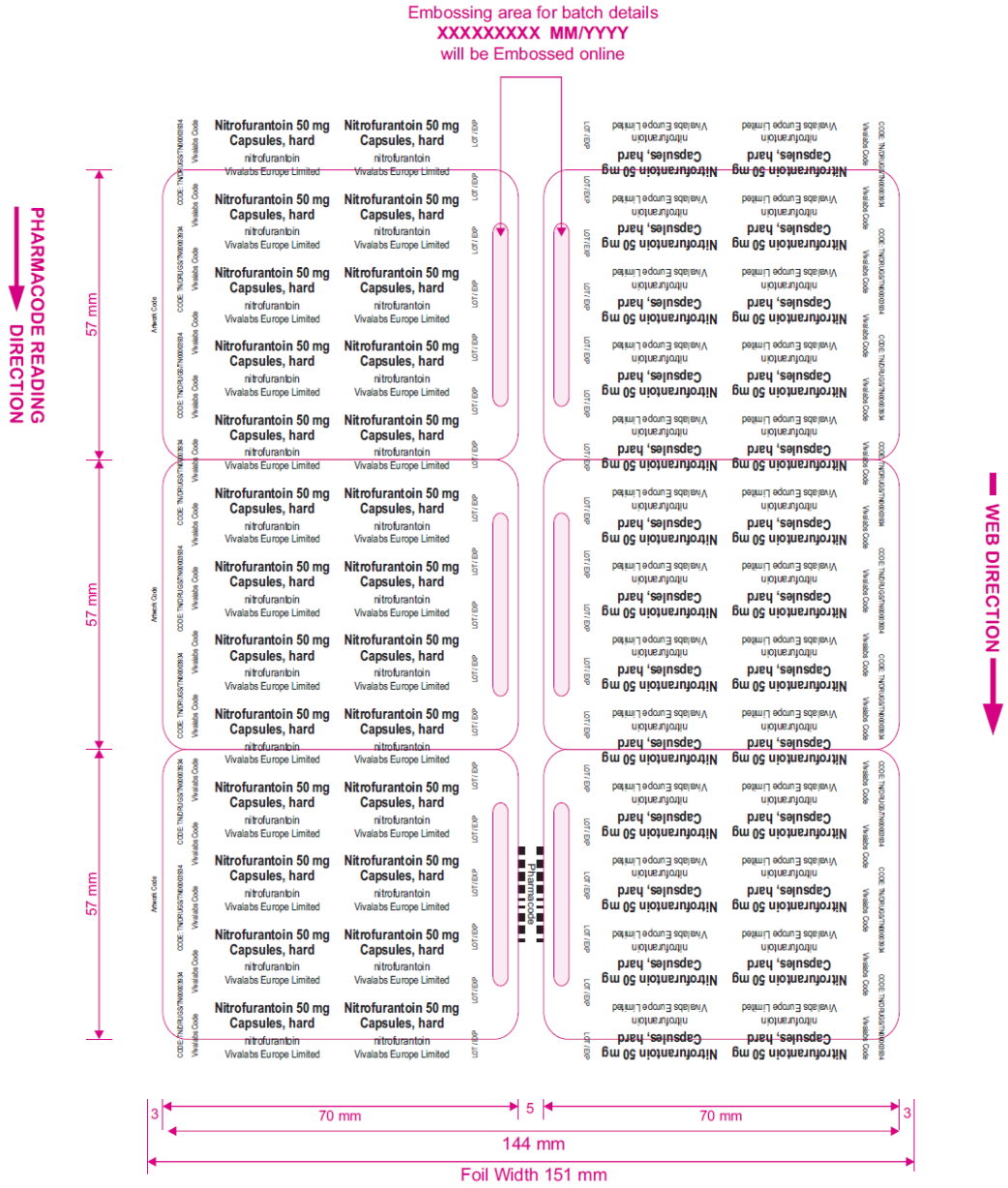
Representative copies of the labels at the time of UK licensing are provided below.

Nitrofurantoin 50 mg capsules, hard

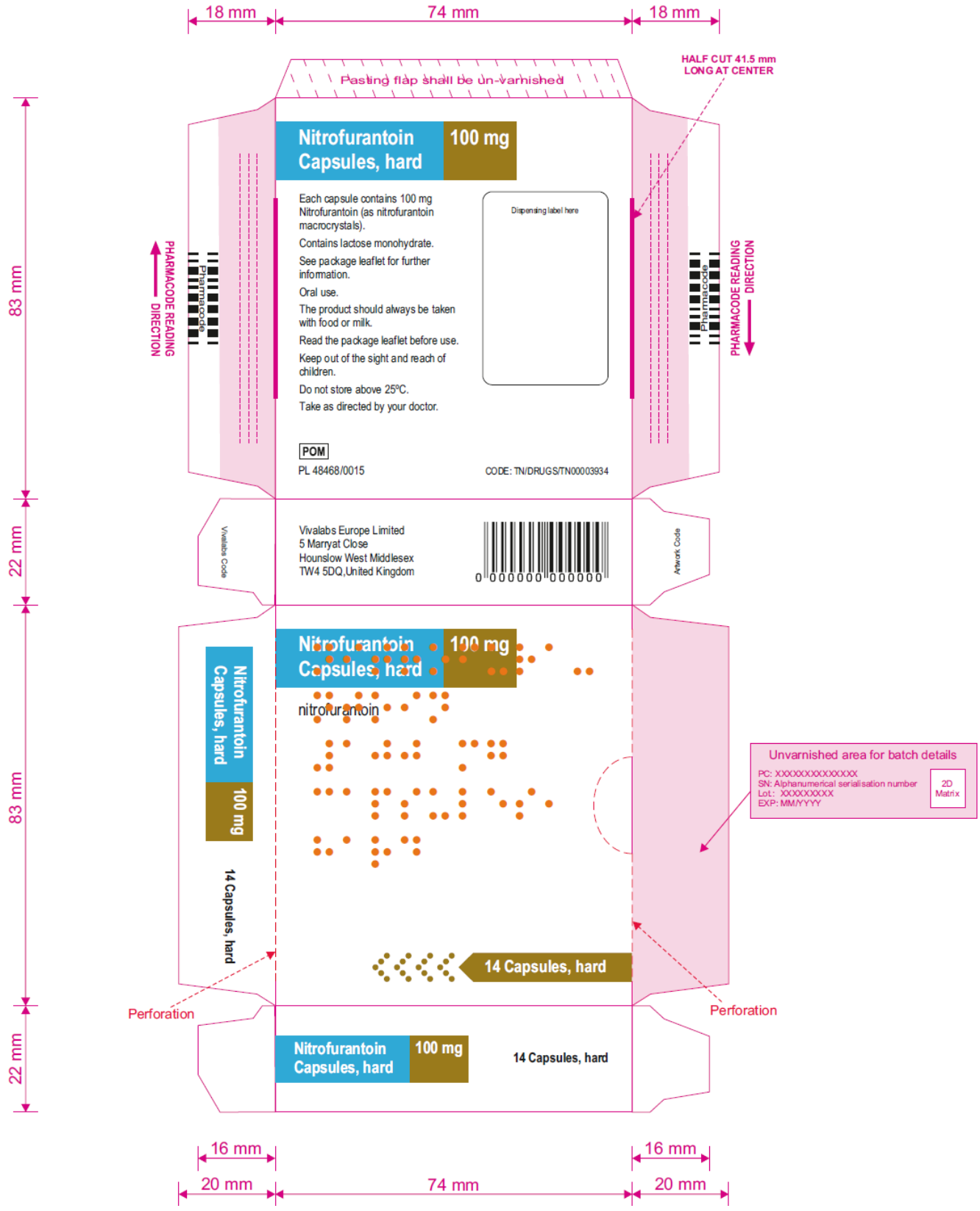


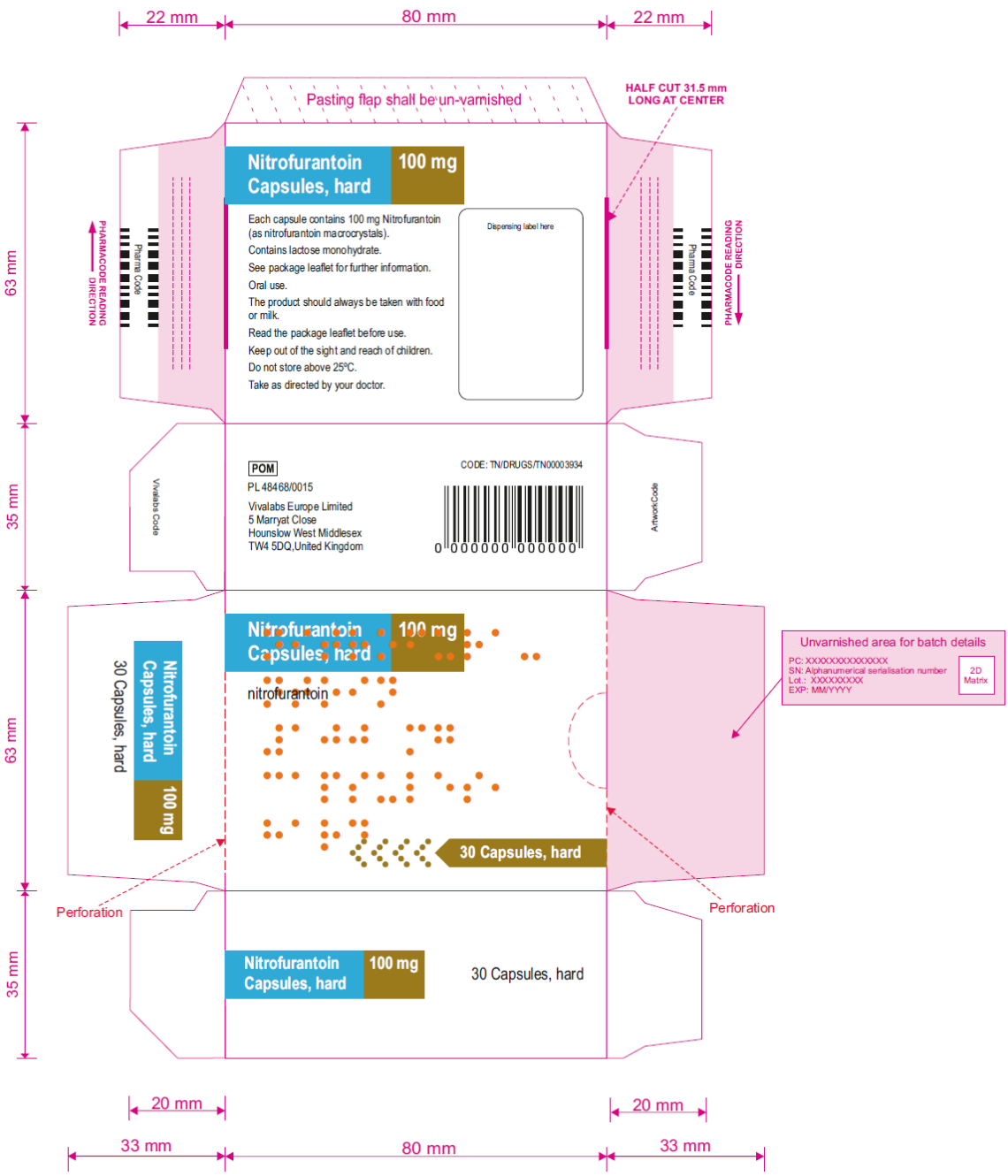

18 mm
74 mm
18 mm
Pasting flap shall be un-varnished
HALF CUT 41.5 mm LONG AT CENTER
83 mm
22 mm
83 mm
22 mm
Nitrofurantoin Capsules, hard
50 mg
Each capsule contains 50 mg Nitrofurantoin (as nitrofurantoin macrocrystals).
Contains lactose monohydrate.
See package leaflet for further information.
Oral use.
The product should always be taken with food or milk.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Do not store above 25ºC.
Take as directed by your doctor.
Dispensing label here
PHARMACODE READING DIRECTION
POM
PL 48468/0014
CODE: TN/DRUGS/TN00003934
Vivalabs Europe Limited
5 Marryat Close
Hounslow West Middlesex
TW4 5DQ,United Kingdom
Vivalabs Code
Artwork Code
Unvarnished area for batch details
PC: XXXXXXXXXXXXX
SN: Alphanumerical serialisation number
Lot.: XXXXXXXX
EXP: MM/YYYY
2D Matrix
nitrofurantoin
28 Capsules, hard
Perforation
Perforation
16 mm
20 mm
74 mm
16 mm
20 mm

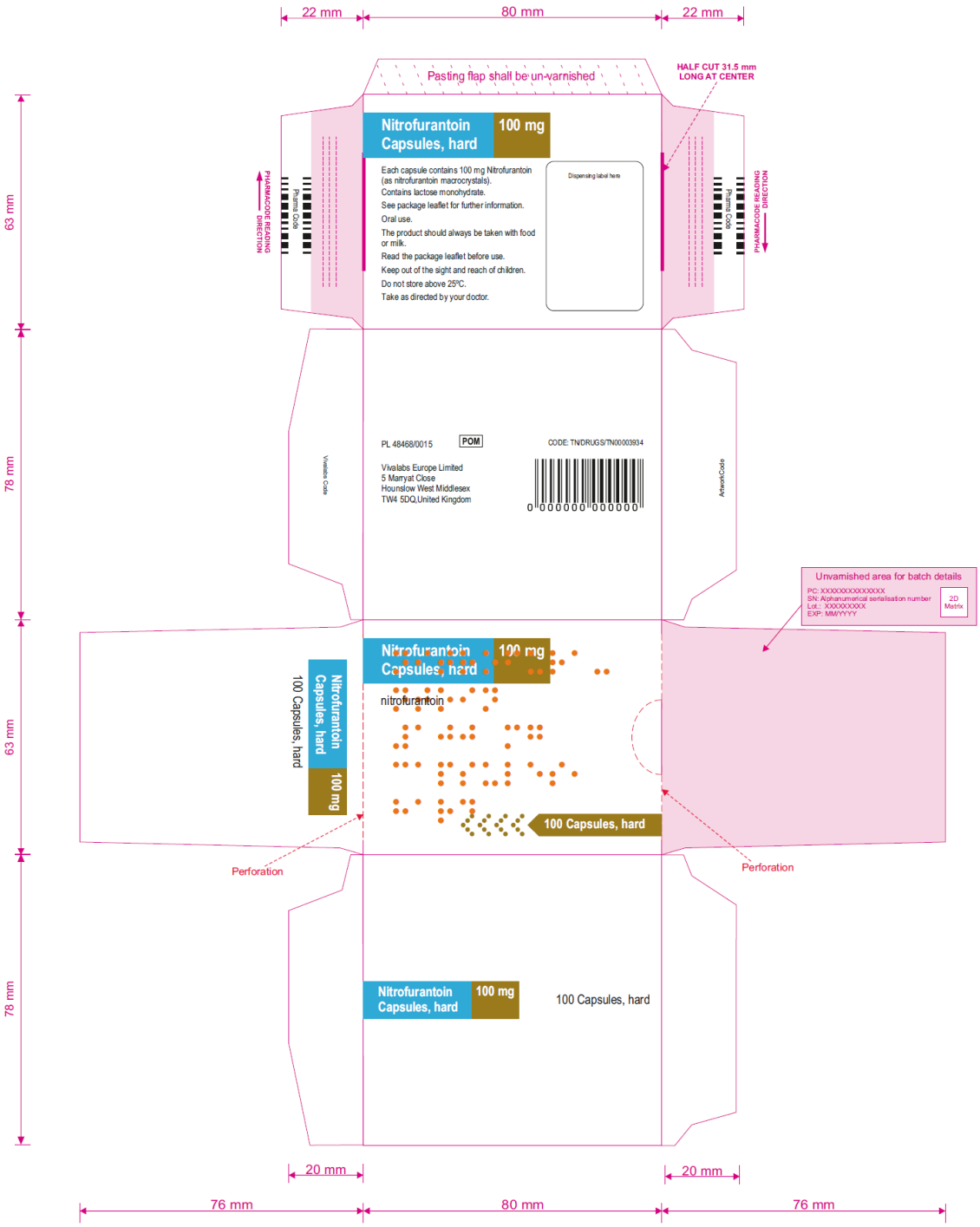

22 mm
80 mm
22 mm
Pasting flap shall be un-varnished
HALF CUT 31.5 mm LONG AT CENTER
63 mm
73 mm
63 mm
73 mm
Nitrofurantoin Capsules, hard 50 mg
Each capsule contains 50 mg Nitrofurantoin (as nitrofurantoin macrocrystals).
Contains lactose monohydrate.
See package leaflet for further information.
Oral use.
The product should always be taken with food or milk.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Do not store above 25ºC.
Take as directed by your doctor.
Dispensing label here
PHARMACODE READING DIRECTION
Pharma Code
PL 48468/0014
POM
CODE: TN/DRUGS/TN00003934
Vivalabs Europe Limited
5 Marryat Close
Hounslow West Middlesex
TW4 5DQ,United Kingdom
Vivalabs Code
Artwork Code
Unvarnished area for batch details
PC: XXXXXXXXXXXXX
SN: Alphanumerical serialisation number
Lot.: XXXXXXXXX
EXP: MM/YYYY
2D Matrix
Nitrofurantoin Capsules, hard 50 mg
nitrofurantoin
100 Capsules, hard
Perforation
Perforation
20 mm
20 mm
71 mm
80 mm
71 mm


Embossing area for batch details
XXXXXXXX MM/YYYY
will be Embossed online
PHARMACODE READING DIRECTION
WEB DIRECTION
57 mm
57 mm
57 mm
Nitrofurantoin 50 mg Capsules, hard
nitrofurantoin
Vivalabs Europe Limited
Pharma Code
3
70 mm
5
70 mm
3
144 mm
Foil Width 151 mm

Nitrofurantoin 100 mg capsules, hard




22 mm
80 mm
22 mm
Pasting flap shall be un-varnished
HALF CUT 31.5 mm LONG AT CENTER
63 mm
35 mm
63 mm
35 mm
Nitrofurantoin Capsules, hard
100 mg
Each capsule contains 100 mg Nitrofurantoin (as nitrofurantoin macrocrystals).
Contains lactose monohydrate.
See package leaflet for further information.
Oral use.
The product should always be taken with food or milk.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Do not store above 25ºC.
Take as directed by your doctor.
Dispensing label here
PHARMACODE READING DIRECTION
Pharma Code
POM
PL 48468/0015
Vivalabs Europe Limited
5 Marryat Close
Hounslow West Middlesex
TW4 5DQ,United Kingdom
CODE: TN/DRUGS/TN00003934
Vivalabs Code
ArtworkCode
Nitrofurantoin Capsules, hard
100 mg
30 Capsules, hard
nitrofurantoin
Unvarnished area for batch details
PC: XXXXXXXXXXXXX
SN: Alphanumerical serialisation number
Lot.: XXXXXXXXX
EXP: MM/YYYY
2D Matrix
30 Capsules, hard
Perforation
Perforation
Nitrofurantoin Capsules, hard
100 mg
30 Capsules, hard
20 mm
20 mm
33 mm
80 mm
33 mm


22 mm
80 mm
22 mm
Pasting flap shall be un-varnished
HALF CUT 31.5 mm LONG AT CENTER
63 mm
78 mm
63 mm
78 mm
Nitrofurantoin Capsules, hard
100 mg
Each capsule contains 100 mg Nitrofurantoin (as nitrofurantoin macrocrystals).
Contains lactose monohydrate.
See package leaflet for further information.
Oral use.
The product should always be taken with food or milk.
Read the package leaflet before use.
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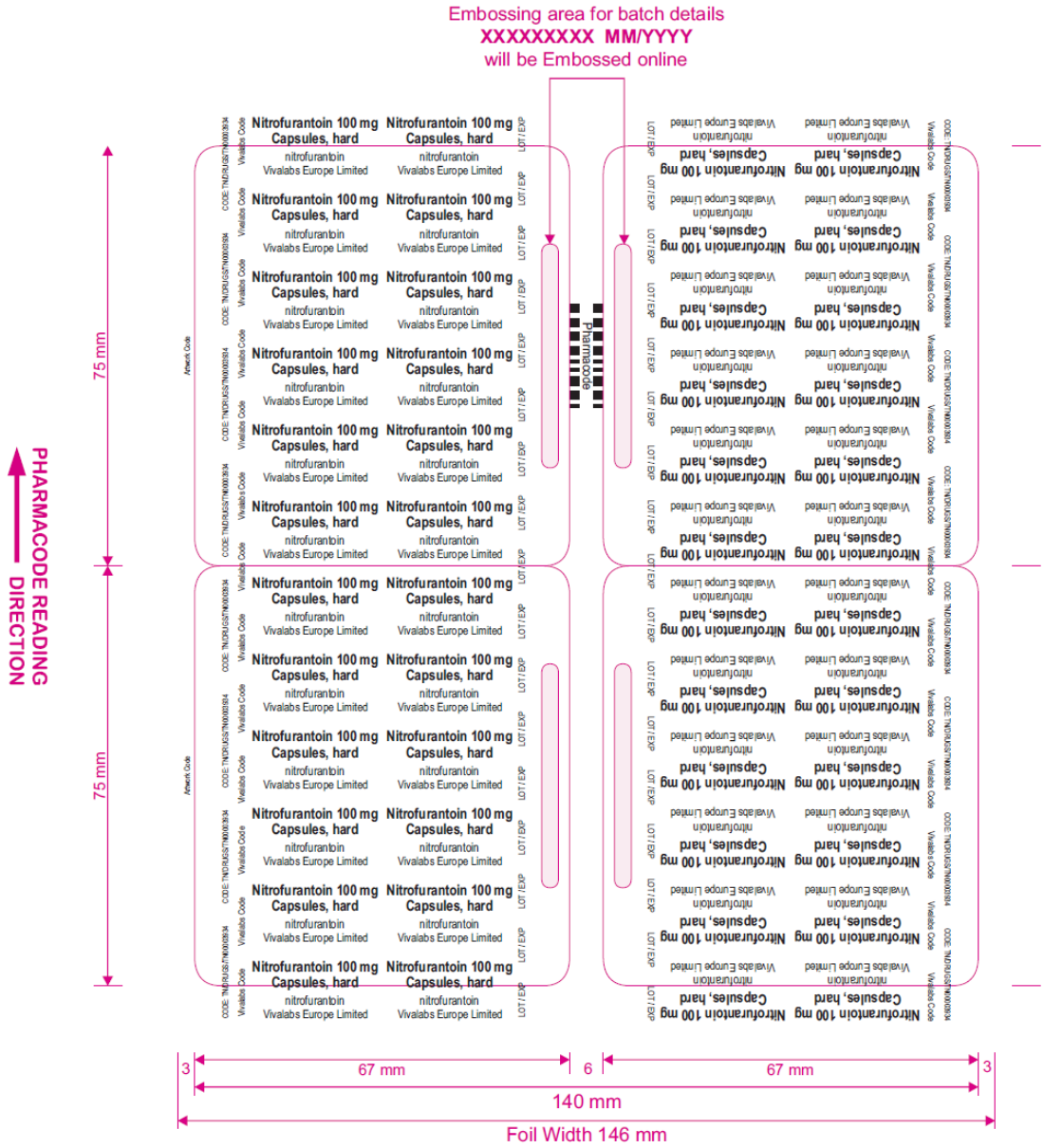
5 Marryat Close
Hounslow West Middlesex
TW4 5DQ,United Kingdom
Vivalabs Code
Artwork Code
Unvarnished area for batch details
PC: XXXXXXXXXXXXX
SN: Alphanumerical serialisation number
Lot.: XXXXXXXX
EXP.: MM/YYYY
2D Matrix
nitrofurantoin
100 Capsules, hard
Perforation
Perforation
20 mm
20 mm
76 mm
80 mm
76 mm


Embossing area for batch details
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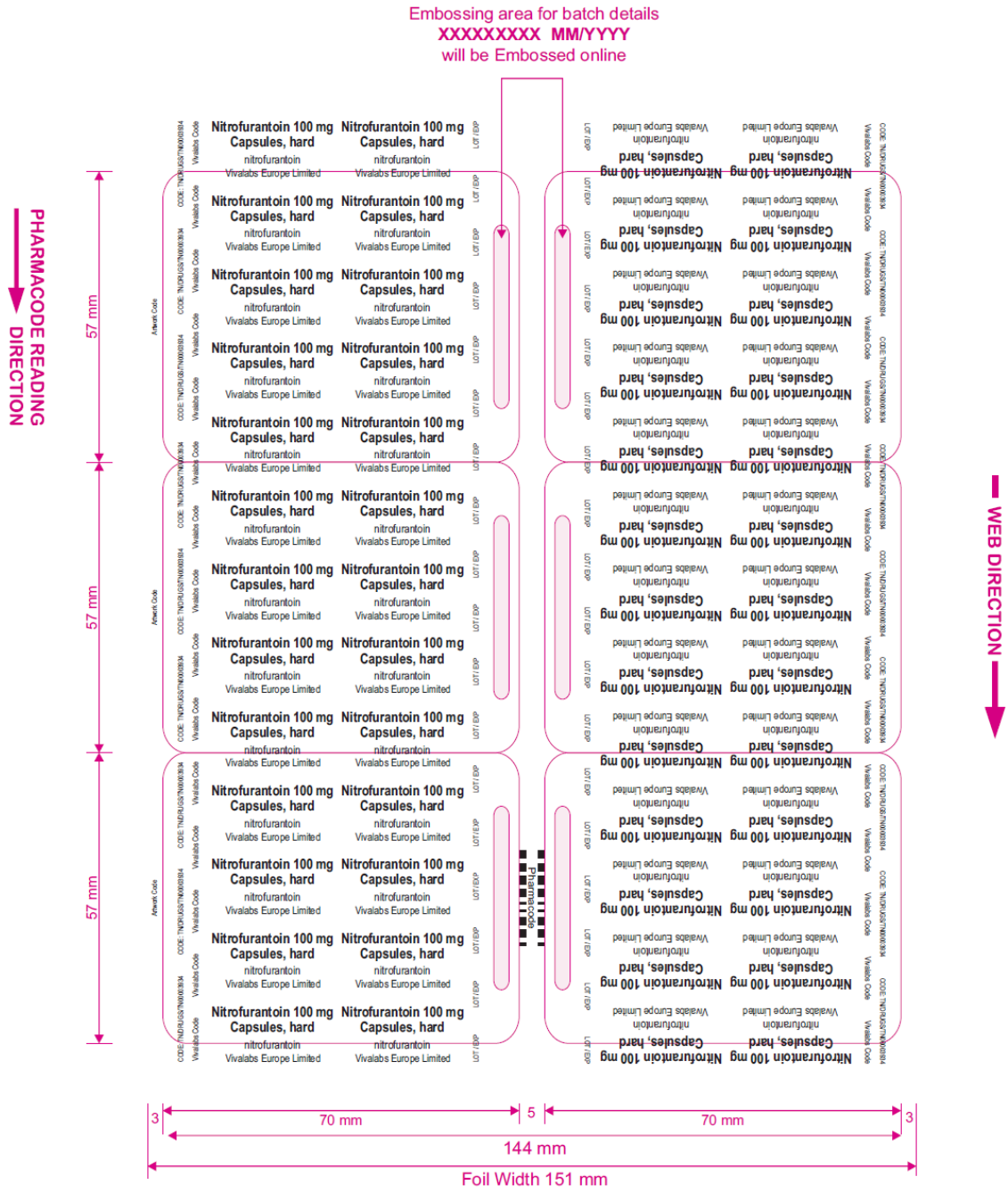
will be Embossed online
Pharmacode
PHARMACODE READING DIRECTION
WEB DIRECTION
75 mm
75 mm
Nitrofurantoin 100 mg Capsules, hard
nitrofurantoin
Vivalabs Europe Limited
3
67 mm
6
67 mm
3
140 mm
Foil Width 146 mm


Embossing area for batch details
XXXXXXXXX MM/YYYY
will be Embossed online
PHARMACODE READING DIRECTION
WEB DIRECTION
57 mm
57 mm
57 mm
Nitrofurantoin 100 mg Capsules, hard
nitrofurantoin
Vivalabs Europe Limited
Pharmacode
3
70 mm
5
70 mm
3
144 mm
Foil Width 151 mm

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**