Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Nortriptyline 10 mg Film-coated Tablets
Nortriptyline 25 mg Film-coated Tablets
(nortriptyline hydrochloride)

PL 49565/0090-0091

Rudipharm Limited

LAY SUMMARY

Nortriptyline 10 mg Film-coated Tablets
Nortriptyline 25 mg Film-coated Tablets
(nortriptyline hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Nortriptyline 10 mg and 25 mg Film-coated Tablets. 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 Nortriptyline Film-coated Tablets in this lay summary for ease of reading.

For practical information about using Nortriptyline Film-coated Tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Nortriptyline Film-coated Tablets and what are they used for?
These applications are the same as Nortriptyline 10 mg and 25 mg Film-coated Tablets (PL 21880/0150-0151) which are already authorised.

The Company responsible for Nortriptyline 10 mg and 25 mg Film-coated Tablets has agreed that its scientific data can be used as the basis for the grant of identical licences for Nortriptyline Film-coated Tablets.

Nortriptyline Tablets are used in the treatment of symptoms of depression in adults.

How do Nortriptyline Film-coated Tablets work?
Nortriptyline Film-coated Tablets contain the active substance, nortriptyline (as hydrochloride), which belongs to a group of medicines called antidepressants.

How are Nortriptyline Film-coated Tablets used?
The pharmaceutical form of these medicines is a film-coated tablet and the route of administration is oral (taken by mouth).

Dosage
Adults:
The usual adult dose is 25 mg three or four times daily or the dose may be given once a day, usually at night. The dose should begin at a low level, 10 mg, 3-4 times daily, for example and be increased gradually as required. The maximum dose is 150 mg per day.

Elderly:
The usual dose is 30 mg to 50 mg/day in divided doses. Treatment may start with 10 mg three times a day.

Use in children and adolescent
Nortriptyline Film-coated Tablets should not be used in children and adolescents aged less than 18 years, as safety and efficacy have not been established.

For further information on how Nortriptyline Film-coated Tablets are used, refer to the PIL 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 Nortriptyline Film-coated Tablets have been shown in studies?
Nortriptyline Film-coated Tablets are considered identical to the previously authorised products with the same benefits and risks. No new studies have been provided for Nortriptyline Film-coated Tablets, however, reference is made to the studies for Nortriptyline 10 mg and 25 mg Film-coated Tablets.

What are the possible side effects of Nortriptyline Film-coated Tablets?
For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with these medicines. Patients can also report suspected side effects themselves, or a report can be made on behalf of the patient by someone else who cares for them, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of these medicines.

Nortriptyline Film-coated Tablets are considered to be identical to the previously authorised products with the same benefits and risks.

Why were Nortriptyline Film-coated Tablets approved?
The MHRA decided that the benefits of Nortriptyline Film-coated Tablets are greater than the risks and recommended that these medicines are approved for use.

What measures are being taken to ensure the safe and effective use of Nortriptyline Film-coated Tablets?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Nortriptyline Film-coated Tablets. The RMP details the important risks of Nortriptyline Film-coated Tablets, how these risks can be minimised, any uncertainties about Nortriptyline Film-coated Tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Nortriptyline Film-coated Tablets:

Table 1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• Drug interaction with monoamine oxidase inhibitors, sympathomimetic agents, anaesthetics and barbiturates. • Patients with a history of suicide-related events (or) exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts (or) suicide attempts. • Withdrawal symptoms including insomnia, irritability and excessive perspiration. • In manic-depressive patients, nortriptyline may cause symptoms of the manic phase to emerge. • Patients with cardiovascular disease should be given nortriptyline only under close supervision. • Elderly patients are particularly liable to experience agitation, confusion and postural hypotension. • Bone-marrow depression including agranulocytosis and aplastic anaemia. • Caution when using Nortriptyline in patients who may be at a high risk of developing seizures or have a known diagnosis of epilepsy.
Important potential risks	• Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Nortriptyline. • Toxicity in overdose. • Nortriptyline should be avoided in patients with narrow angle glaucoma or symptoms suggestive of prostatic hypertrophy. • Contra-indicated for the nursing mothers.
Missing information	• Safety for use during pregnancy has not been established.

The information included in the SmPCs and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Nortriptyline Film-coated Tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

A RMP and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Other information about Nortriptyline Film-coated Tablets
Marketing Authorisations were granted in the UK on 03 March 2022.

The full PAR for Nortriptyline Film-coated Tablets follows this summary.

This summary was last updated in April 2022.

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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 Nortriptyline 10 mg and 25 mg Film-coated Tablets PL 49565/0090-0091) could be approved.

The products are approved for the following indication:

- the relief of symptoms of depression in adults.

The active substance, nortriptyline (as nortriptyline hydrochloride), is a tricyclic antidepressant with actions and uses similar to these of amitriptyline. It is the principal active metabolite of amitriptyline.

These are national abridged applications approved under Regulation 56 of The Human Medicines Regulation 2012, as amended (previously Article 10c of Directive 2001/83/EC, as amended) as informed consent applications. The applications cross-refer to the reference products Nortriptyline 10 mg and 25 mg Film-coated Tablets (PL 21880/0150-0151), currently held by, and originally granted in the United Kingdom (UK) to, Medreich PLC on 26 March 2015.

No new non-clinical or clinical data have been supplied and none are required for these informed consent applications.

Suitable justification has been provided for non-submission of an Environmental Risk Assessment (ERA). As the applications are for identical versions of already authorised products, no increase in environmental exposure is anticipated and no ERA is required.

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.

National Marketing Authorisations were granted in the UK on 03 March 2022.

II. EXPERT REPORT

The applicant cross-refers to the data for Nortriptyline 10 mg and 25 mg Film-coated Tablets (PL 21880/0150-0151; Medreich PLC), to which these applications are claimed to be identical. This is acceptable.

III. ASSESSOR'S COMMENTS ON THE PRODUCT INFORMATION

SUMMARY OF PRODUCT CHARACTERITICS (SmPC)

The SmPCs are in line with those for Nortriptyline 10 mg and 25 mg Film-coated Tablets (PL 21880/0150-0151; Medreich PLC), dated 04/2019.

PATIENT INFORMATION LEAFLET

Leaflet text and a mock-up have been provided which has been aligned with that for Nortriptyline 10 mg and 25 mg Film-coated Tablets (PL 21880/0150-0151), dated for 02/2019. The user test report submitted for PL 21880/0150-0151 has been provided.

LABEL

Label mock-ups have been provided.

IV. QUALITY ASPECTS

IV.1 Drug Substance

Drug substance specifications

The sources of the active substances are in line with the cross-reference products. The proposed drug substance specification is consistent with the details registered for the cross-reference products.

IV.2. Drug Product

Name

The products have been named in line with current requirements.

Strength, pharmaceutical form, route of administration, container and pack sizes

Nortriptyline 10 mg and 25 mg Film-coated Tablets are available in:

1. Aluminium-clear polyvinylchloride blisters, each containing 10 film-coated tablets, in pack sizes of 10, 30 and 100 film-coated tablets.
2. High density polyethylene (HDPE) containers, each with a polypropylene screw on cap, in a pack size of 100 film-coated tablets.

Not all pack sizes may be marketed.

The appearance of the products is identical to that of the cross-reference products.

The proposed shelf life of the product is 3 years for the product in blisters and unopened HDPE container and within 60 days after first opening for the product in the opened HDPE container, with no special storage conditions.

The proposed packaging, shelf life and storage conditions are consistent with the details registered for the reference products.

Legal status

Prescription only medicine (POM).

Manufacturers

The proposed manufacturing sites are consistent with the details registered for the cross-reference products and evidence of Good Manufacturing Practice (GMP) compliance has been provided.

Qualitative and quantitative compositions

The composition of the proposed products are consistent with the details registered for the cross-reference products.

Manufacturing process & control of critical steps

The proposed manufacturing processes and process controls are consistent with the details registered for the reference products and the maximum batch size is stated.

Finished product release/shelf life specifications

The finished product specifications at release and shelf-life are in line with the details registered for the cross-reference products.

TSE Compliance

With the exception of lactose monohydrate, no excipients of animal or human origin are used in the final products.

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).

V. NON-CLINICAL ASPECTS

As these applications are submitted under Regulation 56 of The Human Medicines Regulations 2012, as amended, (as informed consent applications) no new non-clinical data have been supplied and none are required.

VI. CLINICAL ASPECTS

As these applications are submitted under Regulation 56 of The Human Medicines Regulations 2012, as amended, (as informed consent applications) no new clinical data have been supplied and none are required.

VII. RISK MANAGEMENT PLAN (RMP)

The applicant has submitted a RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulations 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

VIII. USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application, in accordance with legal requirements.

The PIL has been evaluated via a user consultation with target patient groups, in accordance with legal requirements, on the basis of a bridging report making reference to Nortriptyline 10 mg and 25 mg Film-coated Tablets (PL 21880/0150-0151). The bridging report submitted by the applicant is acceptable.

IX. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION

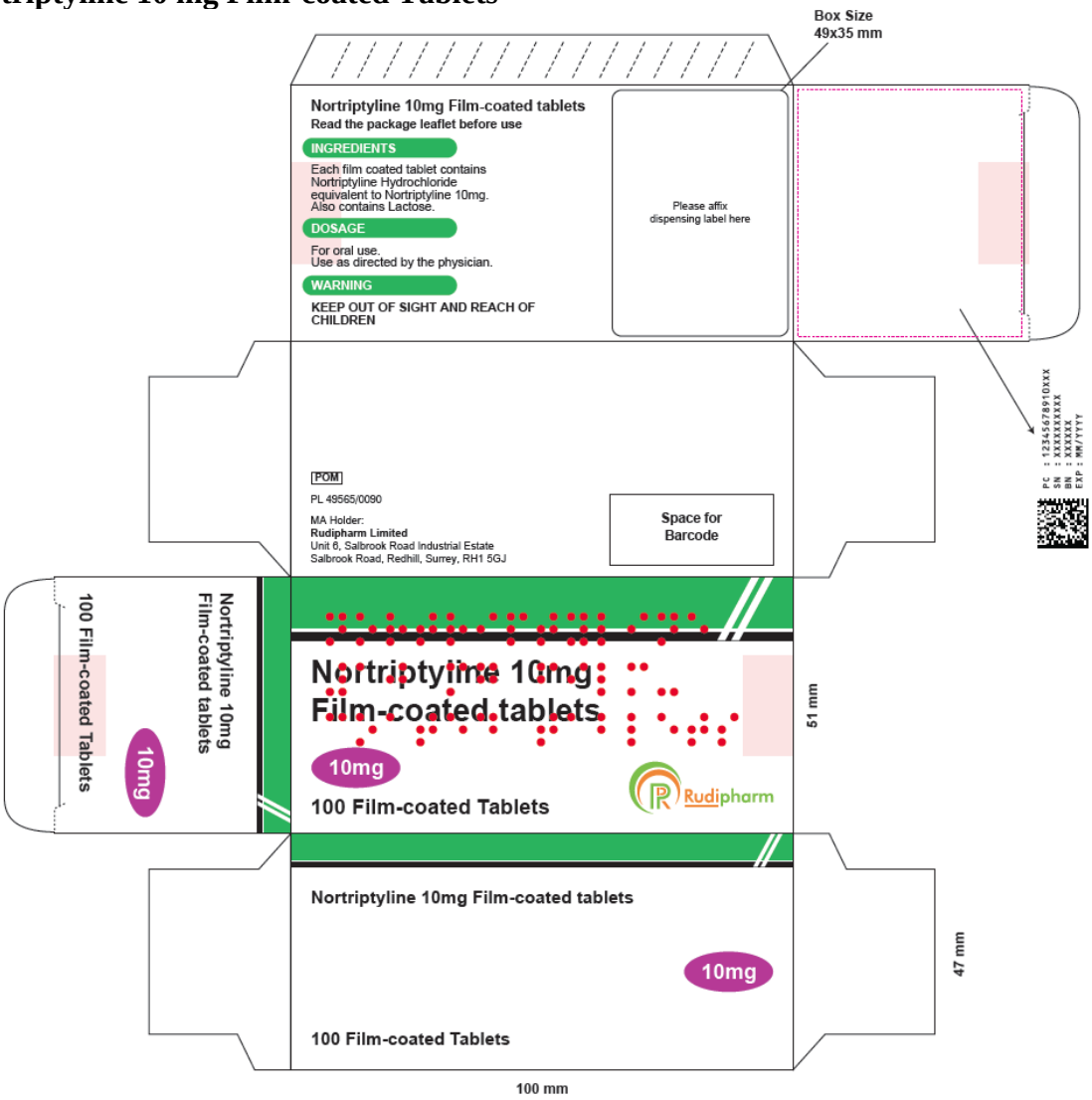
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The applicant's products are identical to the cross-reference products. The benefit/risk balance is, therefore, considered to be the same as for the cross-reference products and positive.

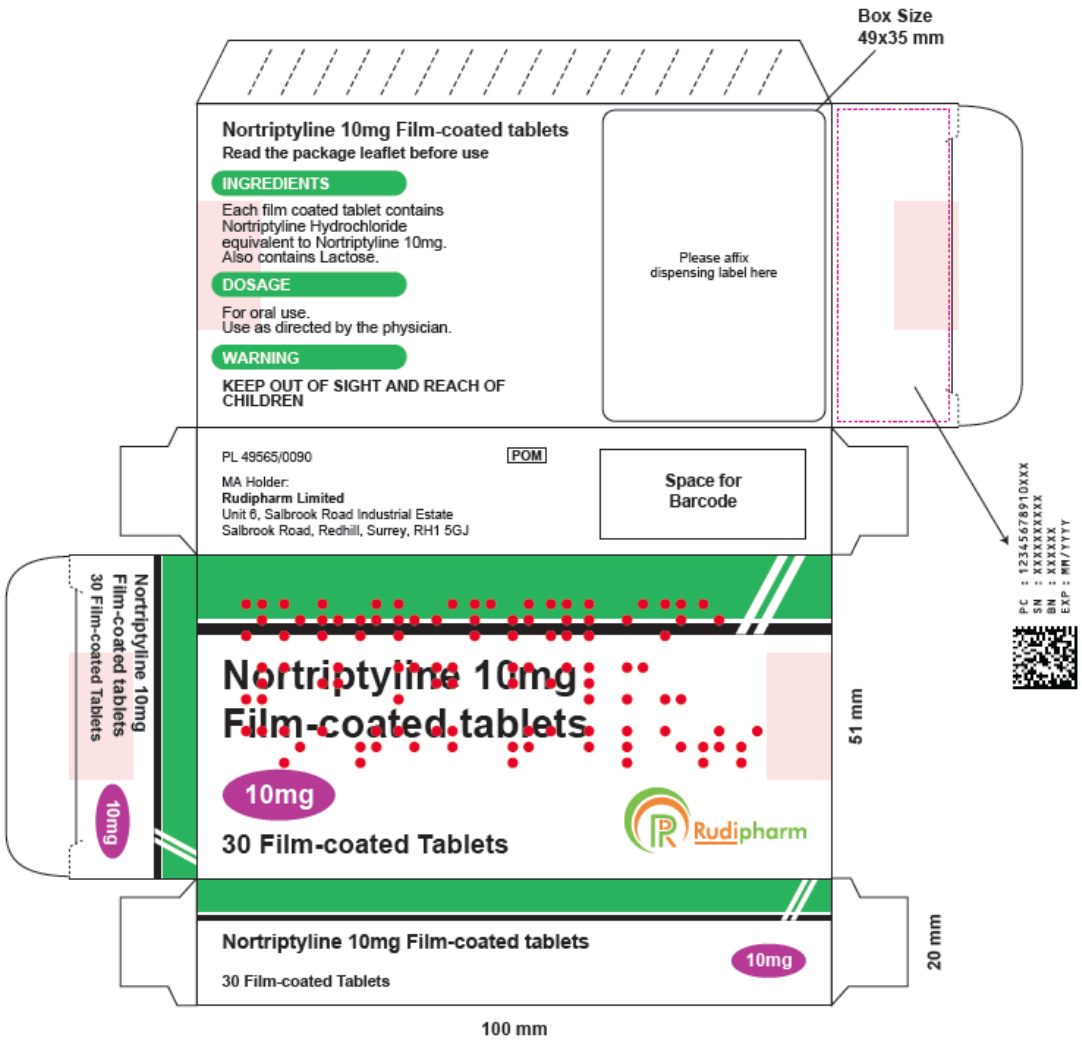
The SmPCs, PIL and labelling are satisfactory, in line with current guidelines and consistent with the cross-reference products.

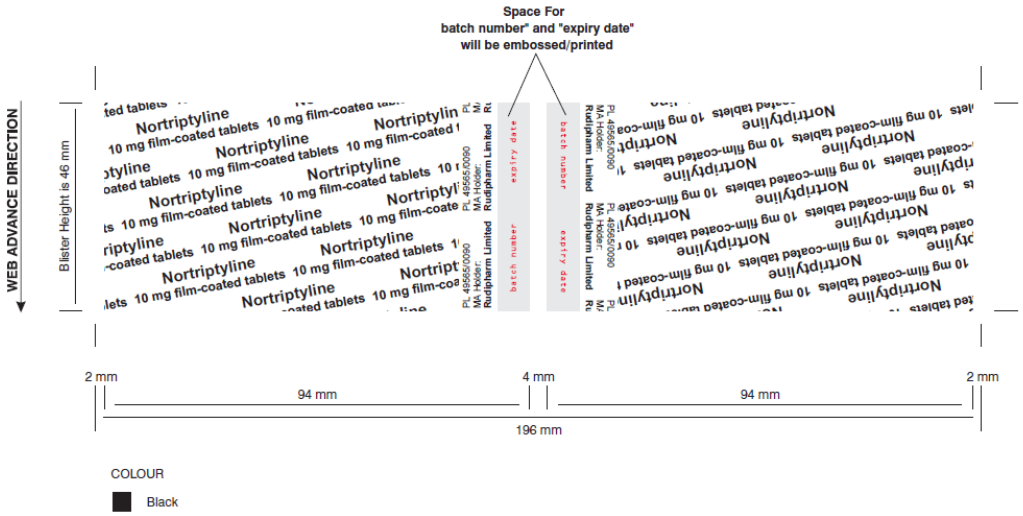
In accordance with legal requirements, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

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

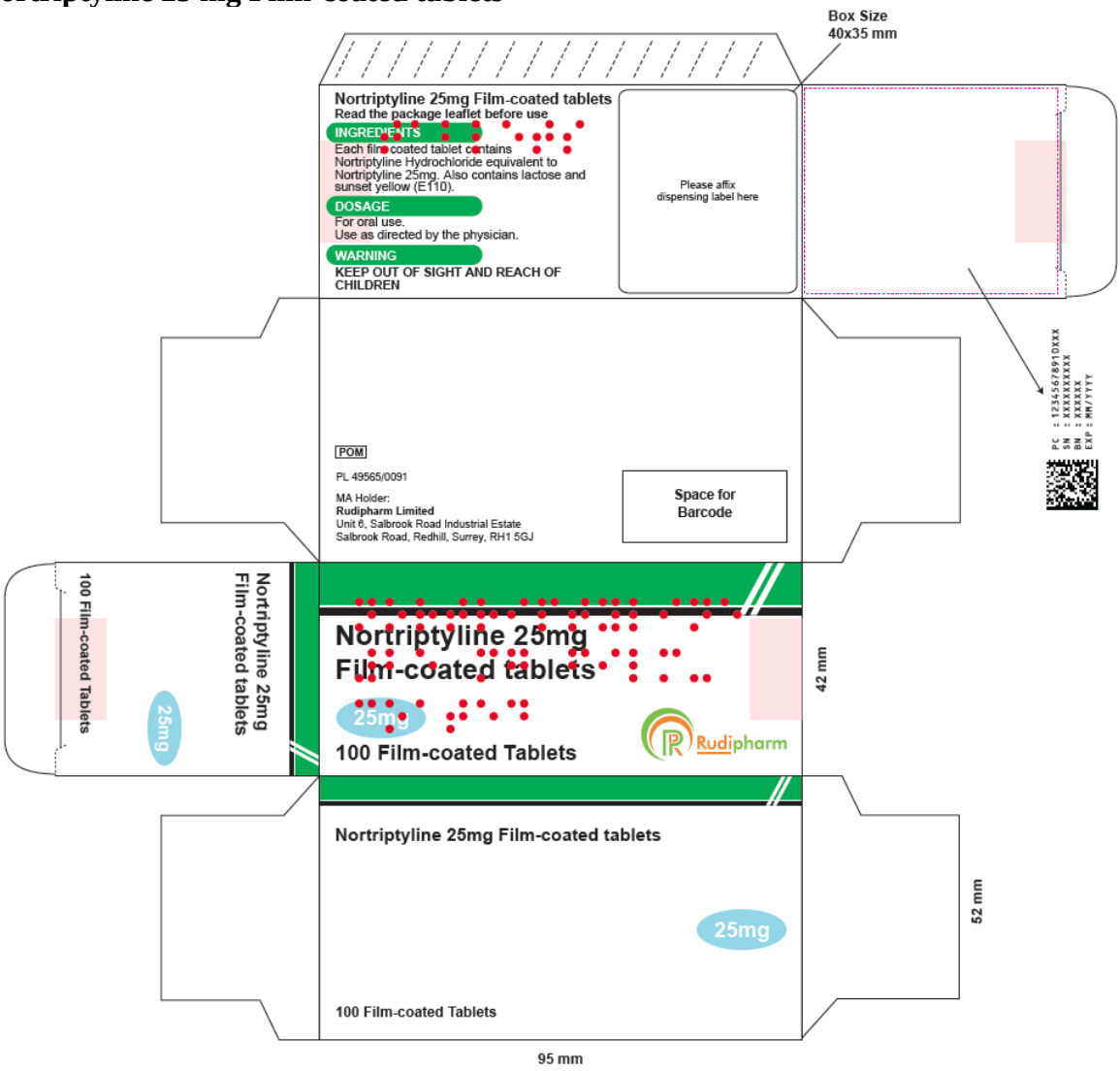
Nortriptyline 10 mg Film-coated Tablets

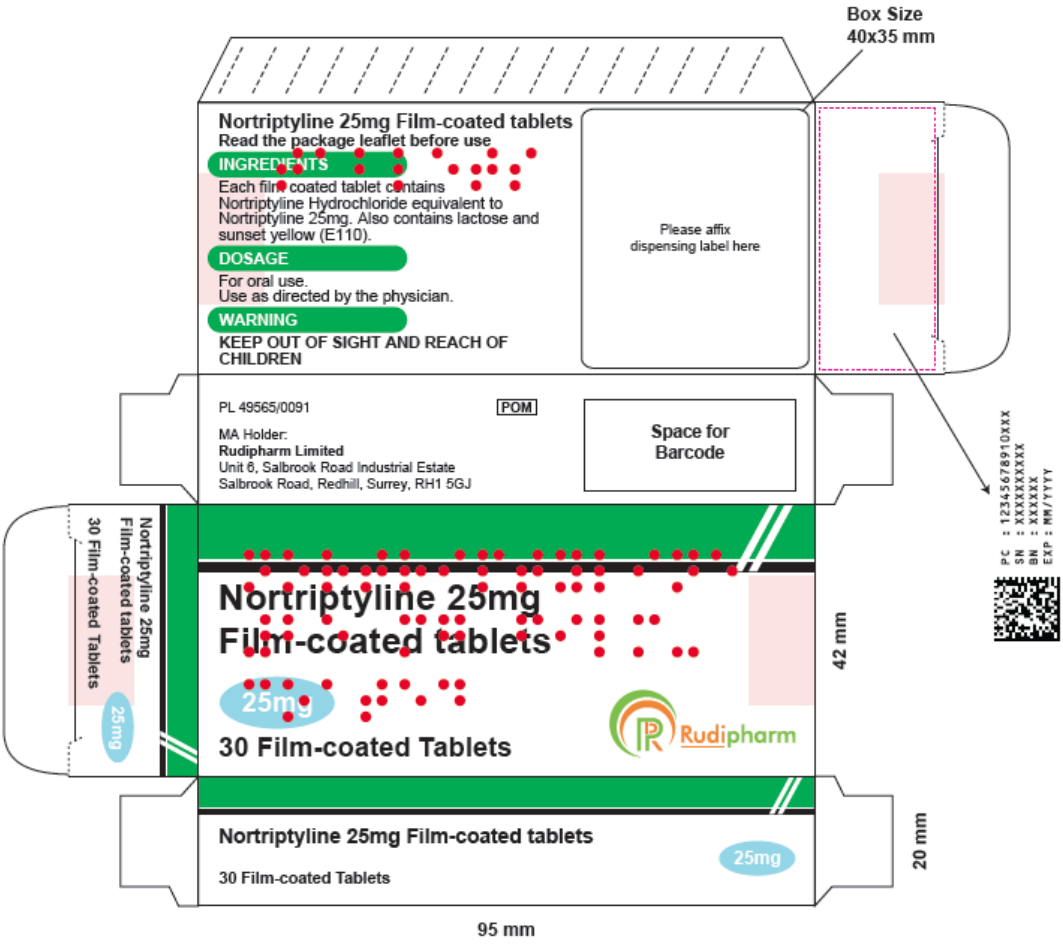


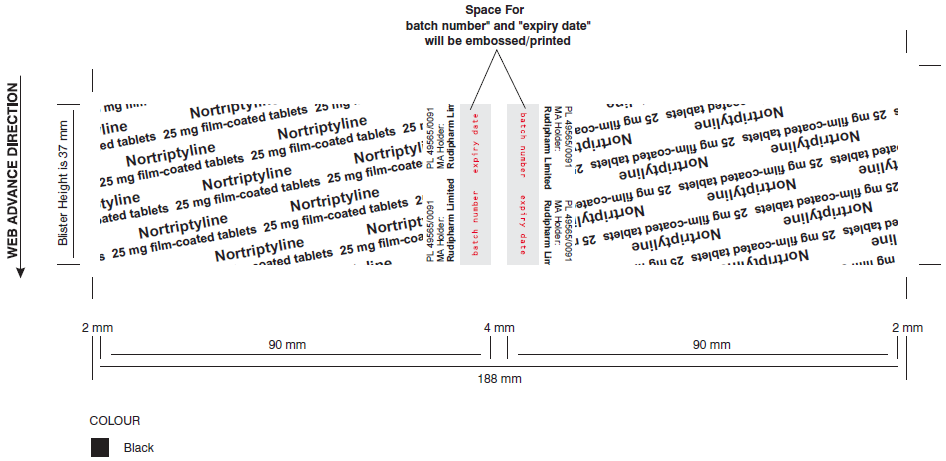

Box Size
49x35 mm
Nortriptyline 10mg Film-coated tablets
Read the package leaflet before use
INGREDIENTS
Each film coated tablet contains Nortriptyline Hydrochloride equivalent to Nortriptyline 10mg. Also contains Lactose.
DOSAGE
For oral use.
Use as directed by the physician.
WARNING
KEEP OUT OF SIGHT AND REACH OF CHILDREN
Please affix dispensing label here
PL 49565/0090
POM
MA Holder:
Rudipharm Limited
Unit 6, Salbrook Road Industrial Estate
Salbrook Road, Redhill, Surrey, RH1 5GJ
Space for Barcode
PC : 1234567891OXXX
SN : XXXXXXXXXX
BN : XXXXXX
EXP : MM/YYYY
Nortriptyline 10mg Film-coated tablets
30 Film-coated Tablets
10mg
Nortriptyline 10mg Film-coated tablets
10mg
30 Film-coated Tablets
Rudipharm
51 mm
Nortriptyline 10mg Film-coated tablets
30 Film-coated Tablets
10mg
20 mm
100 mm


Space For
batch number" and "expiry date"
will be embossed/printed
WEB ADVANCE DIRECTION
Blister Height is 46 mm
Nortriptyline
10 mg film-coated tablets
PL 49565/0090
MA Holder:
Rudipharm Limited
expiry date
batch number
2 mm
94 mm
4 mm
94 mm
2 mm
196 mm
COLOUR
Black

Nortriptyline 25 mg Film-coated tablets




Box Size
40x35 mm
Nortriptyline 25mg Film-coated tablets
Read the package leaflet before use
INGREDIENTS
Each film coated tablet contains Nortriptyline Hydrochloride equivalent to Nortriptyline 25mg. Also contains lactose and sunset yellow (E110).
DOSAGE
For oral use.
Use as directed by the physician.
WARNING
KEEP OUT OF SIGHT AND REACH OF CHILDREN
Please affix dispensing label here
PL 49565/0091
POM
MA Holder:
Rudipharm Limited
Unit 6, Salbrook Road Industrial Estate
Salbrook Road, Redhill, Surrey, RH1 5GJ
Space for Barcode
PC : 12345678910XXX
SN : XXXXXXXXX
BN : XXXXXX
EXP : MM/YYYY
Nortriptyline 25mg Film-coated tablets
30 Film-coated Tablets
25mg
Nortriptyline 25mg
Film-coated tablets
25mg
30 Film-coated Tablets
Rudipharm
42 mm
Nortriptyline 25mg Film-coated tablets
30 Film-coated Tablets
25mg
20 mm
95 mm


Space For
batch number" and "expiry date"
will be embossed/printed
WEB ADVANCE DIRECTION
Blister Height is 37 mm
batch number
expiry date
2 mm
90 mm
4 mm
90 mm
2 mm
188 mm
COLOUR
Black

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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 Authorisations are recorded in the current SmPCs and/or PIL available on the MHRA website.

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