Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Nortriptyline 50 mg Film-coated Tablets (nortriptyline hydrochloride)

PL 34771/0265

Macleods Pharma UK Limited

LAY SUMMARY

Nortriptyline 50 mg Film-coated Tablets (nortriptyline hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Nortriptyline 50 mg Film-coated Tablets . It explains how this product 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 this product.

This product 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 is Nortriptyline film-coated tablets and what is it used for?
This application is for a hybrid medicine. This means that the medicine is similar to a reference medicine already authorised, called Allegron/Nortriptyline 25 mg Tablets, albeit with certain difference(s). In this case, the difference between Nortriptyline film-coated tablets compared to the reference product is a change of strength of the active substance.

Nortriptyline film-coated tablets is indicated for the treatment of major depressive disorders in adults.

How does Nortriptyline film-coated tablets work?
Nortriptyline tablets contain the active ingredient nortriptyline (as nortriptyline hydrochloride), which is a tricyclic antidepressant.

How is Nortriptyline film-coated tablets used?
The pharmaceutical form of this medicine is a film-coated tablet, and the route of administration is oral (by mouth).

Dosage
Use in Adults:
The recommended dose for an adult is 25 mg three or four times per day or the dose may be given once a day, usually at night.

The dose should begin at a low level, 10 mg, three or four per times daily, for example and be increased gradually as required. The maximum dose is 150 mg per day.

If the patient's doctor tells the patient to take more than four 25 mg tablets a day, he or she may arrange for the patient to have regular blood tests.

Use in elderly patients:
The usual dose is 30 to 50 mg/day in divided doses. Treatment may start at a low level (10 – 20 mg daily) and may be increased as required to the maximum dose of 50 mg.
If they require a dose of 50 mg or over, the patient's doctor will arrange for the patient to have a recording of the patient's heart (ECG) and blood tests.

The 50 mg strength tablets are not appropriate for use in elderly patients.

Use in patients with renal impairment:
In case of renal impairment, the patient's doctor will increase or decrease the dose carefully and gradually. In most cases, however, the usual dosage will be given.

Use in patients with hepatic impairment:
Patients with liver diseases or people known as 'poor metabolisers' usually receive lower doses. The patient's doctor may take blood samples to determine the level of nortriptyline in the blood.

Use in children and adolescent patients:
Nortriptyline tablets should not be used in children and adolescents aged less than 18 years, as safety and efficacy have not been established.

Lower dosages are recommended for outpatients than for patients in hospital who will be under close supervision.

Duration of treatment
It may take a few weeks before the patient feels any improvement. Following remission maintenance treatment may be needed longer term, usually up to six months. This should be at the lowest dose that stops the symptoms of depression coming back.

For further information on how Nortriptyline film-coated tablets is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take this medicine 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?
No additional studies were needed as Nortriptyline film-coated tablets contain the same active substance as the reference medicine, and satisfactory data to justify the differences in strength have been provided.

What are the possible side effects of Nortriptyline film-coated tablets?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC 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 the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

As Nortriptyline film-coated tablets is a hybrid medicine and is therapeutically equivalent to the reference medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

Why was Nortriptyline film-coated tablets approved?
It was concluded that Nortriptyline film-coated tablets has been shown to be therapeutically equivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, 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 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:

Summary of safety concerns	
Important identified risks	• Hypersensitivity • Cardiovascular disorders (Myocardial infarction, Arrhythmia, Stroke) • Severe liver disease • Suicide related events • Psychosis and Mania • Blood disorders • Seizures (use in patients with epilepsy)
Important potential risks	• Use in Lactation • Drug Interactions • Fractures • Use in pregnancy • Neonatal withdrawal syndrome
Missing information	• Use in children and adolescent below 18 years of age

The information included in the SmPC 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.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Nortriptyline film-coated tablets

A marketing authorisation for Nortriptyline film-coated tablets was granted in the United Kingdom (UK) on 29 November 2022.

The full PAR for Nortriptyline film-coated tablets follows this summary.

This summary was last updated in May 2023.

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 application for Nortriptyline 50 mg Film-coated Tablets (PL 34771/0265) could be approved.

The product is approved for the treatment of major depressive disorders in adults.

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

This application was approved under Regulation 52B of The Human Medicines Regulation 2012, as amended (previously Article 10(3) of Directive 2001/83/EC, as amended), claiming to be a hybrid medicinal product of a suitable originator product, Allegron/Nortriptyline 25 mg Tablets that has been licensed for a suitable time, in line with the legal requirements. Nortriptyline 50 mg Film-coated Tablets is a line extension of the Nortriptyline 10 mg and 25 mg film-coated tablets already marketed in the UK by the applicant.

No new non-clinical studies were conducted, which is acceptable given that the application is for a hybrid medicinal product of a suitable reference product.

A biowaiver was submitted with this application, which was accepted. No new bioequivalence or therapeutic equivalence studies were required, and none were provided with this application.

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

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

A national marketing authorisation was granted in the United Kingdom (UK) on 29 November 2022.

II QUALITY ASPECTS

II.1 Introduction

This product contains 50 mg of nortriptyline (as nortriptyline hydrochloride), as the active substance, in each film-coated tablet.

In addition to nortriptyline, this product also contains the excipients lactose monohydrate (E473), dicalcium phosphate dihydrate, pregelatinised starch, colloidal silicon dioxide, croscarmellose sodium (E468) and magnesium stearate (E572) in the in the tablet core. The tablet coating contains hypromellose (E464), triacetin (E1518) and titanium dioxide (E171).

The finished product is packaged in aluminium/clear polyvinylchloride/polyvinylidene chloride blisters, in pack sizes of 30 or 100 film-coated tablets.

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

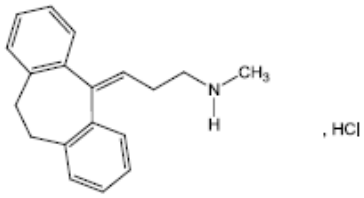
II.2 ACTIVE SUBSTANCE

rINN: Nortriptyline hydrochloride

Chemical Name: 3-(10,11-Dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)-*N*-methylpropan-1-amine hydrochloride.

Molecular Formula: $C_{19}H_{22}ClN$

Chemical Structure:



Molecular Weight: 299.8 g/mol

Appearance: White or almost white powder

Solubility: Sparingly soluble in water, soluble in ethanol (96 per cent) and in methylene chloride

Nortriptyline hydrochloride 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.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution profiles have been provided for the proposed product and the reference Nortriptyline 25 mg film-coated tablets currently marketed by this applicant.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

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

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

Manufacture of the product

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

Satisfactory batch formulation data have been provided for the manufacture of the product, 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 at release and shelf-life 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 30°C.', 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 a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of Nortriptyline hydrochloride 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 this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for this application.

III.4 Toxicology
No new toxicology data were provided, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As this is a hybrid application of an already authorised product, it is not expected that environmental exposure will increase following approval of the marketing authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
In accordance with the regulatory requirements, the applicant has provided a suitable biowaiver. No bioequivalence or therapeutic equivalence studies have been submitted with this application.

IV. 2 Pharmacokinetics
No new pharmacokinetic data have been submitted for this application and none were required.

Reference has been made to the original randomised, open label, two-sequence, two-treatment, two-period, crossover, single oral dose bioequivalence carried out under fasting conditions on the test generic product Nortriptyline 25 mg film-coated tablets marketed by this applicant, and the reference product, Allegron 25 mg Tablets. Based on the submitted bioequivalence study Nortriptyline 25mg film-coated tablets are considered bioequivalent with the reference product Allegron 25 mg Tablets.

As the 50 mg strength of the product meets the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study with the 25 mg product strength can be extrapolated to the 50 mg strength.

IV.3 Pharmacodynamics

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

IV.4 Clinical efficacy

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

IV.5 Clinical safety

No new safety data were submitted with this application, and none were required. The safety profile for this product is considered to be the same as Allegron/Nortriptyline 25 mg Tablets.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, 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 a marketing authorisation is recommended for this application.

V 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 study in accordance with legal requirements. 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 product is acceptable, and no new non-clinical or clinical safety concerns have been identified.

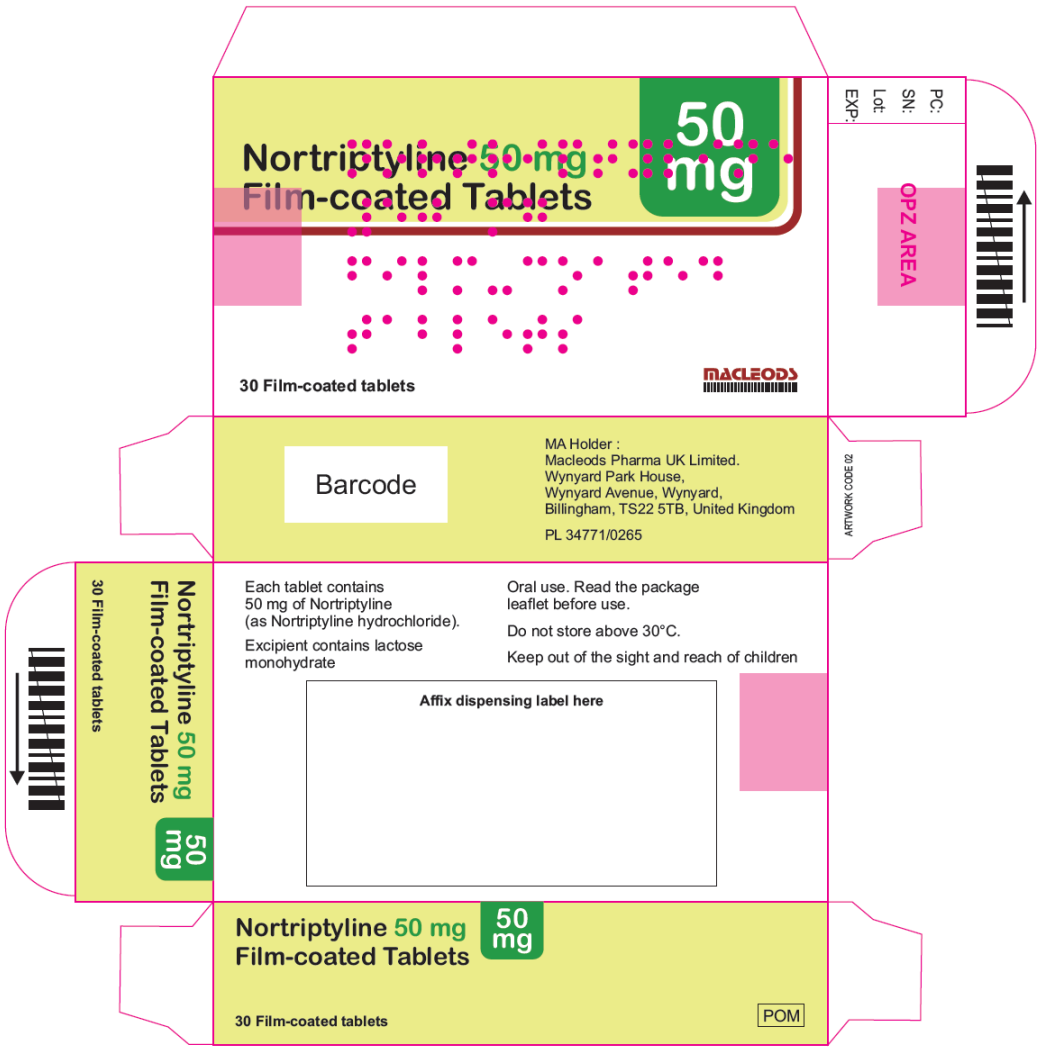
Extensive clinical experience with nortriptyline hydrochloride is considered to have demonstrated the therapeutic value of the product.

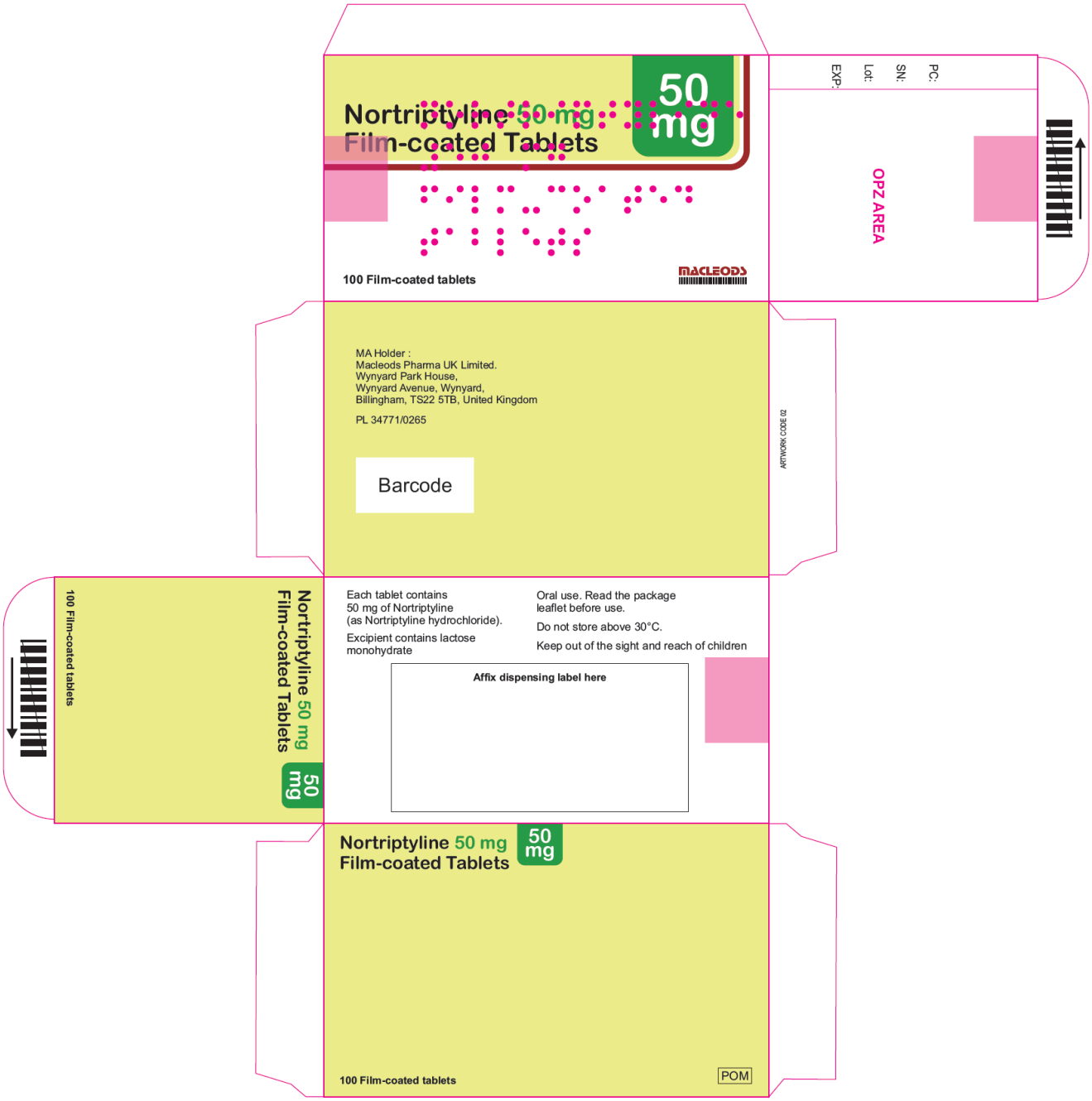
The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), PIL and labelling are satisfactory and in line with current guidelines.

In accordance with legal requirements, the current approved versions of the SmPC and PIL for this product are available on the MHRA website.

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




Nortriptyline 50 mg
Film-coated Tablets
50 mg
100 Film-coated tablets
MACLEODS
EXP:
Lot:
SN:
PC:
OPZ AREA
MA Holder :
Macleods Pharma UK Limited.
Wynyard Park House,
Wynyard Avenue, Wynyard,
Billingham, TS22 5TB, United Kingdom
PL 34771/0265
Barcode
ARTWORK CODE 02
Each tablet contains
50 mg of Nortriptyline
(as Nortriptyline hydrochloride).
Excipient contains lactose
monohydrate
Oral use. Read the package
leaflet before use.
Do not store above 30°C.
Keep out of the sight and reach of children
Affix dispensing label here
100 Film-coated tablets
Nortriptyline 50 mg
Film-coated Tablets
50 mg
Nortriptyline 50 mg Film-coated Tablets
50 mg
100 Film-coated tablets
POM

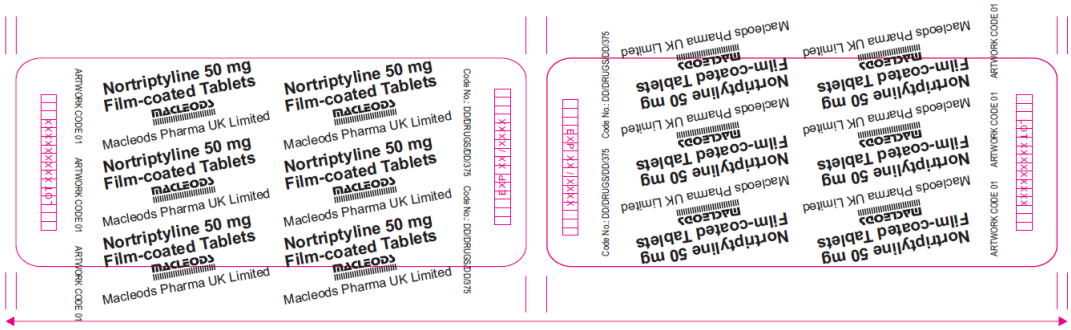

Nortriptyline 50 mg
Film-coated Tablets
MACLEODS
Macleods Pharma UK Limited
ARTWORK CODE 01
Code No.: DD/DRUGS/DD/375

TABLE OF CONTENT OF THE PAR UPDATE

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, is 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**