Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedures

Nortriptyline 10 mg and 25 mg film-coated tablets

(nortriptyline hydrochloride)

Product Licence Numbers: PL 48836/0001-0002

OSGEN Pharmaceuticals Limited

LAY SUMMARY

Nortriptyline 10 mg and 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 Tablets in this lay summary for ease of reading.

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

What are Nortriptyline Tablets 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 United Kingdom (UK) called Allegron/Nortriptyline 10 mg and 25 mg Tablets (King Pharmaceuticals Ltd).

Nortriptyline tablets are indicated for the treatment of major depressive disorders in adults.

How do Nortriptyline Tablets work?
Nortriptyline Tablets contain the active ingredient nortriptyline hydrochloride, which is a tricyclic antidepressant.

How are Nortriptyline Tablets used?
The pharmaceutical form of this medicine is a tablet and the route of administration is oral (by mouth). The score line on the 25 mg tablet is only there to help patients break the tablet if they have difficulty swallowing it whole.

Dosage
Adults:
The usual adult dose is 25mg 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.

The elderly:
The usual dose is 30 to 50mg/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 patients require a dose of 50 mg or over, a doctor will arrange for patients to have a recording of the heart (ECG) and blood tests. The 50 mg tablets are not appropriate for use in elderly patients.

Renal impairment:
In case of renal impairment, a doctor will increase or decrease the dose carefully and gradually. In most cases, however, the usual dosage will be given.

Hepatic impairment:
Patients with liver diseases or people known as 'poor metabolisers' usually receive lower doses. A doctor may take blood samples to determine the level of nortriptyline in the blood.

Children and adolescents:
Nortriptyline 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 you feel any improvement. Following remission maintenance treatment may be needed longer term, usually up to 6 months. This should be at the lowest dose that stops the symptoms of depression coming back.

For further information on how Nortriptyline Tablets are used, refer to the package leaflet and Summaries of Product Characteristics 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 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 Tablets have been shown in studies?
Nortriptyline Tablets are generic medicines that fulfils criteria meaning that no additional studies are required. Nortriptyline Tablets have been considered generic medicines of the reference medicines based on a comparison of their physical and chemical characteristics.

What are the possible side effects of Nortriptyline Tablets?
For the full list of all side effects reported with this medicine, 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 the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, 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 this medicine.

Because Nortriptyline Tablets are generic medicines, its benefits and possible side effects are considered to be the same as for the reference medicines.

Why were Nortriptyline Tablets approved?
It was concluded that, Nortriptyline Tablets has been shown to be comparable 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 Tablets?
A Risk Management Plan (RMP) has been developed to ensure that Nortriptyline Tablets 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 Nortriptyline Tablets
Marketing Authorisations for Nortriptyline Tablets were granted in the UK on 13 August 2021.

The full PAR for Nortriptyline Tablets follows this summary.

This summary was last updated in October 2021.

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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 48836/0001-0002) could be approved.

The products are approved for the treatment of major depressive disorders in adults.

Nortriptyline is a tricyclic antidepressant with actions and uses similar to those of amitriptyline. It is the principal active metabolite of amitriptyline.

These applications were approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as generic medicines of suitable originator medicinal products, Allegron/Nortriptyline 10 mg and 25 mg Tablets (PL 14385/0001 - 0002; King Pharmaceuticals Ltd), that have been licensed within the UK 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.

A biowaiver was submitted with these applications, which was accepted. No bioequivalence study was required, and no new clinical studies were provided with these applications.

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.

Marketing authorisations were granted for these products on 13 August 2021.

II QUALITY ASPECTS

II.1 Introduction

These products are film-coated tablets. Each film-coated tablet contains either 10 mg or 25 mg of nortriptyline (as nortriptyline hydrochloride) as active substance.

In addition to nortriptyline hydrochloride, these products also contain the excipients maize starch, magnesium stearate, lactose monohydrate, calcium hydrogen phosphate, anhydrous making up the tablet core. The tablet coating is composed of glycerol, hypromellose and ethylcellulose.

The finished products are packaged either in polyvinylchloride (PVC) – aluminium foil blister packs with pack sizes of 30, 50, and of 100 tablets.

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.

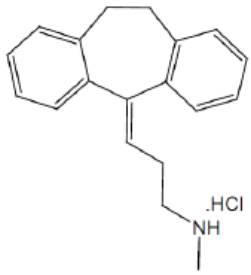
II.2 ACTIVE SUBSTANCE

rINN: 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: 299.84 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 PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

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, 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.

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 processes. The manufacturing processes have been validated and have 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 36 months, with no special storage conditions is approved.

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

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 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 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 nortriptyline hydrochloride are well known. According to the regulatory requirements, the applicant has provided a suitable biowaiver and a bioequivalence study is not required for this product. An overview based on a literature review is, thus, satisfactory.

IV. 2 Pharmacokinetics

No new pharmacokinetic data have been submitted for these applications and none were required.

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

No new safety data were submitted with these applications and none were required. The safety profile for these products is considered to be the same as Allegron/Nortriptyline 10 mg and 25 mg Tablets (King Pharmaceuticals Ltd).

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

A user consultation with target patient groups on the Patient Information Leaflet (PIL) has been performed on the basis of a bridging report making reference to Nortriptyline 10 mg and 25 mg Film-coated Tablets (Flamingo Pharma (UK) Ltd). The bridging report submitted by the applicant is acceptable.

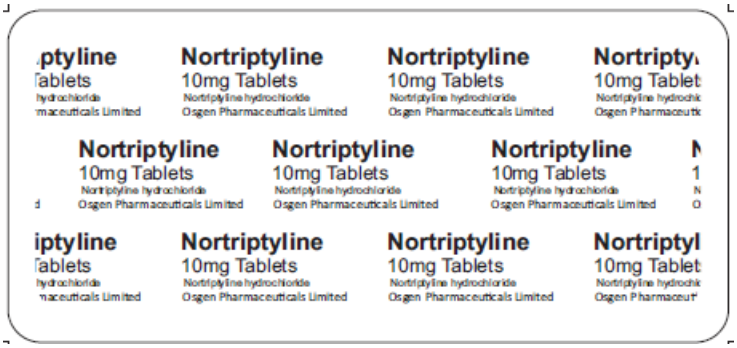
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

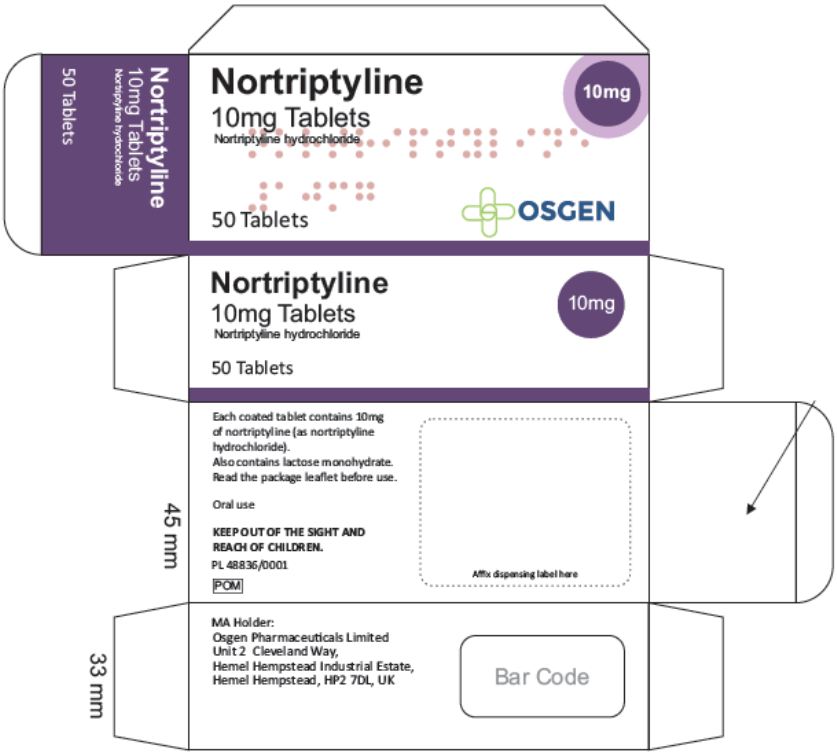
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with nortriptyline hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be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

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.




Nortriptyline
10mg Tablets
Nortriptyline hydrochloride
50 Tablets
10mg
OSGEN
Nortriptyline
10mg Tablets
Nortriptyline hydrochloride
50 Tablets
10mg
Each coated tablet contains 10mg of nortriptyline (as nortriptyline hydrochloride).
Also contains lactose monohydrate.
Read the package leaflet before use.
Oral use
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.
PL 48836/0001
POM
Affix dispensing label here
45 mm
MA Holder:
Osgen Pharmaceuticals Limited
Unit 2 Cleveland Way,
Hemel Hempstead Industrial Estate,
Hemel Hempstead, HP2 7DL, UK
Bar Code
33 mm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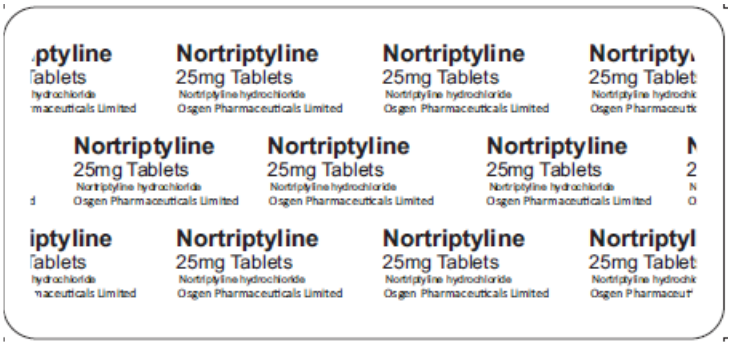
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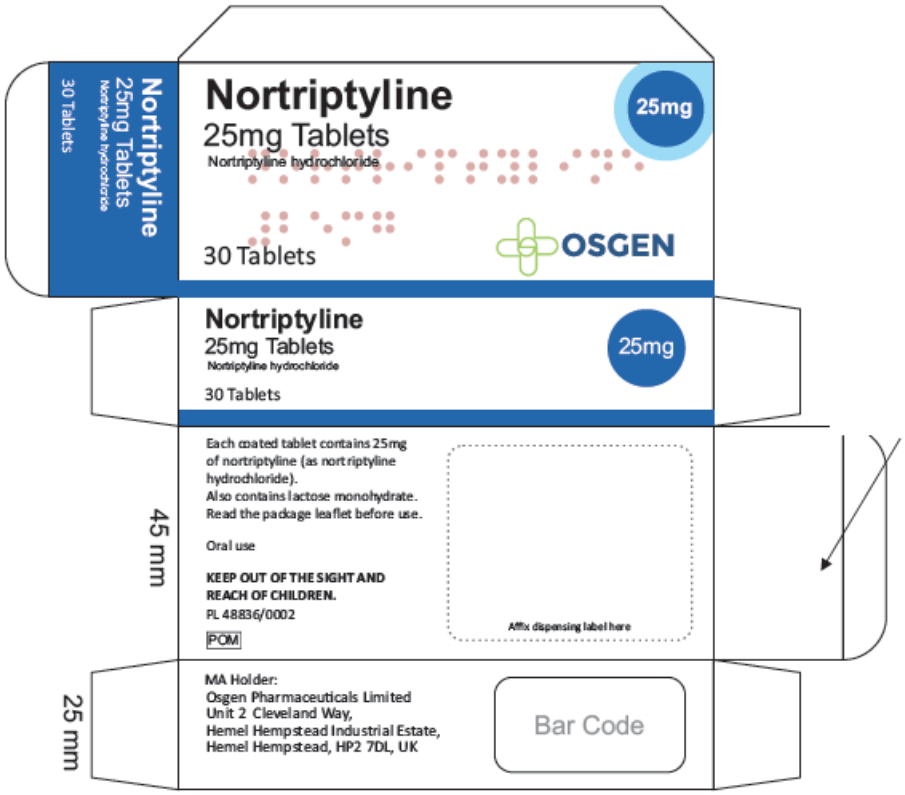
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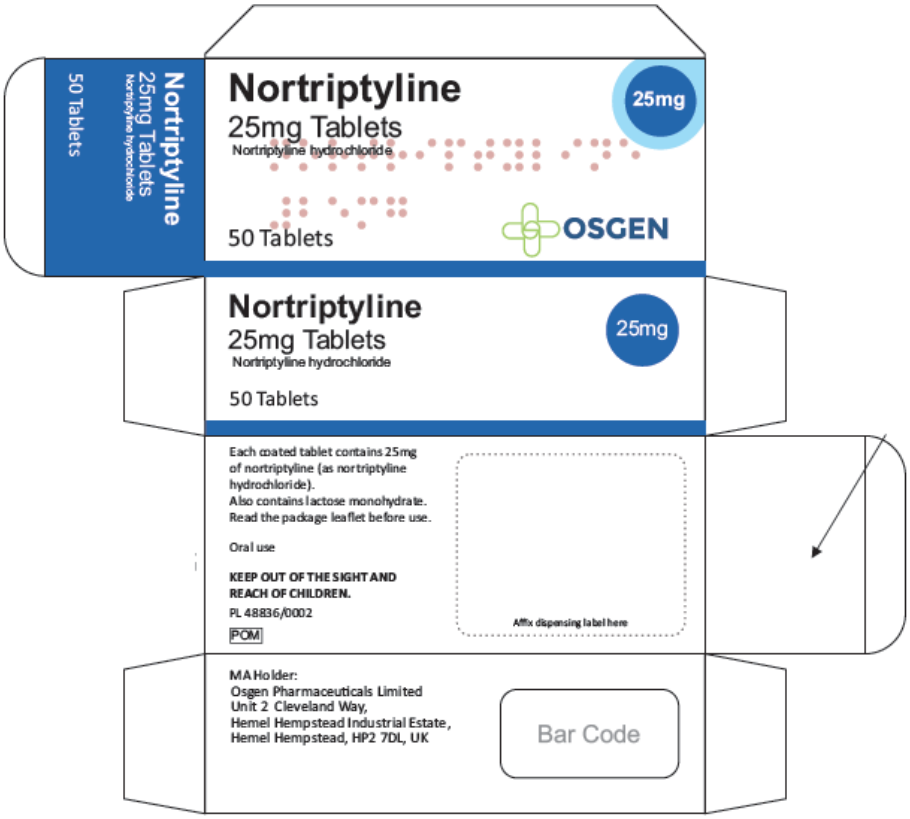
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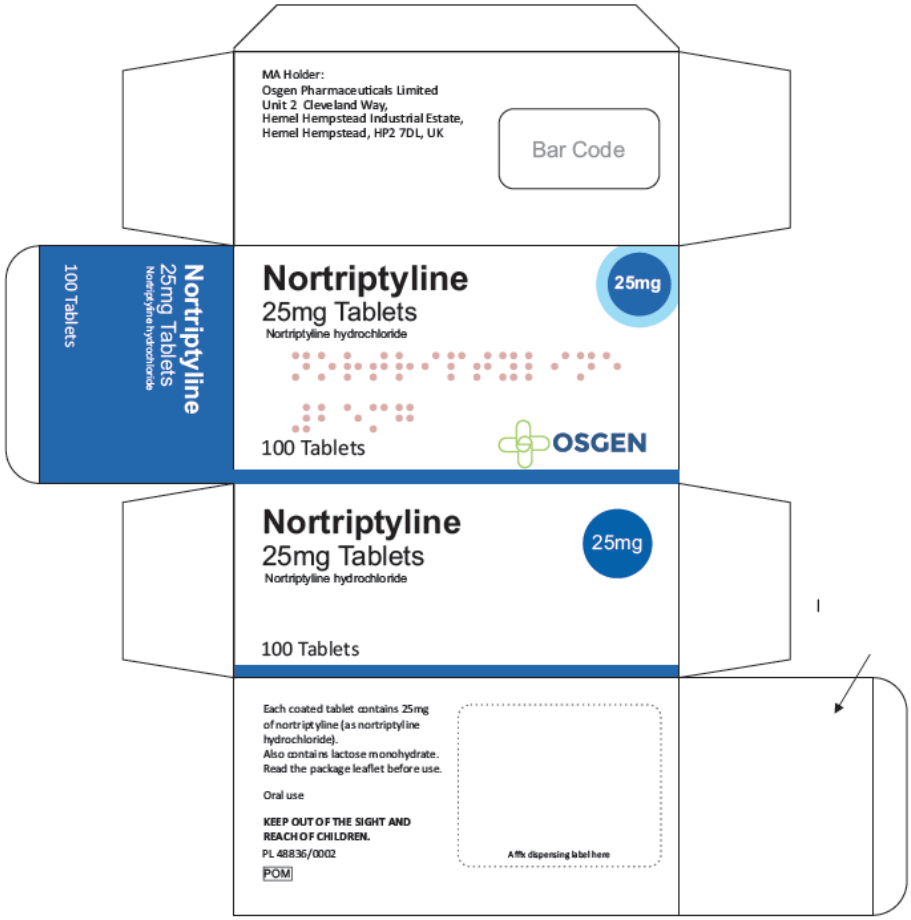
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TABLE OF CONTENT OF THE PAR UPDATE

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 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**