Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Amitriptyline 10mg Film-coated Tablets
Amitriptyline 25mg Film-coated Tablets
Amitriptyline 50mg Film-coated Tablets

(Amitriptyline hydrochloride)

PL 13606/0250-0252

Strides Pharma UK Ltd.

LAY SUMMARY

Amitriptyline 10mg Film-coated Tablets
Amitriptyline 25mg Film-coated Tablets
Amitriptyline 50mg Film-coated Tablets
(Amitriptyline hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Amitriptyline 10, 25 & 50mg 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.

For practical information about using Amitriptyline 10, 25 & 50mg Film-coated Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Amitriptyline 10, 25 & 50mg Film-coated 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 European Union (EU) called Tryptizol 10, 25 and 50 mg comprimidos recubiertos con película.

These medicines are used to treat:

- Depression in adults (major depressive episodes)
- Neuropathic pain in adults
- Chronic tension type headache prophylaxis in adults
- Migraine prophylaxis in adults
- Bed-wetting at night in children aged 6 years and above, only when organic causes, such as spina bifida and related disorders, have been excluded and no response has been achieved to all other non-drug and drug treatments, including muscle relaxants and desmopressin. This medicine should only be prescribed by doctors with expertise in treating patients with persistent bed-wetting.

How do Amitriptyline 10, 25 & 50mg Film-coated Tablets work?
These medicines contain the active ingredient amitriptyline hydrochloride which belongs to a group of medicines known as tricyclic antidepressants. These medicines alter the levels of chemicals in the brain to relieve the symptoms of depression and change the way that nerves receive pain signals.

How are Amitriptyline 10, 25 & 50mg Film-coated Tablets used?
The pharmaceutical form of these medicines is a film-coated tablet and the route of administration is oral (via the mouth).

Not all dosage schemes can be achieved with all the pharmaceutical forms/strengths. The appropriate formulation/strength should be selected for the starting doses and any subsequent dose increases.

Depression
Adults
The recommended initial dose is 25 mg two times daily. Depending on the response to the medicine, the patient's doctor may gradually increase the dose to 150 mg per day divided in two doses.

Elderly (above 65 years of age) and patients with cardiovascular disease)
The recommended initial dose is 10 mg – 25 mg daily. Depending on the patient's response to the medicine, their doctor may gradually increase the dose to a total daily dose of 100 mg divided in two doses. If the patient receive doses in the range of 100 mg – 150 mg, their doctor may need to do more frequent follow-up with them.

Use in children and adolescents
This medicine should not be given to children or adolescents for treatment of depression. For further information please see section 2 of the patient information leaflet (PIL).

Neuropathic pain, chronic tension type headache and migraine prophylaxis
The patient's doctor will adjust the medication according to their symptoms and response to the treatment.

Adults
The recommended initial dose is 10 mg - 25 mg in the evening.
The recommended daily dose is 25 mg - 75 mg.
Depending on the patient's response to the medicine, their doctor may gradually increase the dose. If the patient receives doses above 100 mg daily, their doctor may need to do more frequent follow-ups with them. The patient's doctor will instruct them whether to take the doses once daily or divide into two doses.

Elderly (above 65 years of age) and patients with cardiovascular disease
The recommended initial dose is 10 mg – 25 mg in the evening.
Depending on the patient's response to the medicine, their doctor may gradually increase the dose. If the patient receives doses above 75 mg daily, their doctor may need to do more frequent follow-ups with them.

Use in children and adolescents
This medicine should not be given to children or adolescents for treatments of neuropathic pain, chronic tension type headache prophylaxis and migraine prophylaxis. For further information please see section 2 of the PIL.

Bed-wetting at night
Use in children and adolescents
The recommended doses for children:
• aged below 6 years: see section 2 of the PIL
• aged 6 to 10 years: 10 mg – 20 mg daily. A suitable dosage form should be used for this age group.
• aged 11 years and above: 25 mg – 50 mg.

The dose should be increased gradually. Take this medicine 1-1½ hours before bedtime. Before starting treatment, the patient's doctor will conduct an ECG of their heart to check for sign of unusual heartbeat.

The patient's doctor will re-evaluate their treatment after 3 months and if needed perform a new ECG. Treatment should not be stopped by the patient without consulting their doctor first.

Patients with special risks
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 amitriptyline in the blood (see also section 2 of the PIL).

How and when to take Amitriptyline 10, 25 & 50mg Film-coated Tablets
This medicine can be taken with or without food.
Swallow the tablets with a drink of water. Do not chew them.

Duration of treatment
The patient should not change the dose of the medicine or stop taking the medicine without consulting their doctor first.

Depression
As with other medicines for the treatment of depression it may take a few weeks before you feel any improvement. In treating depression the duration of treatment is individual, and is usually at least 6 months. The duration of treatment is decided by the patient's doctor. The patient should continue to take this medicine for as long as their doctor recommends. The underlying illness may persist for a long time. If the patient stops their treatment too soon, their symptoms may return.

Neuropathic pain, chronic tension type headache and migraine prophylaxis
It might take a few weeks before the patient feels any improvement of their pain.
The patient should talk to their doctor about the duration of their treatment and continue to take this medicine for as long as their doctor recommends.

Bed-wetting at night
Your doctor will evaluate if the treatment should be continued after 3 months.

If the patient stops taking *Amitriptyline 10, 25 & 50mg Film-coated Tablets*
The patient's doctor will decide when and how to stop their treatment to avoid any unpleasant symptoms that might occur if it is stopped abruptly (e.g. headache, feeling unwell, sleeplessness and irritability).
If the patient has any further questions on the use of this medicine, they should ask their doctor or pharmacist.

For further information on how Amitriptyline 10, 25 & 50mg Film-coated 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 Amitriptyline 10, 25 & 50mg Film-coated Tablets have been shown in studies?
Amitriptyline 10, 25 & 50mg Film-coated Tablets are generic medicines that fulfil criteria meaning that no additional studies are required. Amitriptyline 10, 25 & 50mg Film-coated

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 Amitriptyline 10, 25 & 50mg Film-coated Tablets?
Because Amitriptyline 10, 25 & 50mg Film-coated Tablets are generic medicines, their benefits and possible side effects are considered to be the same as for the reference medicines.

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

Why were Amitriptyline 10, 25 & 50mg Film-coated Tablets approved?
It was concluded that, in accordance with EU requirements, Amitriptyline 10, 25 & 50mg Film-coated Tablets have been shown to be comparable to and 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 they can be approved for use.

What measures are being taken to ensure the safe and effective use of Amitriptyline 10, 25 & 50mg Film-coated Tablets?
A Risk Management Plan (RMP) has been developed to ensure that Amitriptyline 10, 25 & 50mg Film-coated 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 Amitriptyline 10, 25 & 50mg Film-coated Tablets
Marketing Authorisations for Amitriptyline 10, 25 & 50mg Film-coated Tablets were granted in the UK on 30 June 2020.

The full PAR for Amitriptyline 10, 25 & 50mg Film-coated Tablets follows this summary.

This summary was last updated in August 2020.

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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 Amitriptyline 10, 25 & 50mg Film-coated Tablets (PL 13606/0250-0252) could be approved.

The products are approved for the following indications:
• the treatment of major depressive disorder in adults
• the treatment of neuropathic pain in adults
• the prophylactic treatment of chronic tension type headache (CTTH) in adults
• the prophylactic treatment of migraine in adults
• the treatment of nocturnal enuresis in children aged 6 years and above when organic pathology, including spina bifida and related disorders, have been excluded and no response has been achieved to all other non-drug and drug treatments, including antispasmodics and vasopressin-related products. This medicinal product should only be prescribed by a healthcare professional with expertise in the management of persistent enuresis.

Amitriptyline is a tricyclic antidepressant and an analgesic. It has marked anticholinergic and sedative properties. It prevents the re-uptake, and hence the inactivation of noradrenaline and serotonin at nerve terminals. Reuptake prevention of these monoamine neurotransmitters potentiate their action in the brain. This appears to be associated with the antidepressant activity.

The mechanism of action also includes ion-channel blocking effects on sodium, potassium and NMDA channel at both central and spinal cord level. The noradrenaline, sodium and the NMDA effects are mechanisms known to be involved in the maintenance of neuropathic pain, chronic tension type headache prophylaxis and migraine prophylaxis. The pain-reducing effect of amitriptyline is not linked to its anti- depressive properties.

Tricyclic antidepressants possess affinity for muscarinic and histamine H_1 receptors to varying degrees.

These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic medicines of suitable originator medicinal products, Tryptizol 10, 25 and 50 mg comprimidos recubiertos con película 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 a 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 30 June 2020.

II QUALITY ASPECTS

II.1 Introduction

Each film-coated tablet contains 10, 25 or 50 mg of the active ingredient amitriptyline hydrochloride.

In addition to amitriptyline hydrochloride, these products also contain the excipients:

Amitriptyline 10mg Film-coated Tablets:

Lactose monohydrate, microcrystalline cellulose, corn maize starch, croscarmellose sodium, colloidal silicon dioxide, talc, magnesium stearate, Opadry Blue (85F99075) [comprised of polyvinyl alcohol-part hydrolysed, titanium dioxide (E171), macrogol, talc and FD&C Blue (E133)], hypromellose and macrogol 6000.

Amitriptyline 25mg Film-coated Tablets:

Lactose monohydrate, microcrystalline cellulose, corn maize starch, croscarmellose sodium, colloidal silicon dioxide, talc, magnesium stearate, Opadry II yellow (85F92349) [comprised of polyvinyl alcohol-part hydrolysed, titanium dioxide (E171), macrogol, talc and iron oxide yellow (E172)], hypromellose and macrogol 6000.

Amitriptyline 50mg Film-coated Tablets:

Lactose monohydrate, microcrystalline cellulose, corn maize starch, croscarmellose sodium, colloidal silicon dioxide, talc, magnesium stearate, Opadry II brown (85F565015) [consisting of polyvinyl alcohol-part hydrolysed, titanium dioxide (E171), macrogol, talc, iron oxide yellow (E172) and iron oxide red (E172)], hypromellose and macrogol 6000.

The finished products are packaged in PVC/PVDC/Alu blisters and are available in pack sizes of 20, 24, 28, 30, 56, 60, 84, 90, 98, 100, 112, 120, 168, 180, 250 film-coated tablets. Not all pack sizes will 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.

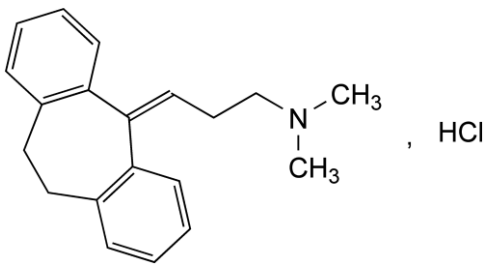
II.2 ACTIVE SUBSTANCE(S)

rINN: Amitriptyline hydrochloride

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

Molecular Formula: $C_{20}H_{24}ClN$

Chemical Structure:



Molecular Weight: 313.9 g/mol

Appearance: White or almost white powder or colourless crystals.

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

Amitriptyline 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.

Comparative *in vitro* dissolution and impurity 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, 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.

This 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 no special storage condition, 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 amitriptyline 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 amitriptyline hydrochloride are well-known. According to the regulatory requirements, the applicant has provided a suitable biowaiver and a bioequivalence study is not required for these products. 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 Tryptizol 10, 25 and 50 mg comprimidos recubiertos con película.

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.

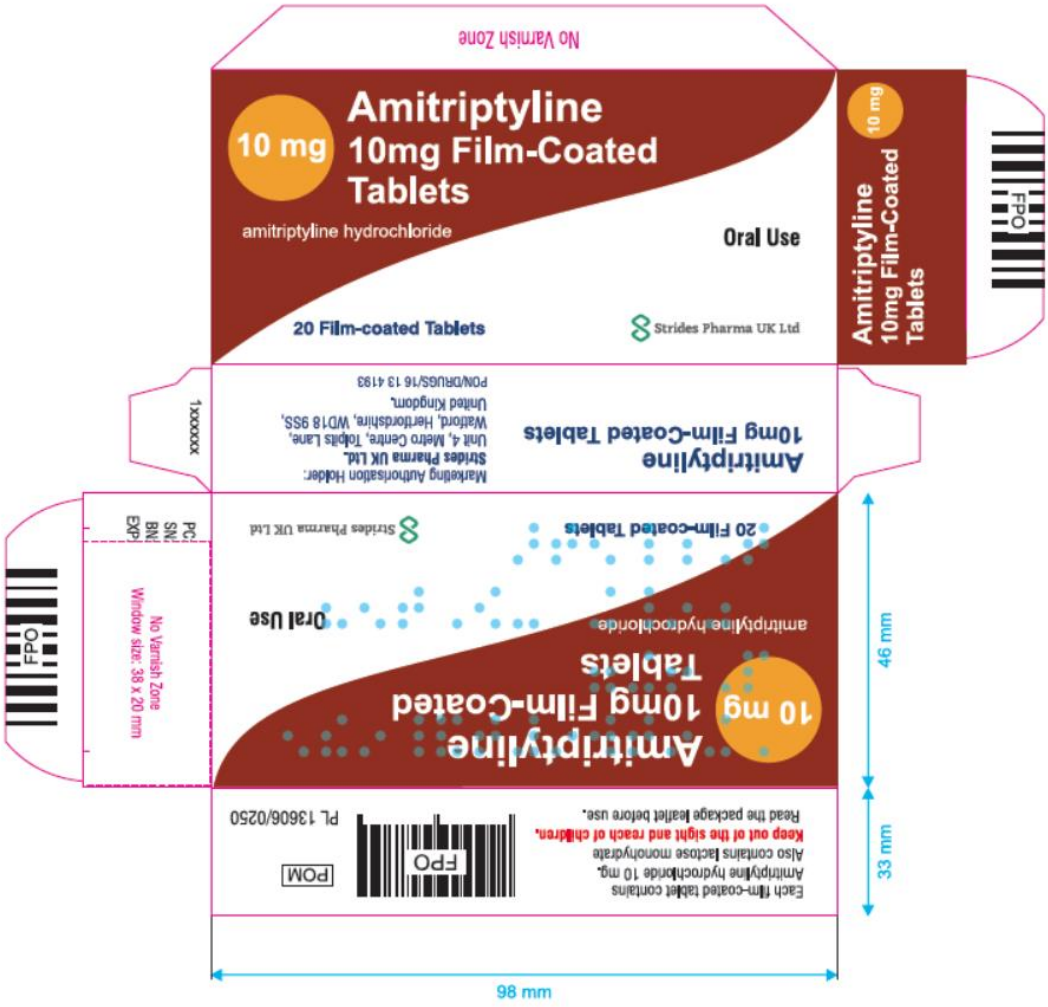
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with amitriptyline 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 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.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Amitriptyline
10mg Film-Coated
Tablets
amitriptyline hydrochloride
Oral Use
20 Film-coated Tablets
Strides Pharma UK Ltd
Amitriptyline
10mg Film-Coated
Tablets
10 mg
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Marketing Authorisation Holder:
Strides Pharma UK Ltd.
Unit 4, Metro Centre, Tolpits Lane,
Watford, Hertfordshire, WD18 9SS,
United Kingdom.
PON/DRUGS/16 13 4193
Amitriptyline
10mg Film-Coated Tablets
20 Film-coated Tablets
Strides Pharma UK Ltd
Oral Use
amitriptyline hydrochloride
10 mg
Amitriptyline
10mg Film-Coated
Tablets
PC:
SN:
BN:
EXP:
No Varnish Zone
Window size: 38 x 20 mm
FPO
Each film-coated tablet contains
Amitriptyline hydrochloride 10 mg.
Also contains lactose monohydrate
Keep out of the sight and reach of children.
Read the package leaflet before use.
PL 13606/0250
POM
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33 mm
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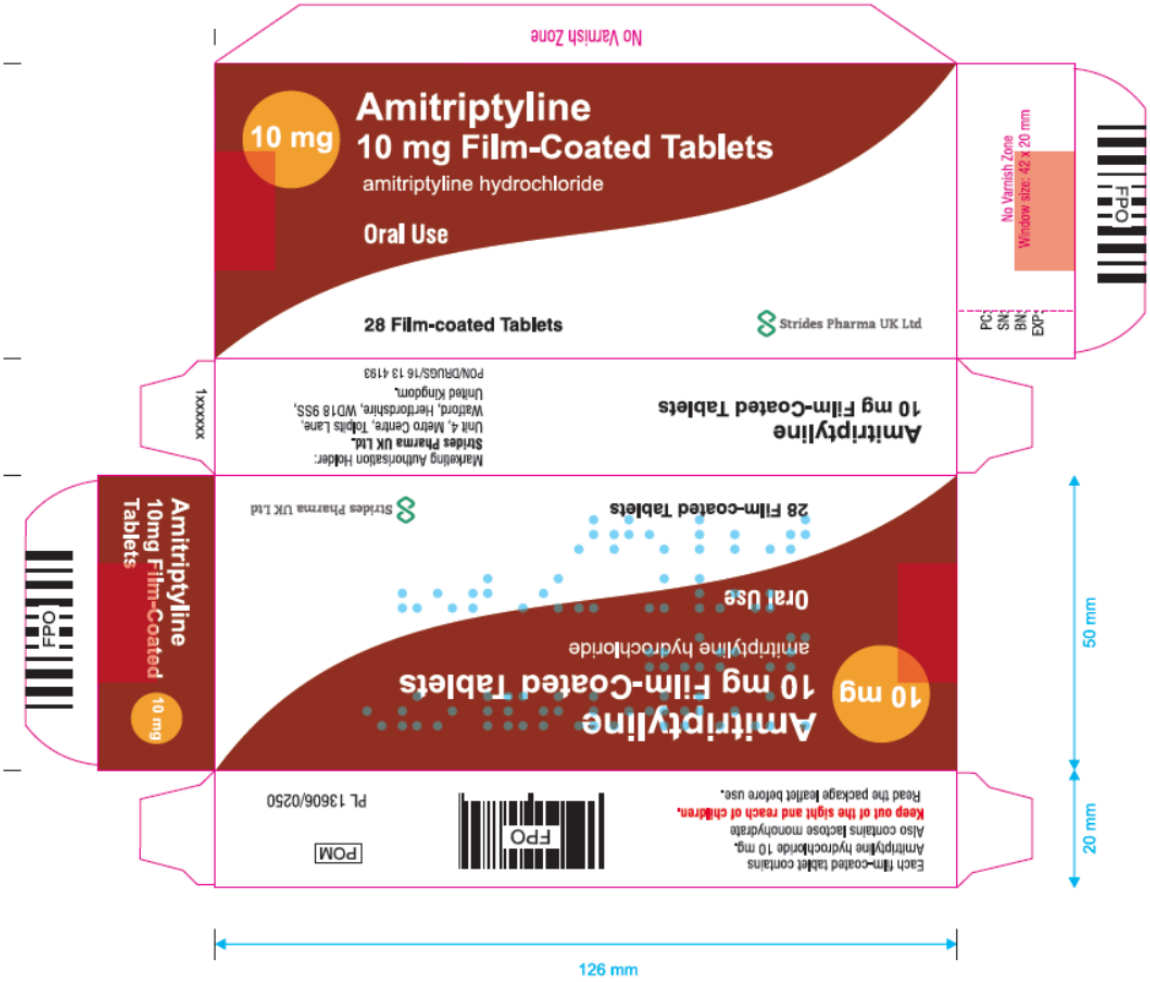
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Oral Use
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Strides Pharma UK Ltd
No Varnish Zone
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FPO
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20 mm
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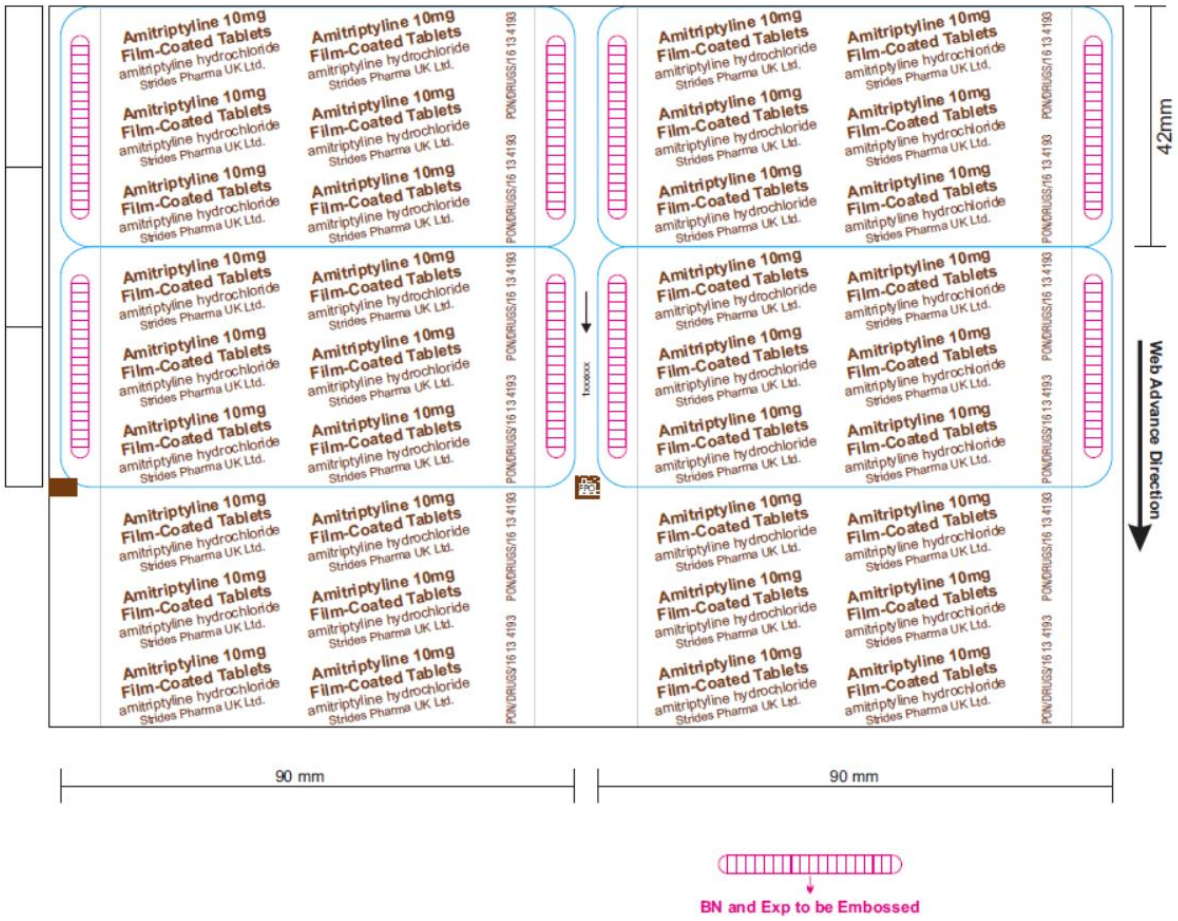
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Strides Pharma UK Ltd.
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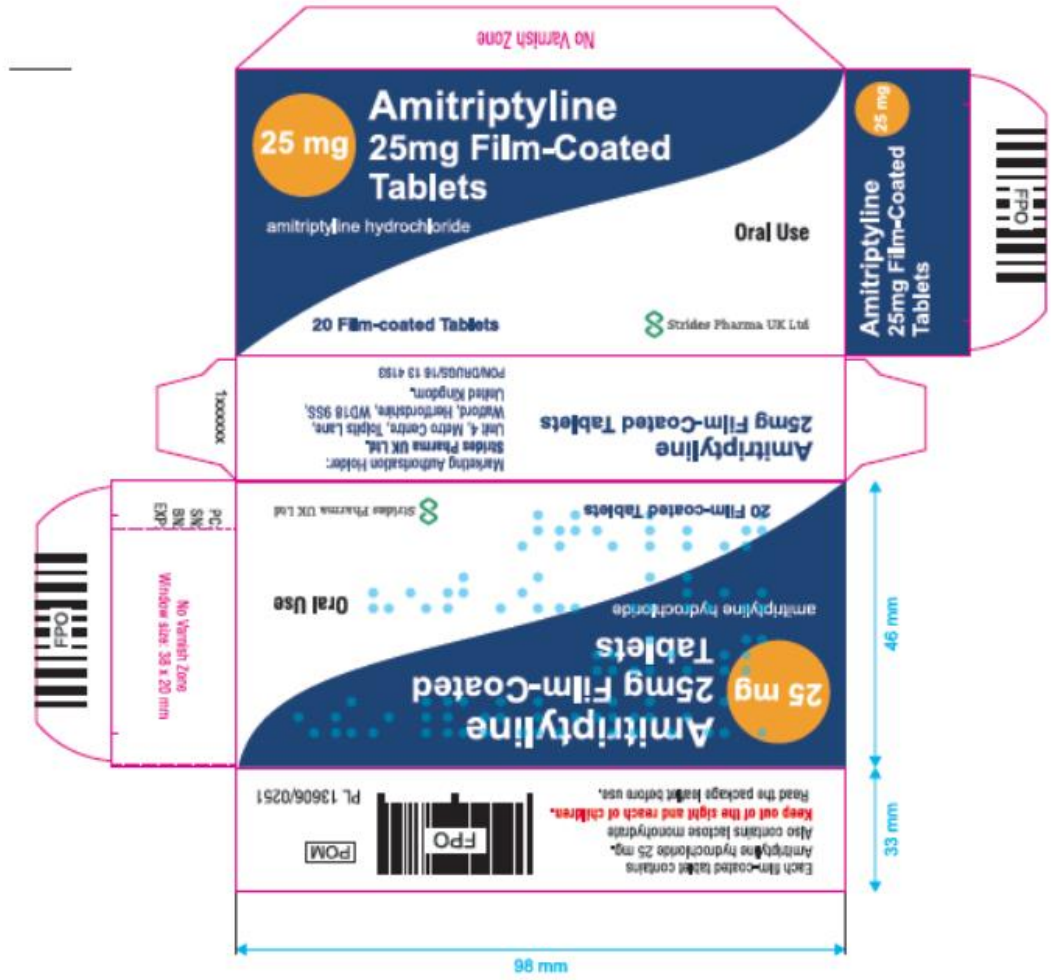
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No Varnish Zone
Window size: 38 x 20 mm
FPO
PC
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EXP
Each film-coated tablet contains
Amitriptyline hydrochloride 25 mg.
Also contains lactose monohydrate
Keep out of the sight and reach of children.
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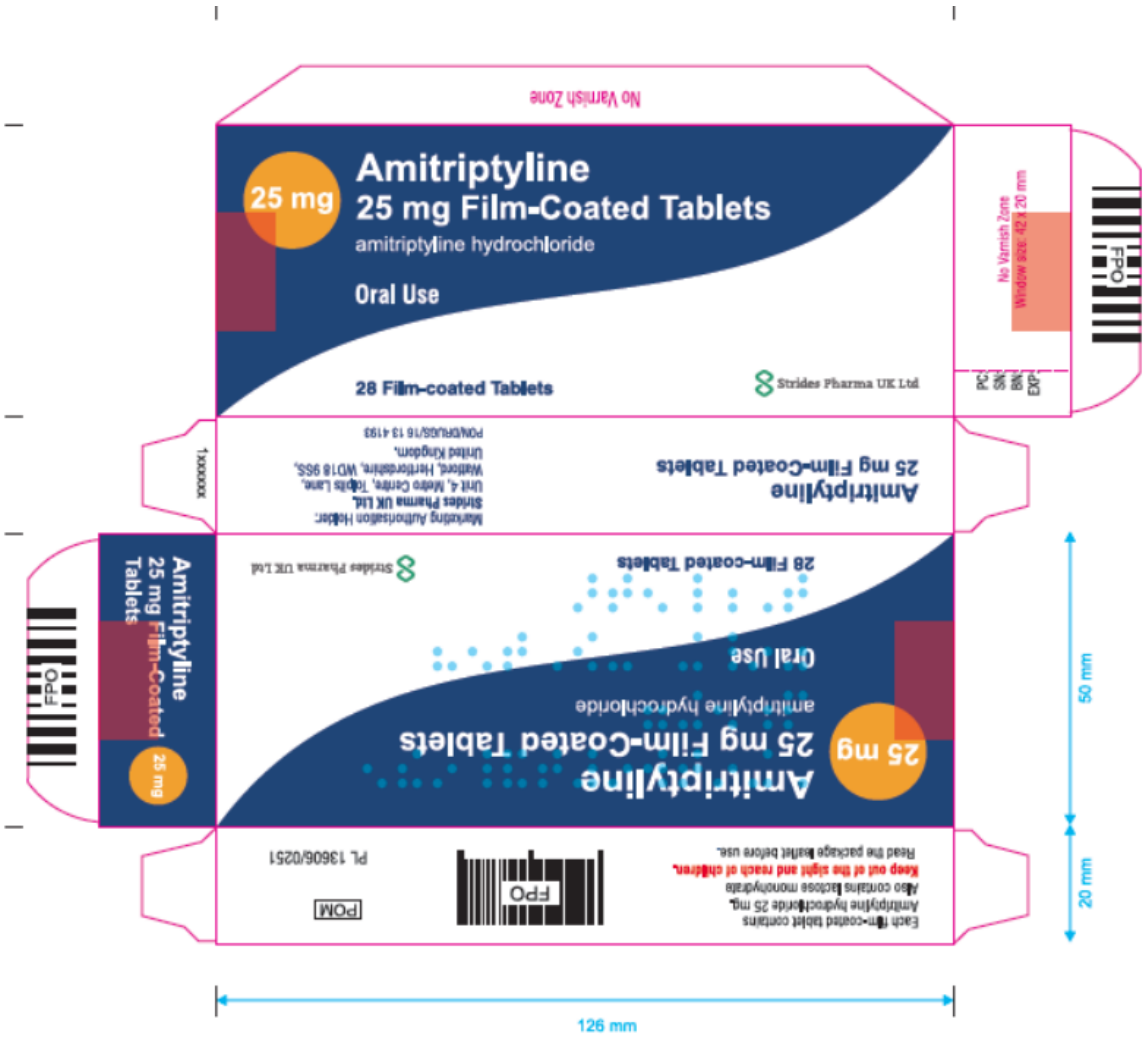
33 mm
98 mm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No Varnish Zone
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25 mg
Strides Pharma UK Ltd
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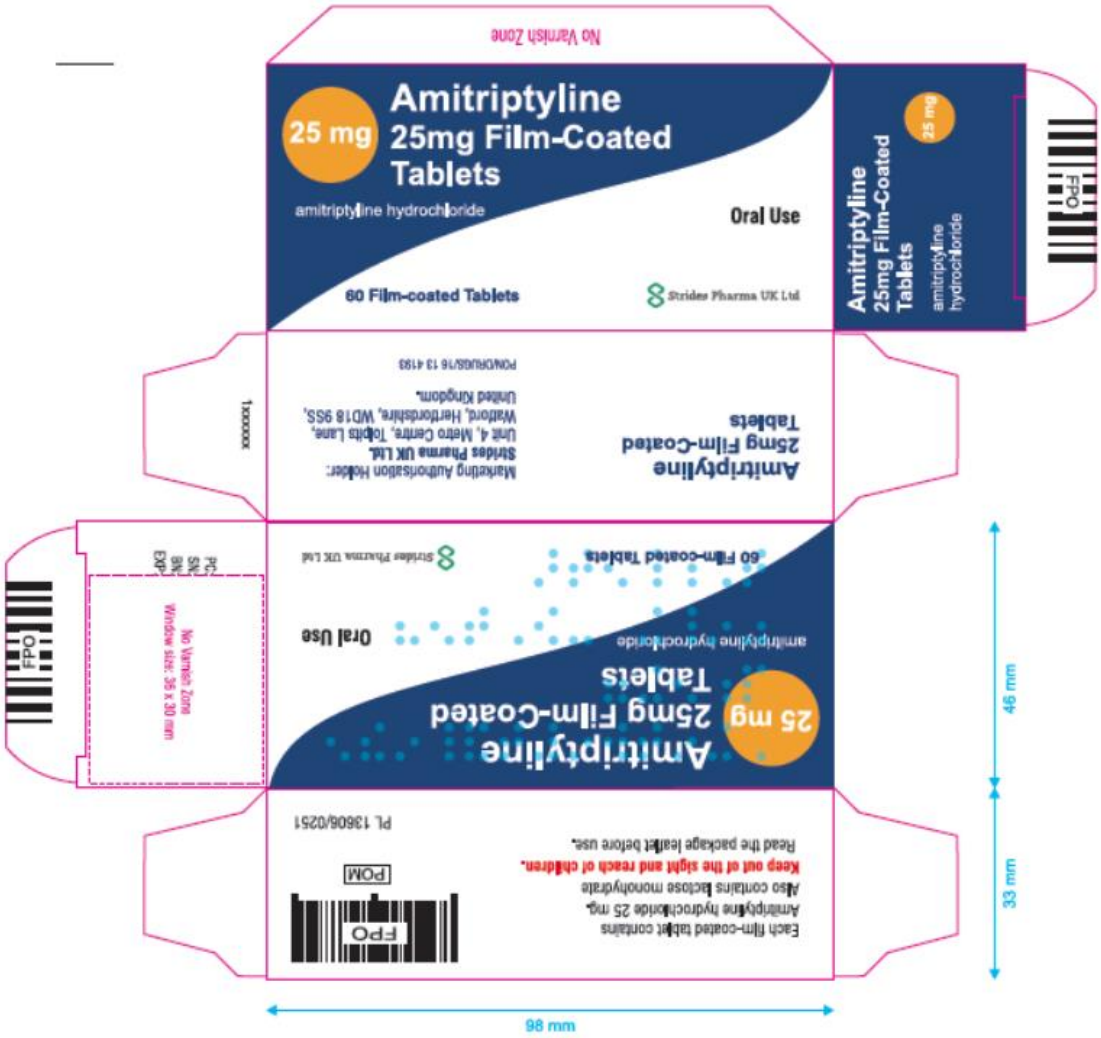
PL 13606/0251
POM
FPO
50 mm
20 mm
126 mm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Tablets
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Oral Use
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Strides Pharma UK Ltd
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25mg Film-Coated
Tablets
amitriptyline
hydrochloride
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Tablets
25 mg
amitriptyline hydrochloride
Oral Use
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Strides Pharma UK Ltd
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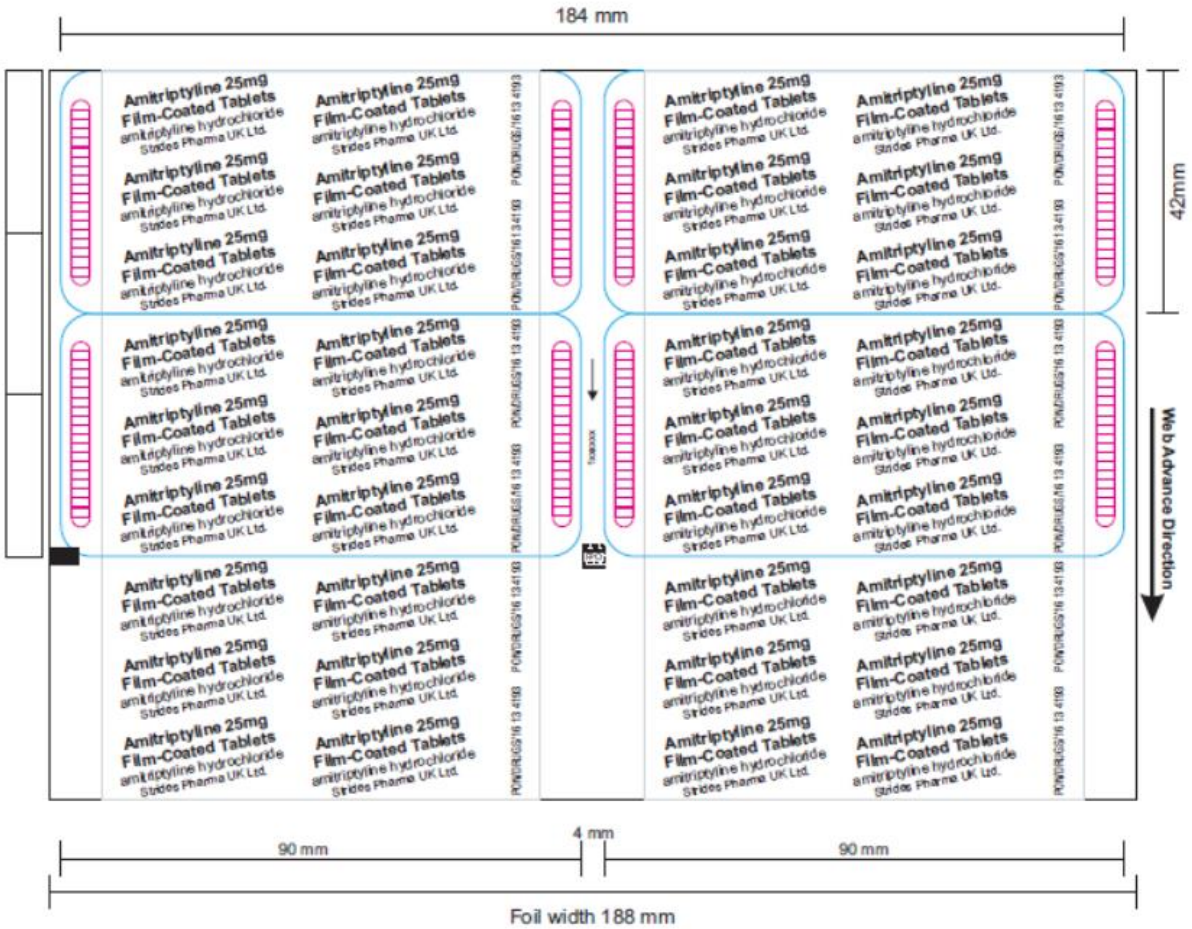
98 mm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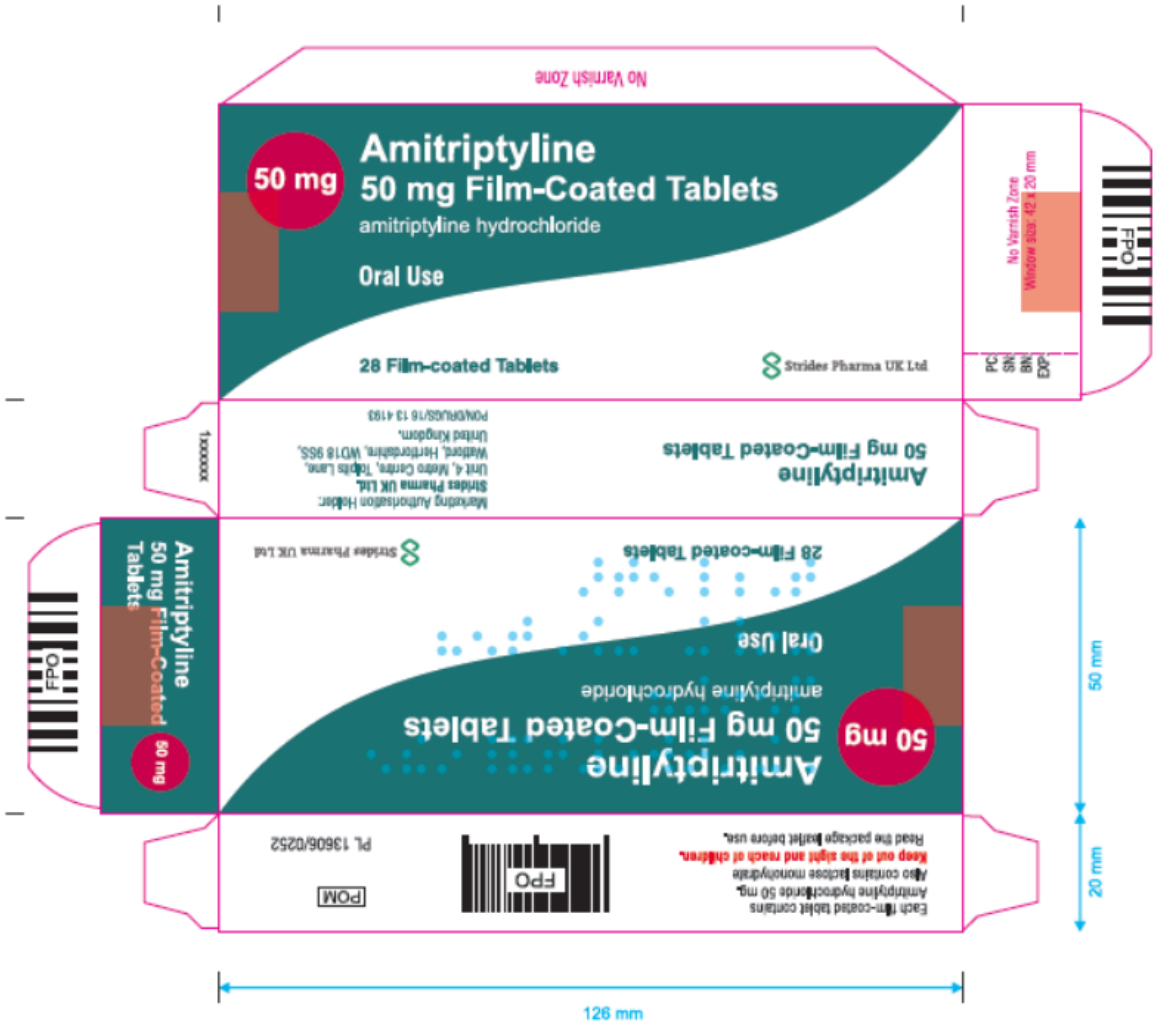
BN and Exp to be Embossed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PQN/BRUG5/16 13 4183
1xxxxx
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Also contains lactose monohydrate
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PL 13606/0252
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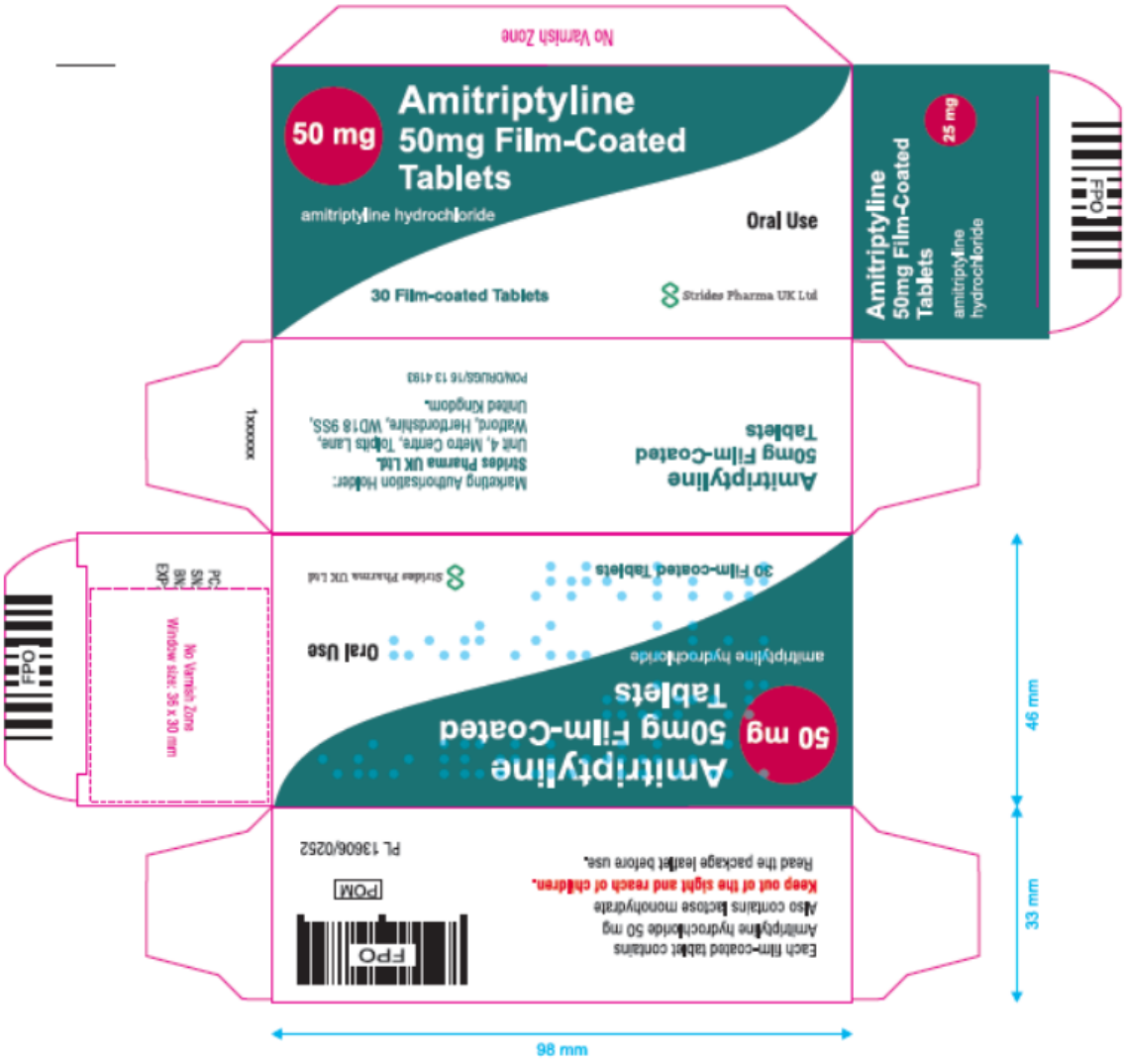
126 mm
50 mm
20 mm


No Varnish Zone
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Amitriptyline
50mg Film-Coated
Tablets
amitriptyline hydrochloride
Oral Use
30 Film-coated Tablets
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PL 13606/0252
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No Varnish Zone
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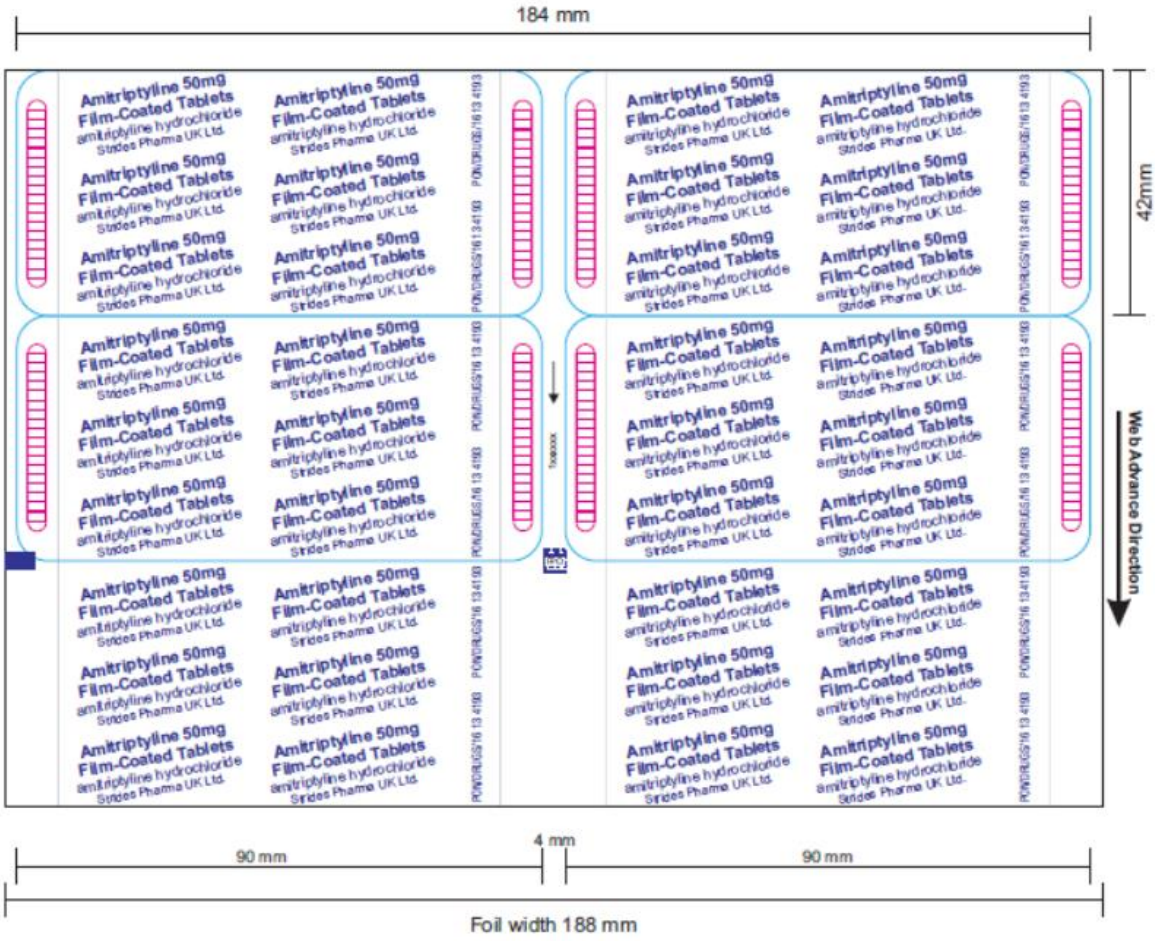
46 mm
33 mm
98 mm


184 mm
42mm
Web Advance Direction
4 mm
90 mm
90 mm
Foil width 188 mm
Amitriptyline 50mg
Film-Coated Tablets
amitriptyline hydrochloride
Strides Pharma UK Ltd.

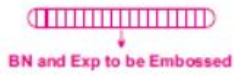

BN and Exp to be Embossed

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**