Public Assessment Report

UKPAR

Amitriptyline 10 mg film-coated tablets
Amitriptyline 25 mg film-coated tablets
Amitriptyline 50 mg film-coated tablets

(Amitriptyline hydrochloride)

UK Licence No: PL 17907/0131-133

Bristol Laboratories Limited
LAY SUMMARY

Amitriptyline 10 mg, 25 mg and 50 mg film-coated tablets
(Amitriptyline hydrochloride, film-coated tablets, 10 mg, 25 mg and 50 mg)

This is a summary of the Public Assessment Report (PAR) for Amitriptyline 10 mg, 25 mg and 50 mg film-coated tablets (PL 17907/0131-0133). It explains how Amitriptyline 10 mg, 25 mg and 50 mg film-coated tablets 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 Amitriptyline 10 mg, 25 mg and 50 mg film-coated tablets.

These products will collectively be referred to as Amitriptyline tablets throughout the remainder of this public assessment report (PAR).

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

What are Amitriptyline tablets and what are they used for?
Amitriptyline tablets are used to treat the symptoms of depression and for the relief of bed-wetting at night by children. The assessment of the applications concluded that Amitriptyline tablets are similar to a ‘reference medicine’ containing the same active substance (amitriptyline hydrochloride) and strength already authorised in the European Union (EU) called Tryptizol 10 mg, 25 mg and 50 mg Tablets (Merck Sharp & Dohme Limited).

How do Amitriptyline tablets work?
Amitriptyline tablets contain the active ingredient amitriptyline hydrochloride, which belongs to a group of medicines called tricyclic antidepressants (TCADS). These medicines alter the levels of chemicals in the brain to relieve the symptoms of depression.

How are Amitriptyline tablets used?
The pharmaceutical form of Amitriptyline tablets is a tablet and the route of administration is by mouth (oral).

The patient must always take Amitriptyline tablets exactly as their doctor has told them to. The patient must check with their doctor or pharmacist if they are not sure.

The recommended dose depends on the reason why this medicine has been prescribed and the age of the patient.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

The tablets should be swallowed with a glass of water.

The patient must not stop taking these tablets suddenly. The patient should continue to take them for as long as the patient’s doctor tells them to. The patient should talk to their doctor before the patient stops taking this medicine and follow their doctor’s advice as the patient may experience withdrawal symptoms (feeling sick, malaise and headache). Gradual withdrawal is associated with reports of symptoms including dream and sleep disturbances, irritability and restlessness, excitement and hyperactivity during the first two weeks of dosage reduction. Feeling elated or over-excited has been
rarely reported when stopping long term treatment with this type of drug. These symptoms are transient and are not a sign of addiction. If the patient has any further questions on the use of this product the patient should ask their doctor or pharmacist.

This medicine can only be obtained with a prescription.

**What benefits of Amitriptyline tablets have been shown in studies?**
Studies in patients have been limited to tests to determine that the tablets are similar to the reference medicine, Amitriptyline 10 mg, 25 mg and 50 mg Tablets (Teva UK Limited). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Amitriptyline tablets?**
Like all medicines, Amitriptyline tablets can cause side-effects, although not everybody gets them.

For the full list of all side effects reported with Amitriptyline tablets, see section 4 of the package leaflet available on the MHRA website.

**Why was Amitriptyline tablets approved?**
The MHRA decided that the benefits of Amitriptyline tablets are greater than their risks and recommended that they be approved for use.

**What measures are being taken to ensure the safe and effective use of Amitriptyline tablets?**
Safety information has been included in the Summary of Product Characteristics and the package leaflet for Amitriptyline tablets 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/reviewed continuously.

**Other information about Amitriptyline tablets**
Marketing Authorisations were first granted in the UK on 27 January 2015.

The full PAR for Amitriptyline tablets follows this summary.

For more information about treatment with Amitriptyline tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in April 2015.
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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) granted Bristol Laboratories Limited, marketing authorisations for the medicinal products Amitriptyline tablets (PL 17907/0131-0133). The products are prescription-only medicines (POM) indicated for symptoms of depression (especially where sedation is required) and for nocturnal enuresis where organic pathology is excluded.

These applications were submitted under Article 10(3) of Directive 2001/83/EC, as amended, cross-referencing to Tryptizol 10mg, 25mg and 50mg tablets which was originally licenced on 13 July 1983 to Merck Sharp & Dohme Limited (PL 00025/0093-0095R). These licences were subsequently cancelled on 01 April 2008. As the brand leader’s products (all strengths and pharmaceutical forms) are no longer available on the EU market, the applications were submitted under Article 10(3), in line with CMDh Questions & Answers Generic Applications guidance (CMDh/272/2012, Rev0).

In the absence of the brand leader’s products, for comparison purposes the reference products used for these applications are Amitriptyline 10 mg, 25 mg and 50 mg Tablets (Teva UK Limited) which were originally licensed on 30 July 1991, 22 July 1991 and 10 September 1991 respectively in the UK to Teva UK Limited (PL 00289/00178-0180). These applications were originally approved as simple applications referring to Domical 10mg, 25mg and 50mg Tablets granted to Berk Pharmaceuticals Limited on 17 August 1972 (10 mg and 25 mg strength; PL 00152/0065-66R) and 02 October 1981 (50 mg strength; PL 00152/0114).

Amitriptyline is a tricyclic antidepressant. It has marked antimuscarinic and sedative properties and prevents the re-uptake (and hence the inactivation) of noradrenalin and serotonin (5HT) at presynaptic nerve terminals and this has been thought to be their mode of action. However the antidepressant effect does not appear until 10-14 days after starting treatment whereas a block in activity can be shown within an hour. This suggests that other pharmacological actions may also contribute.

One bioequivalence study was submitted to support these applications comparing the applicant’s test product Amitriptyline 50 mg film-coated tablets (Bristol Laboratories Limited) with the reference product Amitriptyline 50 mg Tablets (Teva UK Limited) under fasting conditions. The applicant has stated that the bioequivalence study was conducted in compliance with ICH, Good Clinical Practices (GCP) and Good Laboratory Practices (GLP) requirements.

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that these applications were based on a product being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Amitriptyline tablets outweigh the risks and Marketing Authorisations were granted.
II QUALITY ASPECTS

II.1 Introduction
Each film-coated tablet contains 10 mg, 25 mg or 50 mg of the active ingredient amitriptyline hydrochloride. Other ingredients consist of the pharmaceutical excipients microcrystalline cellulose, lactose monohydrate, crospovidone, maize starch, colloidal anhydrous silica, talc, magnesium stearate and the tablet coatings which consist of:

10 mg strength:
- Hypromellose, talc, titanium dioxide (E171), macrogol 6000 and Indigo Carmine Al Lake (E 132)

25 mg strength:
- Hypromellose, talc, titanium dioxide (E171), macrogol 6000 and Quinoline yellow (E104)

50 mg strength:
- Hypromellose, talc, titanium dioxide (E171), macrogol 6000 and Quinoline yellow (E104) and Ferric oxide red (E172).

All strengths of the finished product (10 mg, 25 mg and 50 mg) are packed into polyvinyl chloride (PVC)/aluminium foil blisters containing 7, 10, 14, 21, 28, 30, 56, 60, 84, 90, 100, 110, 112, 120, 150, 160 or 168 tablets. Not all pack sizes may be marketed. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance
INN: Amitriptyline hydrochloride
Chemical names: 3-(10,11-Dihydro-5H-dibenzo[a,d][7]annulen-5-ylidene)-N,N-dimethylpropan-1-amine hydrochloride

Structural formula:

![Structural formula of Amitriptyline hydrochloride]

Molecular formula: C_{20}H_{23}N.HCl.
Molecular mass: 313.9 g/mol
Appearance: A white or almost white powder or colourless crystals.
Solubility: Freely soluble in water, ethanol (96%) and methylene chloride.

Amitriptyline hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, amitriptyline hydrochloride, are covered by the 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 has been shown to comply with current guidelines concerning contact with food.

II.3 Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious, film-coated tablets containing 10 mg, 25 mg or 50 mg amitriptyline hydrochloride per tablet that are comparable in performance to the reference products Tryptizol 10 mg, 25 mg and 50 mg Tablets (Merck Sharp &
Dohme Limited). The licences for Tryptizol 10mg, 25mg and 50 mg tablets PL 00025/0093-0095R were cancelled on 01 April 2008. As the brand leader’s products (all strengths and pharmaceutical forms) are no longer available on the EU market comparisons have been made using Amitriptyline 10 mg, 25 mg and 50 mg Tablets (Teva UK Limited) during development.

Suitable pharmaceutical development data have been provided for these applications.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the colourings Indigo Carmine Al Lake (E 132) and Quinoline yellow (E104) which are controlled to suitable in-house specifications and Ferric oxide red (E172) which is controlled to United States Pharmacopeia-National Formulary (USP-NF) standards. The applicant has also provided confirmation that the colourings comply with EEC specific purity requirements. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of lactose monohydrate none of the excipients used contain material of animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption. No genetically modified organisms (GMO) have been used in the preparation of these products.

Manufacture of the product
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 at pilot-scale batch size and shown satisfactory results. The marketing authorisation holder (MAH) has committed to perform additional process validation on future full scale commercial batches of each tablet strength.

Finished Product Specification
The finished product specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of each tablet strength in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years with the storage conditions ‘Do not store above 30°C. Store in the original package (blister) in order to protect from moisture and light.’

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
There are no objections to the approval of these applications from a pharmaceutical viewpoint.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Amitriptyline tablets is presented below:
Amitriptyline 25 mg, 25 mg and 50 mg film-coated tablets

PL 17907/0131-0133

Amitriptyline Hydrochloride

Size: 116 x 15 x 50 mm

Artwork Same Size

Foil Width: 230 mm
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.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Amtriptyline tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable for these applications.

There are no objections to the approval of these applications from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology of amitriptyline hydrochloride is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of amitriptyline hydrochloride.

Based on the data provided, Amitriptyline tablets can be considered bioequivalent to Amitriptyline 10 mg, 25 mg and 50 mg Tablets (Teva UK Limited).
IV.2 Pharmacokinetics

In support of these applications, the applicant submitted the following bioequivalence study:

STUDY

An open label, randomised, two-period, two-treatment, two-sequence, single dose, crossover study to compare the pharmacokinetics of the applicant’s test product Amitriptyline 50 mg film-coated tablets (Bristol Laboratories Limited) versus the reference product, Amitriptyline 50 mg Tablets (Teva UK Limited), in healthy adult subjects under fasting conditions.

The subjects were administered a single dose (50 mg) of either the test or the reference product with water, after an overnight fast of at least 10 hours.

Blood samples were collected for the measurement of plasma amitriptyline and nortriptyline concentrations before dosing and up to and including 168 hours after each administration. The washout period between the treatment phases was 22 days. The pharmacokinetic results are presented below:

Table: Summary of geometric means and 90% confidence intervals for test and reference product for amitriptyline.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Geometric Mean*</th>
<th>% Ratio</th>
<th>90% Confidence Interval for Log-transformed data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test (A)</td>
<td>Reference (B)</td>
<td>A/B</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt;</td>
<td>468.491</td>
<td>482.401</td>
<td>97.12%</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt;</td>
<td>455.556</td>
<td>468.845</td>
<td>97.17%</td>
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<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>21.647</td>
<td>23.043</td>
<td>93.94%</td>
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*Geometric mean has been taken as the antilog (exponential) of the least square mean of the log-transformed data.

AUC<sub>0-inf</sub> area under the plasma concentration-time curve from time zero to infinity

AUC<sub>0-t</sub> area under the plasma concentration-time curve from zero to t hours

C<sub>max</sub> maximum plasma concentration

Table: Summary of geometric means and 90% confidence intervals for test and reference product for nortriptyline.

<table>
<thead>
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<th>Parameters</th>
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<tr>
<td></td>
<td>Test (A)</td>
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<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt;</td>
<td>357.20</td>
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<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt;</td>
<td>334.96</td>
<td>338.56</td>
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<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>5.94</td>
<td>5.69</td>
<td>104.42%</td>
</tr>
</tbody>
</table>

Conclusion

The 90% confidence intervals of the test/reference ratio for AUC, and C<sub>max</sub> values for amitriptyline (and metabolite nortriptyline) for the 50 mg strength lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant’s test product is bioequivalent to the reference product Amitriptyline 50 mg Tablets (Teva UK Limited).

As the 25 mg and 50 mg strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence study with the 50 mg tablet strength can be extrapolated to the 25 mg strength tablets. In addition, as per the Guideline on the
Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1 Corr**) Amitriptyline 10 mg film-coated tablets (Bristol Laboratories Limited) meet the criteria for Biopharmaceutics Classification System (BCS) Class 1 biowaiver as they exhibit high solubility and complete absorption; similarly rapid (> 85% within 30 minutes) \textit{in vitro} dissolution characteristics and excipients are similar and not expected to have any relevant impact on bioavailability.

**IV.3 Pharmacodynamics**  
No new pharmacodynamic data were submitted and none were required for an application of this type.

**IV.4 Clinical efficacy**  
No new efficacy data were submitted and none were required for an application of this type.

**IV.5 Clinical safety**  
No new safety data were submitted and none were required for this application.

**IV.6 Risk Management Plan (RMP) and Pharmacovigilance System**  
The applicant has provided a suitable justification for the non-submission of a Risk Management Plan (RMP). These applications were submitted prior to 21 July 2012 (the date when the requirement for the submission of RMPs for all initial marketing authorisation (MA) applications came into effect).

The applicant has provided details of a suitable pharmacovigilance system that fulfils the requirements and provides adequate evidence that they have the services of a qualified person responsible for pharmacovigilance, and have the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

**IV.7 Discussion on the clinical aspects**  
With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable for these applications.

Bioequivalence has been demonstrated between the applicant’s product Amitriptyline 50 mg film-coated tablets and the reference product Amitriptyline 50 mg Tablets (Teva UK Limited), under fasting conditions.

As the 25 mg and 50 mg strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence study with the 50 mg tablet strength can be extrapolated to the 25 mg strength tablets. The applicant submitted data to justify a BCS-based biowaiver for the 10mg tablet strength. The data submitted are in line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1 Corr**) and are acceptable.

The grant of marketing authorisations is recommended for these applications.

**V User consultation**  
The applicant has provided confirmation that these products will not enter the UK market without prior MHRA approval of a user consultation study (in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC) to demonstrate that the package leaflet meets the criteria for readability, as set out in the \textit{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 amitriptyline hydrochloride is considered to have
demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.