

**PUBLIC ASSESSMENT REPORT  
of the Medicines Evaluation Board  
in the Netherlands**

**Amitriptyline BB 10 mg, 25 mg and 50 mg film-coated tablets  
Brown & Burk UK Ltd, United Kingdom**

**amitriptyline (as hydrochloride)**

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

**EU-procedure number: NL/H/1967/001-003/DC  
Registration number in the Netherlands: RVG 107084, 107092-107093**

**8 October 2012**

Pharmacotherapeutic group:	non-selective monoamine reuptake inhibitors
ATC code:	N06AA09
Route of administration:	oral
Therapeutic indication:	major depressive episodes
Prescription status:	prescription only
Date of authorisation in NL:	13 August 2012
Concerned Member States:	Decentralised procedure with BE, DE
Application type/legal basis:	Directive 2001/83/EC, Article 10(1), 10(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

## I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Amitriptyline BB 10 mg, 25 mg and 50 mg film-coated tablets from Brown & Burk UK Ltd. The date of authorisation was on 13 August 2012 in the Netherlands.

The product is indicated for the treatment of major depressive episodes. The indication enuresis nocturna, although accepted as indication in the Netherlands for amitriptyline containing products, was withdrawn during the application procedure on request of the two CMSs.

A comprehensive description of the indications and posology is given in the SPC.

Amitriptyline is a tricyclic antidepressant with a sedative effect. It can be used to treat an episode of major depression.

The presence of vital markers, such as anhedonia, psychomotor retardation, inability to sleep through (early morning wakening) and weight loss, increase the possibility of a positive response. Other vital markers are: loss of interest, suicidal thoughts and diurnal fluctuation (a better mood in the evening than in the morning). The effect generally starts to be noticeable only after 1-2 weeks.

Amitriptyline has antiserotonergic, antihistaminic, anti-alpha-adrenergic and class 1 antiarrhythmic properties. Amitriptyline and its active metabolite nortriptyline inhibit the reuptake of norepinephrine and serotonin from the synaptic cleft.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Laroxyl Roche 25 mg and 50 mg film-coated tablets, which have been registered in France by Roche since 1991 (original product). In the Netherlands, Laroxyl Roche 10 mg and 25 mg were authorised in 1969, but withdrawn in 1971.

In the Netherlands and Belgium for the 10 and 25 mg strength reference is made to previously authorised products of Roche. In Germany the European reference product is used for these strengths. For the 50 mg strength the European reference product (Laroxyl 50 mg, France) is used in RMS and all involved CMS.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC for all products except for the 10 mg strength in Germany, where the application is made according to article 10(3) - hybrid application.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Laroxyl Roche 50 mg, film-coated tablets registered in France. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

## II SCIENTIFIC OVERVIEW AND DISCUSSION

### II.1 Quality aspects

#### **Compliance with Good Manufacturing Practice**

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

#### **Active substance**

The active substance is amitriptyline hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.\*). It is a white or almost white powder or colourless crystals, which is freely soluble in water, in ethanol and in methylene chloride. The amitriptyline hydrochloride manufactured does not exhibit polymorphism and no isomerism.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

#### Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

#### Quality control of drug substance

The drug substance specification has been established by the MAH. All the tests specified in the monograph are adopted in the specification of the drug substance. The additional tests included in the specification of amitriptyline hydrochloride are tests for residual solvents, particle size and bulk density. Limits for particle size and bulk density are set based on the developmental studies.

Batch analytical data demonstrating compliance with the drug substance specification have been provided for 2 batches.

#### Stability of drug substance

A retest period of 5 years is applicable when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

\* *Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

### **Medicinal Product**

#### Composition

Amitriptyline BB 10 mg, 25 mg and 50 mg film-coated tablets contain 10/25/50 mg amitriptyline equivalent to 11.30, 28.25 and 56.50 mg amitriptyline hydrochloride.

Amitriptyline BB 10 mg tablets are circular, biconvex, yellow film-coated tablets.

Amitriptyline BB 25 mg are circular, biconvex, light brown film-coated tablets.

Amitriptyline BB 50 mg are circular, biconvex, brown film-coated tablets.

The film-coated tablets are packed in PVC/PVdC/PE-aluminium blister packs or polypropylene tablet containers.

The excipients are:

*Tablet core* - lactose, microcrystalline cellulose, sodium starch glycolate, talc, colloidal anhydrous silica, magnesium stearate;

*Film-coat 10 mg* - Opadry yellow 03A 82450: hydroxypropylmethylcellulose (HPMC 2910), hypromellose 6cP, titanium dioxide, yellow iron oxide, talc

*Film-coat 25 mg* - Opadry brown 03A 86954: hydroxypropylmethylcellulose (HPMC 2910), hypromellose 6cP, titanium dioxide, red iron oxide, yellow iron oxide, talc

*Film-coat 50 mg* - Opadry brown 03A 86955: hydroxypropylmethylcellulose (HPMC 2910), hypromellose 6cP, titanium dioxide, red iron oxide, talc

The formulation of the tablets is dose proportional.

#### Pharmaceutical development

The development of the product was described and the choice and function of the excipients explained. Amitriptyline is considered a BCS class I drug substance. A bioequivalence study has been submitted for the 50 mg strength. The absence of bioequivalence studies with the 10 mg and 25 mg tablets is considered acceptable from a chemical-pharmaceutical point of view. Dissolution studies and comparative dissolution profiles with the test and reference medicinal product have been provided and dissolution characteristics are considered satisfactory. Moreover the formulation of the tablets is dose proportional.

#### Manufacturing process

The direct compression approach is conventional. Adequate in-process controls have been set up. The narrative process description and flow chart are acceptable. Validation is performed with two pilot-scale batches per strength. The validation protocol for full scale (commercial) batches has been submitted.

#### Control of excipients

All excipients comply with the European Pharmacopoeia, except for the Opadry colourants. The Opadry colourants are composed of well-known excipients that are controlled to Ph.Eur. monographs. The specifications are acceptable.

#### Quality control of drug product

The product specification includes tests for appearance, identification, average mass, uniformity of mass, diameter, thickness, hardness, water content, dissolution, uniformity of dosage units, related substances, assay, and microbial contamination. The release and shelf-life limits are identical. The analytical methods were adequately described. Validation data was provided for the HPLC methods for assay, dissolution and related substances. Batch analytical data from the proposed production sites demonstrating compliance with the release specification were provided on two pilot-scale batches per strength.

#### Stability of drug product

Stability data on the product was provided for 24 months on two pilot-scale batches per strength stored at 25°C/60% RH (bulk container and blister) and at 40°C/75% RH (bulk container and blister). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed commercial packaging. All batches comply with the requirements of the specification. Results of a photostability study show that the drug product is photo-stable. An in-use stability study was performed using two batches per strength stored in an open container at long term conditions. Once the container is open, the tablets should be used within 6 months.

Based on the stability data provided, the proposed shelf life of 36 months has been granted. The medicinal product does not require any special storage conditions.

Several commitments have been made with regard to stability; these can be found on page 9 of this report.

#### Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

All excipients are chemically produced, except for anhydrous lactose (animal milk) and magnesium stearate (plant origin). BSE/TSE certificates have been provided.

## II.2 Non-clinical aspects

This product is a generic formulation of Laroxyl, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

### Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of amitriptyline released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

## II.3 Clinical aspects

Amitriptyline is a well-known active substance with established efficacy and tolerability.

A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Amitriptyline BB 50 mg (Brown & Burk UK Ltd, United Kingdom) is compared with the pharmacokinetic profile of the reference product Laroxyl Roche 50 mg, film-coated tablets (Roche, Cedex, France).

### *The choice of the reference product*

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

### *Design*

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 19-39 years. Each subject received a single dose (50 mg) of one of the 2 amitriptyline formulations. The tablet was orally administered with 240 ml water under fasted conditions. There were 2 dosing periods, separated by a washout period of 25 days.

Blood samples were collected pre-dose (within 1-h before dosing) and at 0.5, 1, 1.50, 2., 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 10, 11, 12, 16, 20, 24, 36, 48, 72, 96, 120, 144,168 and 192 hours after administration of the products.

The study design is acceptable as this is in accordance to the Guideline on the Investigation of Bioequivalence. The procedures followed for a fasted condition and wash-out period of 25 days (i.e. at least 5 terminal half-lives) were according to the guideline.

### *Analytical/statistical methods*

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

### *Results*

Twenty-four subjects completed the study.

Four subjects were withdrawn due to the following reasons:

- One subject dropped out from the study due to personal reason (subject did not report to center for the enrolment of period II).
- Two subjects were withdrawn from the study due to positive urine drug of abuse test on the enrolment day of period II
- A fourth subject was withdrawn from the study after 2.50 hours blood sample collection in period I due to the occurrence of an adverse event.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean  $\pm$  SD,  $t_{max}$  (median, range)) of amitriptyline under fasted conditions.

Treatment N=24	AUC <sub>0-t</sub> ng.h/ml	AUC <sub>0-∞</sub> ng.h/ml	C <sub>max</sub> ng/ml	t <sub>max</sub> h	t <sub>1/2</sub> h
<b>Test</b>	1080 $\pm$ 505	1148 $\pm$ 521	42.4 $\pm$ 14.7	4.5 2.0 – 7.0	32.6 $\pm$ 9.7
<b>Reference</b>	1042 $\pm$ 473	1123 $\pm$ 489	42 $\pm$ 15	4.5 2.5 – 7.0	34.1 $\pm$ 11.2
<b>*Ratio (90% CI)</b>	1.03 (0.96 – 1.11)	1.02 (0.95 – 1.10)	1.00 (0.91 – 1.10)	--	--
<b>CV (%)</b>				--	--
<b>Intra-subject</b>	14.9	14.6	18.7		
<b>Inter-subject</b>	45.2	44.1	31.8		
<b>AUC<sub>0-∞</sub></b> area under the plasma concentration-time curve from time zero to infinity <b>AUC<sub>0-t</sub></b> area under the plasma concentration-time curve from time zero to t hours <b>C<sub>max</sub></b> maximum plasma concentration <b>t<sub>max</sub></b> time for maximum concentration <b>t<sub>1/2</sub></b> half-life					

*\*In-transformed values*

The 90% confidence intervals calculated for AUC<sub>0-t</sub>, AUC<sub>0-∞</sub> and C<sub>max</sub> are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80–1.25. Based on the pharmacokinetic parameters of amitriptyline under fasted conditions, it can be concluded that Amitriptyline BB 50 mg and Laroxyl Roche 50 mg, film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

#### Safety

Both test product and reference product were well-tolerated and the adverse events were mild and transient in nature. The adverse events occurred during the study were giddiness, vomiting, abdominal pain, toothache and headache. There were no relevant differences in safety between the 2 formulations.

Amitriptyline may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of amitriptyline. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

#### Extrapolation to different strengths

A biowaiver for the 10 mg and 25 mg strengths has been granted with the following justification:

- Amitriptyline BB 10 mg, 25 mg & 50 mg are manufactured by the same manufacturer using the same manufacturing process.
- The pharmacokinetics of amitriptyline is linear over the therapeutic dosage range.
- The qualitative composition of Amitriptyline BB 10 mg & 25 mg is the same as that of Amitriptyline BB 50 mg tablets.

- Amitriptyline BB 10 mg & 25 mg tablets are dose-proportional with the 50 mg strength.
  - The dissolution profile of Amitriptyline BB 10 mg & 25 mg strength is similar to the 50 mg strength.
- The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

### **Clinical efficacy/safety**

Initially, the indications major depression and enuresis nocturna were claimed, which are in line with the reference product Laroxyl. The use of amitriptyline in major depression is widely known. However, the indication enuresis nocturna has not been approved in the two involved member states. Relevant evidence for the use of amitriptyline in this indication is available from another Dutch innovator product. The RMS considered that this information is sufficient to support the enuresis indication, as the same known active substance was shown to be effective in this indication. However, it was agreed to leave out this indication since it was not acceptable to both CMSs.

The drug product is produced in three strengths; 10 mg, 25 mg and 50 mg amitriptyline tablets, corresponding to 11.30, 28.25 and 56.50 mg amitriptyline hydrochloride. In the Netherlands currently other authorised immediate-release generic amitriptyline-containing products all contain 10 and 25 mg amitriptyline hydrochloride. This may also be the case in other member states. The MAH has discussed the clinical implications to prevent confusion in clinical practice in case of switching from another generic to the current product. Following an extensive literature review, no supportive data/literature/comparative studies were found indicating that the difference in strength would lead to changes in safety/efficacy. The difference is not considered clinically relevant. In addition, the product information is amended with the text 'Each film-coated tablet contains 10/25/50 mg amitriptyline equivalent to 11.30, 28.25 and 56.50 mg amitriptyline hydrochloride' in section 4.2.

### Risk management plan

Amitriptyline was first approved in 1969, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of amitriptyline can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

### **Product information**

#### SPC

The content of the SPC approved during the decentralised procedure is in accordance with those accepted for other amitriptyline containing products.

#### Readability test

The package leaflet 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 test consisted of two rounds with 10 participants each. The questionnaire for this user test contained 16 questions specific to the key safety issues of Amitriptyline and 3 questions general to the format of the leaflet. The questions sufficiently address the key safety messages. In addition, 3 general questions about the leaflet and its lay-out were drawn up. A satisfactory test outcome was when 9 of the 10 participants of each round are able to find the information requested within the PIL, of whom at least 8 of these 9 subjects can show that they understand it.

At round 1 all the participants were able to find the information requested and all participants showed that they understood and acted upon it (most of the participants simple and easy). No corrective actions were taken to the PIL for round 2.

In round 2, almost all the participants were able to find the information requested (except for one participant (question 7 and 10)) and all showed that they understood and acted upon it (simple and easy). The correct answer was traced in all of 16 questions by all participants. All subjects were able to show

comprehension of the information, and the PIL passed the test criteria. The contents and lay-out of the PIL are acceptable. The readability test has been sufficiently performed.



### III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Amitriptyline BB 10 mg, 25 mg and 50 mg film-coated tablets have a proven chemical-pharmaceutical quality and are a generic form of Laroxyl Roche film-coated tablets. Laroxyl Roche is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other amitriptyline containing products.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Amitriptyline BB 10 mg, 25 mg and 50 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 28 June 2012. Amitriptyline BB 10 mg, 25 mg and 50 mg film-coated tablets were authorised in the Netherlands on 13 August 2012.

The date for the first renewal will be: 28 June 2017.

The following post-approval commitments have been made during the procedure:

#### Quality - medicinal product

- The MAH committed to perform the in-use stability study on one of the batches of finished product at the end of the shelf life.
- The MAH committed that all on-going stability studies will be completed, according to the presented stability protocol, at least up to the authorised or claimed shelf life.
- The MAH committed to start stability studies with three commercial-scale batches of each strength in order to fully establish the shelf-life of 36 months.

## List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C <sub>max</sub>	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
t <sub>1/2</sub>	Half-life
t <sub>max</sub>	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

