CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Lamotrigine Aurobindo 5 mg, 25 mg, 50 mg, 100 mg, 200 mg, dispersible tablets Aurobindo Pharma B.V., the Netherlands

lamotrigine

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/2260/001-005/MR
Registration number in the Netherlands: RVG 105238, 105240-105243

3 October 2011

Pharmacotherapeutic group:	other antiepileptics
ATC code:	N03AX09
Route of administration:	oral
Therapeutic indication:	epilepsy; bipolar disorder in adults only
Prescription status:	prescription only
Date of first authorisation in NL:	8 June 2010
Concerned Member States:	Mutual recognition procedure with DE, FR, IE, IT, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

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 Lamotrigine Aurobindo 5 mg, 25 mg, 50 mg, 100 mg, 200 mg, dispersible tablets from Aurobindo Pharma B.V. The date of authorisation was on 8 June 2010 in the Netherlands.

The product is indicated for:

- Epilepsy
  Adults and adolescents aged 13 years and above
  - Adjunctive or monotherapy treatment of partial seizures and generalised seizures, including tonic-clonic seizures.
  - Seizures associated with Lennox-Gastaut syndrome. Lamotrigine is given as adjunctive therapy but may be the initial antiepileptic drug (AED) to start with in Lennox-Gastaut syndrome.

  Children and adolescents aged 2 to 12 years
  - Adjunctive treatment of partial seizures and generalised seizures, including tonic-clonic seizures and the seizures associated with Lennox-Gastaut syndrome.
  - Monotherapy of typical absence seizures.

- Bipolar disorder
  Adults aged 18 years and above
  - Prevention of depressive episodes in patients with bipolar I disorder who experience predominantly depressive episodes (see section 5.1).

Lamotrigine Aurobindo is not indicated for the acute treatment of manic or depressive episodes.
A comprehensive description of the indications and posology is given in the SPC.

The results of pharmacological studies suggest that lamotrigine is a use- and voltage-dependent blocker of voltage gated sodium channels. It inhibits sustained, repetitive firing of neurones and inhibits release of glutamate (the neurotransmitter which plays a key role in the generation of epileptic seizures). These effects are likely to contribute to the anticonvulsant properties of lamotrigine.
In contrast, the mechanisms by which lamotrigine exerts its therapeutic action in bipolar disorder have not been established, although interaction with voltage gated sodium channels is likely to be important.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Lamictal dispersible tablets which has been registered in Denmark by GlaxoSmithKline since 1993. The Dutch reference product is Lamictal Dispers 5/25/50/100/200 mg, dispergeerbare/ kauwtabletten (NL License RVG 19115-19117, 20926-20927) registered by GlaxoSmithKline, which was subsequently recognised in other EEA countries through MRP NL/H/1539/002-006.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

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 two bioequivalence studies in which the pharmacokinetic profile of the 5 mg and 200 mg products is compared with the pharmacokinetic profile of the reference products Lamictal 5 mg and 200 mg, obtained from Germany. 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 lamotrigine, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is slightly soluble in anhydrous ethanol, practically insoluble in dilute hydrochloric acid and in water. Several polymorphs and pseudo-polymorphs of Lamotrigine are reported in the chemical literature.

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 new 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 is in line with the Ph.Eur., with additional requirements for particle size and microbial contamination. The specification is acceptable in view of the route of synthesis and the various European guidelines. The specification is acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scaled batches.

Stability of drug substance
The active substance is stable for 3 years 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
Lamotrigine Aurobindo 5 mg are white to off-white, capsule shaped uncoated tablets debossed with ‘H’ on one side and ‘81’ on the other side.
Lamotrigine Aurobindo 25 mg are white to off-white, rounded square shaped uncoated tablets debossed with ‘H’ the on multifaceted side and ‘80’ on the flat side.
Lamotrigine Aurobindo 50 mg are white to off-white, rounded square shaped uncoated tablets debossed with ‘H’ on the multifaceted side and ‘79’ on the flat side.

Lamotrigine Aurobindo 100 mg are white to off-white, rounded square shaped uncoated tablets debossed with 'H' on the multifaceted side and '78' on the flat side.
Lamotrigine Aurobindo 200 mg are white to off-white, rounded square shaped uncoated tablets debossed with 'H' on the multifaceted side and '77' on the flat side.

The dispersible tablets packed in PVC/Aclar/Al blisters. The 25 mg, 50 mg, 100 mg and 200 mg tablets are also available in HDPE bottles.

The excipients are: microcrystalline cellulose, heavy magnesium carbonate, polacrilin potassium, sucralose, povidone (K-30), magnesium stearate and blackcurrant flavour.

With the exception of the 5 mg strength, the strengths are dose proportional.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Development studies were performed to find an optimised formulation and to have similar dissolution as the innovator product (Lamictal).
The dissolution profiles of 5 and 200 mg tablets were established in different media at different pH values. These were comparable with the other strengths and with the innovator. A wet granulation process was chosen. Two bioequivalent studies were performed, using the 5 mg and 200 mg test products, which were made with the proposed manufacturing process and had the proposed composition. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
A wet granulation process is used. It includes sieving, mixing, granulation, milling and compression steps. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two full-scale batches of each strength. The product is manufactured using conventional manufacturing techniques. Process validation for the third batch and three largest size full-scaled batches will be performed post authorisation.

Control of excipients
The excipients comply with Ph.Eur., USP-NF and USP requirements or in-house requirements (blackcurrant flavour). Purified water complies with both the Ph.Eur. and USP requirements. A safety statement for the ingredients of the flavour, as well as quantitative and qualitative composition has been provided. The specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification, average weight, dissolution, uniformity of dosage units, assay, related substances, disintegration time, fineness of dispersion, thickness and microbial contamination. The shelf-life specification differs from the release specification only in the limits of the related substances. The specifications are acceptable. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on two full-scale batches of each strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on two full-scale batches stored at 25 °C/60% RH (12 months) and 40 °C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in clear PVC/Aclar-Alu blisters, white HDPE bottles or bulk pack. No out of specifications have been observed. A photostability study has been carried out on one batch of each 5 mg, 25 mg and 200 mg. The samples were tested for description, assay and related substance. The products were not susceptible to light.
The proposed shelf-life of 24 months can be granted, based on the provided data. No specific storage conditions are necessary. In-use stability data of the HDPE bottles has been provided, showing the material to be stable for 3 months.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a generic formulation of Lamictal, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

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 lamotrigine 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

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

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test products Lamotrigine Aurobindo 5 mg and 200 mg (Aurobindo Pharma B.V, the Netherlands) is compared with the pharmacokinetic profile of the reference products Lamictal 5 mg and 200 mg dispersible tablets (GlaxoSmith Kline & Co. KG, Germany).

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

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

Bioequivalence study I – 5 mg tablet
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy adult, male subjects. Each subject received four tablets (4 x 5 mg) of one of the 2 lamotrigine formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. Water was not allowed 1 hour before and until 1 hour after dosing. There were 2 dosing periods, separated by a washout period of 16 days.
Blood samples were collected pre-dose and at 0.20, 0.40, 0.60, 0.80, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0, 24.0, 36.0, 48.0, 72.0, 96.0, 120.0 and 144.0 hours after administration of the products.

Results
One subject was withdrawn from the study during Period I, two subjects were absent for Period-II check-in, and a fourth subject was voluntarily withdrawn from the study before dosing in Period II. The remaining 24 subjects completed the study successfully and were included in pharmacokinetic analysis.

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

Treatment N=24	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	13038 ± 6850	14566 ± 9515	280 ± 92	3.25 (1.00-8.00)	37.36 ± 13.25
Reference	13125 ± 6289	14540 ± 7606	285 ± 91	4.00 (0.80-8.00)	34.58 ± 8.15
***Ratio (90% CI)**	0.98 (0.94-1.03)	0.97 (0.94-1.01)	0.98 (0.94-1.01)	--	--
CV (%)	9.81	8.12	7.13	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} 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 lamotrigine under fasted conditions, it can be concluded that Lamotrigine Aurobindo 5 mg and Lamictal 5 mg dispersible tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Bioequivalence study II – 200 mg tablet

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy adult, male subjects. Each subject received a single dose (200 mg) of one of the 2 lamotrigine formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. Water was not allowed 1 hour before and until 1 hour after dosing. There were 2 dosing periods, separated by a washout period of 17 days.
Blood samples were collected pre-dose and at 0.20, 0.40, 0.60, 0.80, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0, 24.0, 36.0, 48.0, 72.0, 96.0, 120.0 and 144.0 hours after administration of the products.

Results

Four subjects were absent for Period-II check-in. The remaining 24 subjects completed the study successfully and were included in pharmacokinetic analysis.

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

Treatment N=24	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	136574 ± 54670	146722 ± 67599	3210 ± 746	3.00 (0.60-8.00)	31.75
Reference	130514 ± 46717	142051 ± 64423	3183 ± 728	2.25 (0.40-8.00)	33.35
***Ratio (90% CI)**	1.03 (1.00-1.07)	1.03 (0.99-1.06)	1.01 (0.96-1.05)	--	--
CV (%)	7.22	7.39	9.34	--	--

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity				
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours				
C_{max}	maximum plasma concentration				
t_{max}	time for maximum concentration				
$t_{1/2}$	half-life				

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} 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 lamotrigine under fasted conditions, it can be concluded that Lamotrigine Aurobindo 200 mg and Lamictal 200 mg dispersible tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Extrapolation to different strengths
A separate bioequivalence study with 5 mg tablet has been performed, as this tablet is not dose-proportional with any other tablet strength.
A biowaiver for the 25, 50 and 100 mg tablets was granted based on the bioequivalence study with 200 mg, as:
- the pharmaceutical products are manufactured by the same manufacturer and process
- the pharmacokinetics has been shown to be linear over the therapeutic range
- the qualitative composition of the different strengths is the same
- the ratio between amounts of active substance and excipients is the same
- the dissolution profiles are similar under identical conditions for the additional strengths and the strength of the biobatch.

Pharmacokinetics of lamotrigine is linear up to 450 mg. The 25 mg, 50 mg and 100 mg tablets are dose proportional to the 200 mg tablets. Dissolution is fast, with more than 85% of the drug product dissolved within 15 min at different pH values for the concerned tablet strengths and the biobatch.

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

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).

Risk management plan
Lamotrigine was first approved in 1991, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of lamotrigine 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 mutual recognition procedure is in accordance with that accepted for the reference product Lamictal.

Readability test

No user testing has been performed. A bridging statement has been submitted with reference to the PIL of a previously approved lamotrigine product. However, some important differences between the content of the two PILs were noted. Bridging was accepted based on the fact that the PIL is in full accordance with the approved innovator PIL.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Lamotrigine Aurobindo 5 mg, 25 mg, 50 mg, 100 mg, 200 mg, dispersible tablets have a proven chemical-pharmaceutical quality and generic forms of Lamictal 5, 25 mg, 50 mg, 100 mg and 200 mg. Lamictal 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 is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. Lamotrigine Aurobindo 5 mg, 25 mg, 50 mg, 100 mg, 200 mg, dispersible tablets were authorised in the Netherlands on 8 June 2010.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Lamotrigine Aurobindo 5 mg, 25 mg, 50 mg, 100 mg, 200 mg, dispersible tablets with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 20 June 2011.

The date for the first renewal will be: July 2013.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to complete validate for commercial batches prior to batch release.

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_{max}	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
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia of the United States
USP-NF	Pharmacopoeia of the United States - National Formulary

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached