LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Lamotrigin Pfizer
Lamotrigine

SE/H/915/01-04/DC

This module reflects the scientific discussion for the approval of Lamotrigin Pfizer tablets. The procedure was finalised at 2010-11-30. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Pfizer AB has applied for a marketing authorisation for Lamotrigin Pfizer tablets 25, 50, 100, 200 mg, claiming essential similarity to "Lamictal 25 mg tablets marketed in Sweden by GlaxoSmithkline". The product contains Lamotrigine" as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Lamictal tablet 200 mg" marketed by GlaxoSmithKline in UK.

II. QUALITY ASPECTS

II.1 Introduction

Lamotrigin Pfizer is presented in the form of tablets containing 25, 50, 100, 200 mg of lamotrigine. The excipients are microcrystalline cellulose, lactose monohydrate, sodium starch glycolate (Type A), magnesium stearate, povidone (K30), indigo carmine aluminium lake (E132) (For 200 mg only) and sunset yellow aluminium lake (E110) (For 100 mg only). The t*ablets* are packed in clear PVC/aluminium blister or HDPED bottles with polypropylene cap and cotton coil.

II.2 Drug Substance

Lamotrigine has a monograph in the Ph Eur.

Lamotrigine is a white or almost white powder which is very slightly soluble in water and slightly soluble in anhydrous ethanol. The structure of lamotrigine has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Lamotrigin Pfizer tablets are formulated using excipients described in the current Ph Eur, except for the colorants sunset yellow aluminium lake (E110) and indigo carmine aluminium lake (E132) which are controlled according to acceptable in house specifications. All raw materials used in the product are of vegetable origin/has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as poor aqueous solubility.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with no special storage precautions.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Lamotrigine has a rapid and complete absorption from the gut with no significant first-pass metabolism. Following an oral dose of lamotrigine maximal plasma concentrations occur at approximately 2.5 hours. The pharmacokinetics of lamotrigine is not affected by food; there is a slight delay in rate of absorption but extent of absorption is unaffected; and therefore there are no restrictions with respect to food in the SPC of the originator. Clearance of lamotrigine is primarily metabolic via UDP-glucuronyl transferases. The half-life has been estimated to approximately 33 hours, but with large variability (range 14 – 133 hours). The pharmacokinetic of lamotrigine are linear up to 450 mg administered as single dose.

To support the application, the applicant has submitted as report one bioequivalence study (Ltg-03/07), in which Lamotrigin Pfizer tablet 200 mg are compared with Lamictal tablet 200 mg following a single dose under fasting conditions. Based on the submitted bioequivalence study Lamotrigin Pfizer tablet 200 mg is considered bioequivalent to Lamictal tablet 200 mg, see results below.

Treatment	**AUC_{0-t}** ng*h/ml	**$AUC_{0-\infty}$** ng*h/ml	**C_{max}** ng/ml	**t_{max}** h
Lamotrigine 200 mg tablets	109791.27 (32828.399)	116204.89 (37022.423)	2445.02 (579.475)	2.50 (0.40 – 12.00)
Lamictal 200 mg tablets	111105.99 (41928.311)	117565.66 (45528.623)	2457.13 (643.282)	2.50 (0.40 – 8.00)
***Ratio (90% CI)**	100.48 (97.32 – 103.75)	100.36 (97.22 - 103.60)	100.14 (95.44 – 105.07)	-

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

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report, making reference to Lamotrigine Aurobindo tablets, UK/H/1259/01-04/DC. The bridging report submitted by the applicant has been found acceptable.

The results of the conducted bioequivalence study can be extrapolated to other strengths since the criteria for biowaiver for additional strengths are fulfilled according to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence.

The risk/benefit ratio is considered positive and "Lamotrigin Pfizer tablets is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Lamotrigin Pfizer tablets was successfully finalised on 2010-11-30.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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