LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Levetiracetam Tiefenbacher
SE/H/1129/01-04/DC

(Levetiracetam)

This module reflects the scientific discussion for the approval of Levetiracetam Tiefenbacher. The procedure was finalised at 2012-01-17. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

ALFRED E. TIEFENBACHER (GmbH & Co. KG) has applied for a marketing authorisation for Levetiracetam Tiefenbacher, film-coated tablet, 250 mg, 500 mg, 750 mg and 1000 mg, claiming essential similarity to Keppra, film-coated tablet, 250 mg, 500 mg, 750 mg and 1000 mg, marketed the EU by UCB Pharma SA. The product contains levetiracetam as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Keppra, film-coated tablet marketed in Germany.

II. QUALITY ASPECTS

II.1 Introduction

The Finished product is presented in the form of film-coated tablets containing 250, 500 750 and 1000 mg of levetiracetam. The excipients are maize starch, povidone, magnesium stearate, colloidal anhydrous silica, partially hydrolyzed polyvinyl alcohol, titanium dioxide (E171), macrogol, talc (E553b), indigo carmine aluminium lake (E132), iron oxide (E172) and sunset yellow FCF aluminium lake (E110). The tablets are packed in HDPE bottles with PP caps and desiccant or blisters (PVC or PVC/PVdC with aluminium foil).

II.2 Drug Substance

Levetiracetam has a monograph in the Ph Eur.

Levetiracetam is a white or almost white crystalline powder which is very soluble in water, soluble in acetonitrile, practically insoluble in hexane. The structure of levetiracetam 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

The film-coated tablet, 250 mg, 500 mg, 750 mg and 1000 mg are formulated using excipients described in the current Ph Eur, except for the coating mixtures which are controlled according to acceptable in house specifications. All raw materials used in the product are of vegetable origin.

The product development has taken into consideration the physico-chemical characteristics of the active substance.

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.

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

Levetiracetam has an oral bioavailability of almost 100 %. Following an oral dose of levetiracetam maximal plasma concentrations occur at approximately 1.3 hours. The pharmacokinetics of levetiracetam is not affected by food, and therefore there are no restrictions with respect to food in the SPC of the originator. The SPC of the originator states that the pharmacokinetics of levetiracetam is linear, that the extent of absorption is dose-independent and that absorption is linear. The terminal half-life is 7±1 hours. The main route of elimination is urinary excretion.

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 24 (22 completed) healthy volunteers, comparing Levetiracetam 1000 mg tablets, with Keppra 1000 mg film-coated tablets under fasting conditions. Blood samples were collected pre-dose and up to 48 hours post-dose. The study design is considered acceptable. Plasma concentrations of levetiracetam were determined with an adequately validated LC/MS/MS method. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Based on the submitted bioequivalence study, the applied 1000 mg tablets are considered bioequivalent with Keppra 1000 mg film-coated tablets.

From a pharmacokinetic point of view, absence of studies with the additional strengths 250, 500 and 750 mg is acceptable, as the pharmacokinetics of levetiracetam is linear.

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

No user consultation of the *content* of the package information leaflet (PIL) has been required, since the leaflet is harmonised with the centrally authorised originator Keppra. User consultation with target patient groups on the PIL *layout* has been performed on the basis of bridging reports, making reference to several products with the established corporate PL layout of the companies respectively. Procedure numbers for mother PLs together with evidence of assessment and approval (e.g. copy of Public AR for the reference product) have been submitted by the applicants. The bridging reports have 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 Levetiracetam Tiefenbacher, film-coated tablet, 250 mg, 500 mg, 750 mg and 1000 mg, is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Levetiracetam Tiefenbacher, film-coated tablet, 250 mg, 500 mg, 750 mg and 1000 mg, was successfully finalised on 2012-01-17.

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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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