LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Levetiracetam Krka
(Levetiracetam)

SE/H/1067/01-04/DC

This module reflects the scientific discussion for the approval of Levetiracetam Krka. The procedure was finalised at 2011-06-09. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

TAD Pharma GmbH has applied for a marketing authorisation for Levetiracetam Krka, 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets, claiming essential similarity to Keppra, 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets 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 tablets, marketed by UCB Pharma SA in Germany.

II. QUALITY ASPECTS

II.1 Introduction

Levetiracetam Krka is presented in the form of film-coated tablets containing 250, 500, 750 and 1000 mg of levetiracetam respectively. The excipients are maize starch, crospovidone, copovidone, colloidal anhydrous silica, magnesium stearate, hypromellose, talc, titanium dioxide, macrogol, indigotine lake, yellow iron oxide and red iron oxide. The tablets are packed in PVC/PVDC-aluminium blister packages.

II.2 Drug Substance

Levetiracetam is described in a monograph in the Ph. Eur.

Levetiracetam is a white crystalline powder. It is very soluble in water, freely soluble in chloroform, methanol and ethanol, soluble in acetonitrile and practically insoluble in hexane. The structure of levetiracetam has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism and chirality has been presented. Levetiracetam is the levorotatory enantiomer of etiracetam. 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

Levetiracetam Krka film-coated tablets are formulated using excipients described in the current Ph. Eur., except for the colouring agents indigotine lake and iron oxide yellow and red which are controlled according to acceptable specifications. No ingredients of animal or human origin are used.

The development of the drug product and the manufacturing process have been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure 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

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.

Bioequivalence was evaluated in one randomised, single-dose, two-way crossover study conducted in 32 healthy volunteers, comparing Levetiracetam 1000 mg film-coated tablets with Keppra 1000 mg, film-coated tablets. The study was conducted at "Sf. Ioan cel Nou" Emergency Hospital, Suaceva County, Romania between 19th September and 5th October 2009. 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%.

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 Nimvastid, EMEA/H/C/1029. 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 Levetiracetam Krka, 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets, is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Levetiracetam Krka, 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets, was successfully finalised on 2011-06-09.

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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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