LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Noepix
(levetiracetam)

SE/H/1138/01-04/DC

This module reflects the scientific discussion for the approval of Noepix. The procedure was finalised at 9th of September 2011. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Sigillata Limited has applied for a marketing authorisation for Noepix, film-coated tablets, 250 mg, 500 mg, 750 mg and 1000 mg claiming essential similarity to Keppra, 250, 500, 750 and 1000 mg, film-coated tablets, marketed in the EU since 2000 by UCB SA Pharma Sector. 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, 1000 mg, film-coated tablets marketed by UCB SA Pharma Sector in BE.

II. QUALITY ASPECTS

II.1 Introduction

Noepix is presented in the form of film-coated tablets containing 250 mg, 500 mg, 750 mg or 1000 mg of levetriracetam. The excipients are crospovidone, magnesium stearate, povidone, colloidal anhydrous silica, macrogol, partially hydrolysed polyvinyl alcohol, talc and titanium dioxide. In addition, the 250 mg tablet contains indigo carmine; the 500 mg tablet contains indigo carmine and yellow iron oxide; and the 750 mg tablet contains indigo carmine, red iron oxide and sunset yellow FCF. The film-coated tablets are packed in blister packages.

II.2 Drug Substance

Levetiracetam has a monograph in the Ph Eur.

Levetiracetam is a white or almost white powder which is very soluble in water, soluble in acetonitril 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 is presented. 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

Noepix film-coated tablets are formulated using excipients described in the current Ph Eur, except for indigo carmine, sunset yellow, red and yellow iron oxides 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.

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

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 28 healthy volunteers, comparing Levetiracetam 1000 mg tablets (manufactured by Actavis group) with Keppra 1000 mg, film-coated tablets under fasting conditions. The study was conducted at Lotus Labs Pvt, Ltd., Mylapore, Chennai, India between 19th July and 8th August 2006. Blood samples were collected pre-dose and up to 36 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%. Thus, bioequivalence compared to the reference product has been demonstrated.

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

The PL is harmonised with the originator. Therefore, a full user test is not considered necessary. 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 Levetiracetam Actavis 250 mg, 500 mg, 750 mg and 1000 mg film-coated tablets EMEA/H/C/002355. 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 Noepix, film-coated tablets, 250 mg, 500 mg, 750 mg and 1000 mg is recommended for approval.

VI. APPROVAL

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

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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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