Public Assessment Report
Scientific discussion

Levetiracetam Ranbaxy
(levetiracetam)

SE/H/1004/01-04/DC

This module reflects the scientific discussion for the approval of Levetiracetam Ranbaxy. The procedure was finalised at 2011-10-12. For information on changes after this date please refer to the module ‘Update’.
I. INTRODUCTION

Ranbaxy UK Ltd has applied for a marketing authorisation for Levetiracetam Ranbaxy, Film-coated tablet, 250 mg, 500 mg, 750 mg and 1000 mg claiming essential similarity to Keppra, 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets marketed in Sweden 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, 750 mg and 1000 mg, film-coated tablets from UK with UCB Pharma SA as marketing authorisation holder.

II. QUALITY ASPECTS

II.1 Introduction

Levetiracetam Ranbaxy is presented in the form of film-coated tablets containing 250 mg, 500 mg, 750 mg or 1000 mg of levetiracetam. The excipients are maize starch, povidone, microcrystalline cellulose, colloidal anhydrous silica, crospovidone, talc, magnesium stearate, hypromellose, titanium dioxide, macrogol, indigo carmine aluminium lake (250 mg, 500 mg and 750 mg strengths), yellow iron oxide (500 mg) and red iron oxide (750 mg). The tablets are packed in Al/Al blister packs.

II.2 Drug Substance

Levetiracetam has a monograph in the Ph Eur.

Levetiracetam is a white to off-white, crystalline powder which is very soluble in water and aqueous buffers. 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

Levetiracetam Ranbaxy film-coated tablets are formulated using excipients described in the current Ph Eur, except for the ready to use Opadry film-coatings which are controlled according to acceptable in house specifications. All raw materials used in the product are of vegetable origin or 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 hygroscopic properties, polymorphism and stability.
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

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.

One bioequivalence study has been submitted for the 750mg strength and one bioequivalence study has been submitted for the 1000mg strength.

Study TR-003-LEVET-09
Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 26 healthy volunteers, comparing Levetiracetam, 750mg, film coated tablet with Keppra, 750mg, film coated tablet under fasting conditions. The study was conducted at Bioequivalence/Bioavailability Department in Romania between February 02nd 2010 and February 12th 2010. Blood samples were collected pre-dose and up to 48 hours post-dose. The study design is considered acceptable.

The plasma concentrations of Levetiracetam were determined by a validated LC/MS/MS method. For AUC₀₋₄ and Cₘₐₓ the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Study TR-028-Levet-09
Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 26 healthy volunteers, comparing Levetiracetam, 1000mg, film coated tablet with Keppra,
1000mg, film coated tablet under fasting conditions. The study was conducted at Bioequivalence/Bioavailability Department in Romania between 05th July 2010 and 17th July 2010. 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\textsubscript{0-t} and C\textsubscript{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
250mg, 500 mg and 750 mg film-coated tablets:
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

1000 mg film-coated tablets:
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 the PIL for the lower strengths. 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 Ranbaxy, 250 mg, 500 mg, 750mg, 1000mg, film-coated tablets is recommended for approval.

VI. APPROVAL

Decentralised procedure for Levetiracetam Ranbaxy, film-coated tablet, 250 mg, 500 mg, 750 mg and 1000 mg were successfully finalised on 2011-10-12.
## Public Assessment Report – Update

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