LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Azitromycin Evolan
(azithromycin (dihydrate))

Asp no: 2013-0087-0089

This module reflects the scientific discussion for the approval of Azitromycin Evolan. The procedure was finalised at 2014-02-13. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Azitromycin Evolan, 250 mg, 500 mg and 600 mg, film-coated tablets, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Evolan Pharma AB applies through the Swedish National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Azitromax, 250 mg, 500 mg and 600 mg, film-coated tablets, authorised in SE since 1995 with Pfizer AB as marketing authorisation holder.
The reference product used in the bioequivalence study is Azitromax, 600 mg, film-coated tablets, from IT with Pfizer AB as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Azitromycin Evolan is presented in the form of film-coated tablets containing azithromycin dihydrate corresponding to 250 mg, 500 mg or 600 mg of azithromycin. The excipients are starch maize pregelatinized, calcium hydrogen phosphate anhydrous, croscarmellose sodium, magnesium stearate, sodium laurilsulfate, lactose monohydrate, hypromellose, titanium dioxide and triacetin. The film-coated tablets are packed in white opaque PVC-aluminum blister.

II.2 Drug Substance

Azithromycin has a monograph in the Ph Eur.

Azithromycin dihydrate is a white crystalline powder which is practically insoluble in water, freely soluble in anhydrous ethanol and in methylene chloride. The structure of azithromycin dihydrate 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

Azitromycin Evolan film-coated tablets are formulated using excipients described in the current Ph Eur. None of the raw materials used in the product are from human or animal 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, 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

Azithromycin has an oral bioavailability of approximately 37 %. Following an oral dose of azithromycin maximal plasma concentrations occur at approximately 2-3 hours. Concomitant food intake increases the C_{max} but the AUC is not affected, and therefore there are no restrictions with respect to food in the SmPC of the originator. The terminal half-life is 2-3 days.

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Azithromycin/LAMBDA, 600 mg, film-coated tablets with Azitromax, 600 mg, film-coated tablets under fasting conditions. The study was conducted at Ramnicu Sarat City Hospital, Buzau County, Romania between 2nd May and 25th June 2003. Blood samples were collected pre-dose and up to 576 hours post-dose. The study design is considered acceptable. Plasma concentrations of azithromycin were determined with a 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%. From a pharmacokinetic point of view, absence of studies with the additional strengths is acceptable, as the overall evidence in the references submitted by the applicant support that the pharmacokinetics of azithromycin is linear between 250 mg and 600 mg.

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 Azitromycin Jubilant 250 mg and 500 mg film-coated tablet, approved in NL/H/1917/001-002/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 Azitromycin Evolan, 250 mg, 500 mg and 600 mg, film-coated tablets are recommended for approval.

VI. APPROVAL

Azitromycin Evolan, 250 mg, 500 mg and 600 mg, film-coated tablets were approved in the national procedure on 2014-02-13.

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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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