LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Alprazolam Krka
(alprazolam)

SE/H/1093/01-03/MR

This module reflects the scientific discussion for the approval of Alprazolam Krka. The procedure was finalised at 2011-07-07. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Krka d.d. Novo Mesto has applied for a marketing authorisation for Alprazolam Krka, prolonged-release tablet, 0,5 mg, 1 mg and 2 mg claiming essential similarity to Xanor Depot, prolonged release tablet marketed in Sweden by Pfizer AB. The product contains alprazolam as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Xanax SR, tablet, 0,5 mg, 1 mg and 2 mg from the Netherlands and with Pharmacia (Pfizer).

II. QUALITY ASPECTS

II.1 Introduction

Alprazolam Krka is presented in the form of prolonged release tablets containing 0.5 mg, 1 mg and 2 mg of alprazolam respectively. The excipients are lactose monohydrate, hypromellose, magnesium stearate and the colorants indigo carmine E132 (only in 0.5 mg and 2 mg tablets) and quinoline yellow E104 (only in 0.5 mg tablets). The prolonged release tablets are packed in blister of OPA/Al/PVC and Al foil.

II.2 Drug Substance

Alprazolam has a monograph in the Ph Eur.

Alprazolam is a white, crystalline powder which is practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in acetone and in ethanol (96 per cent). The structure of alprazolam has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism 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

Alprazolam Krka prolonged release tablets are formulated using excipients described in the current Ph Eur, except for indigo carmine E132 and quinoline yellow E104 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, such as poor aqueous solubility and polymorphism.

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

Bioequivalence studies have been submitted for all three strengths:

- single dose studies in fasting conditions for the 0.5 mg and 2 mg strengths
- a single dose fed study for the 1 mg strength
- a steady state study in fasting conditions for the 1 mg strength.

The absence of single-dose studies in the fasting state with the 1 mg strength can be accepted as the pharmacokinetics of alprazolam is linear up to 10 mg and due to that the compositions are dose proportional. The highest strength, 2 mg, was not used for the steady state study as recommended in guideline. Instead, due to safety reasons, the 1 mg strength was administered. These deviations from recommendations in guideline can be accepted. Thus, the study package is considered acceptable.

Studies 04-100 (0.5 mg fasting), 04-108 (1 mg fed) and 04-109 (2 mg fasting) were performed at University Medical Centre, Clinical of Internal Medicine, Cardiovascular Disease Centre, Ljubljana, Slovenia. Study 05-139 (1 mg steady state) was performed at Clinical Hospital of the Ministry of Health of the Republic of Moldova, Chisinau, The Republic of Moldavia. Two different methods for analysis of Alprazolam in plasma were used. One LC MS/MS method at Institute of Public Health Maribor, Environmental Protection Institute, Prvomajska ulica 1, 2000 Maribor, Slovenia was applied in the first three studies and another LC MS/MS method at Analytical Laboratory of Pharma Serv International S.r.l., Bucharest, Romania were used for the steady state study.

Bioequivalence could be concluded for all four bioequivalence studies submitted as 90% C.I. for the ratio of the means of the primary pharmacokinetic parameters are within 0.80 and 1.25. Approval can be recommended from a pharmacokinetic point of view.

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 Zomiren, LT/1/08/1222/001-012. The bridging report submitted by the applicant has been found acceptable.

The risk/benefit ratio is considered positive and Alprazolam Krka, 0,5 mg, 1 mg and 2 mg, prolonged-release tablet is recommended for approval.

VI. APPROVAL

The Mutual recognition procedure for Alprazolam Krka, 0,5 mg, 1 mg and 2 mg, prolonged-release tablet was successfully finalised on 2011-07-07.

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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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