LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Kappadi

(diclofenac potassium)

SE/H/1162/01-02/MR

This module reflects the scientific discussion for the approval of Kappadi. The procedure was finalised at 2011-12-07. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Mimer Medical has applied for a marketing authorisation for Kappadi, 25 mg and 50 mg, film-coated tablet, claiming essential similarity to Voltaren T 25 and 50 mg, marketed in Sweden by Novartis. Kappadi was developed with the aim to achieve quicker absorption compared to the reference products. It is therefore applied as a so called hybrid application. The product contains diclofenac potassium as active substance. For approved indications see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Kappadi is presented in the form of film-coated tablets containing 25 mg or 50 mg of diclofenac potassium which corresponds to 22 mg or 44 mg diclofenac acid. The excipients are potassium hydrogen carbonate, mannitol, sodium lauryl sulphate, macrogol, crospovidone, magnesium stearate, hypromellose and macrogol. The film-coated tablets are packed in blister packages.

II.2 Drug Substance

Diclofenac potassium has a monograph in the Ph Eur.

Diclofenac potassium is a white, or slightly yellowish, crystalline powder which is Slightly soluble in acetone, soluble in alcohol, practically insoluble in chloroform, freely soluble in methanol and sparingly soluble in water. The structure of diclofenac potassium 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

Kappadi film-coated tablets are formulated using excipients described in the current Ph Eur. All raw materials used in the product 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.

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 to other approved diclofenac-containing products with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Diclofenac potassium has a rather fast absorption, after the intake of 50 mg immediate release tablets, maximum concentrations of approximately 1 μg/ml are reached after 20-60 minutes. Diclofenac undergoes first-pass metabolism which decreases the systemic availability to approximately 50 %. The amount active substance that is absorbed is not affected by food. In synovial fluid, maximum concentrations are reached after 2-4 hours. The half-life in synovial fluid is approximately 3-6 hours. After 4-6 hours the concentration in synovial fluid is higher than in plasma and remains higher up to 12 hours.

The serum protein binding is high; approximately 99.7 %, of which 99.4 % is bound to albumin. The volume of distribution is approximately 0.5 L/kg.

Pharmacokinetic properties remain unchanged after repeated administration. No accumulation is seen within the recommended dosages.

The biotransformation of diclofenac consists of single and multiple hydroxylation and glucuronidation. Approximately 60 % of the dose is excreted in the urine as metabolites. Less than 1 % is excreted unchanged. The remainder of the dose is eliminated as metabolites in bile and faeces.

Diclofenac is eliminated from plasma with a total clearance of approximately 250±50 ml/min. The half-life is 1-2 hours.

This product was developed with the aim to achieve quicker absorption compared to the reference product, resulting in lower t_{max} and higher c_{max} compared to the reference product. It is therefore applied as a hybrid application.

Two bioequivalence studies have been submitted. One of the studies (IPAS-KDICLO-180-99)

was a three way randomised cross-over study investigating bioavailability of both the 25 mg and the 50 mg test formulation. It is unclear where the reference in this study comes from (only stated Swiss market) why that study has not been assessed.

The other study (DIC-BESD-03) was a two-way cross-over randomised study of the 50 mg test product compared with the reference Voltfast, 50 mg, Novartis Pharma under fasting conditions. Blood samples were collected pre-dose and up to 12 hours post dose. The study design is considered acceptable. Plasma concentrations of diclofenac were determined with an adequately validated LC/MS/MS method.

Bioequivalence in terms of extent of absorption compared to the reference product has been shown. Bioequivalence was not shown for C_{max} in the actual study. However, given the clinical safety data, the formulation can be accepted from a pharmacokinetic point of view.

Based on information from the originator, linear kinetics within the therapeutic dose range prevails. Therefore, absence of studies with the additional strength 25 mg is acceptable from a pharmacokinetic point of view.

IV.2 Discussion on the clinical aspects

The applicant has conducted two bioequivalence studies. As C_{max} was not shown in the clinical bioequivalence studies a safety study was conducted.

No new comparative studies between Kappadi tablets and well-established products have been performed. One safety study comparing a diclofenac potassium oral solution with two commercially available diclofenac products (diclofenac potassium tablet and diclofenac sodium gastro- resistant tablet) has been performed. These products are considered to have the same properties as Kappadi tablets quality wise but a more pronounced C_{max}. This is therefore considered acceptable to bridge the submitted gastric tolerability safety data to the Kappadi tablets.

The formulation is being approved based on the clinical safety data, and no further studies on pharmacodynamics or clinical efficacy are deemed necessary for the evaluation of this product.

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 Eezeneo, 115:2009/76940. 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 Kappadi, 25 mg and 50 mg, film-coated tablet, is recommended for approval.

VI. APPROVAL

The Mutual recognition for Kappadi, 25 mg and 50 mg, film-coated tablet, was successfully finalised on 2011-12-07.

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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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