LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Diklofenak BMM Pharma
Diclofenac

SE/H/600/01-02/MR

This module reflects the scientific discussion for the approval of Diklofenak BMM Pharma. The procedure was finalised at March 29, 2007 (day 150). For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

BMM Pharma has applied for a marketing authorisation for Diklofenak BMM Pharma, gastro-resistant capsule 25 and 50 mg, claiming essential similarity to Voltaren, gastro-resistant tablets 25 and 50 mg, marketed by Novartis. The product contains diclofenac as active substance and is indicated for the treatment of rheumatoid arthritis. The reference product used in the bio-equivalence study is Voltarène 50 mg enteric coated tablets (e) marketed by Laboratoires Ciba-Geigy, in France.

Potential serious risk to public health was raised by two Member States mainly due to the lack of a post-prandial study. The national approval in the RMS was based on a bioequivalence study under fasting conditions only. However, during the MRP a post-prandial study became available to the applicant and was submitted. Although submitted during the ongoing procedure, the study was accepted and assessed by the RMS. The study could however not be accepted for formal reasons.
Since the post-prandial study could not be formally accepted during the MRP, it was re-submitted during the CMD referral. There was a discussion regarding the widening of the acceptance criteria to 70-143%. The RMS argued that such a widening was in accordance with the relevant guideline although the EWP Q&A document was unclear as to whether a widening outside 75-133% would be acceptable. The Member States involved in the procedure agreed that the widening of the acceptance criteria in this case did not have any clinical relevance. A contributing fact was that the product is recommended not to be administered with food. Agreement of approval was reached.

II. QUALITY ASPECTS

II.1 Introduction

Diklofenak BMM Pharma is presented in the form of tablets containing 25 mg or 50 mg of diclofenac sodium. The excipients are lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinised starch, sodium starch glycolate, maize starch, macrogol, methacrylic acid-ethyl acrylate copolymer, dimethicone, polysorbate 80, sorbic acid, talc, colourings (iron oxide E172, titanium dioxide E171) The tablets are packed in/filled in blisters.

II.2 Drug Substance

Diclofenac sodium has a monograph in the Ph Eur and the manufacturer holds a CoS of the monograph.
Diclofenac sodium is a white or slightly yellowish, crystalline powder which is slightly hygroscopic, sparingly soluble in water, freely soluble in methanol, soluble in alcohol, slightly soluble in acetone. The structure of diclofenac sodium 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

Diklofenak BMM Pharma, gastro-resistant tablet is formulated using excipients described in the current Ph. Eur.. 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.

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

The Part IVA documentation initially consisted of one bioequivalence study. The submitted study is a single-dose 2-way crossover study where the pharmacokinetics of diclofenac has been compared when administering a single-dose of 50 mg of the substance orally under fasting conditions as Diclofenacnatrium 50 “pharbita” (Pharmachemie B.V. the Netherlands) and as Voltarène 50 mg enteric coated tablets (Laboratoires Ciba-Geigy, France). Twenty-four healthy Caucasian male volunteers, 19-37 years old, 60-88 kg body weight, were enrolled in and completed the study. Blood-sampling was performed at appropriate time points for 9 hours post-dose. The analysis of the plasma was performed using a HPLC system with UV detection. Conventional non-compartmental methods were used. Point estimates and 90 % confidence intervals for the test/reference mean ratios were calculated for C_{max} and AUC. The acceptance criterion for C_{max} and AUC was 80-125 %. The results of the study are presented below.

Bioequivalence was shown regarding C_{max} and AUC. The results are given in the following table as mean (SD) for C_{max} and AUC and median (range) for T_{max} and T_{lag}.

Formulation	**C_{max} (ng/ml)**	**AUC_{0-t} (ng*h/ml)**	**T_{max} (h)**	**T_{lag} (h)**
Reference	1334 ± 489	1092 ± 269	2.00 (1.33 – 3.67)	1.50 (0.67-3.67)
Test	1227 ± 416	1105 ± 255	2.00 (1.00 – 4.33)	1.67 (1.00-4.00)
90% CI	81.6-1.01	95.8-107	Na	Na

A post-prandial bioequivalence study has also been submitted (see Section 1: Introduction). The study was a single-dose two-way crossover bioequivalence study, performed in healthy male and female subjects aged 18-45 years. Twenty-three out of 24 randomized subjects completed the trial. Each subject received a single oral dose of 50 mg diclofenac gastro-resistant tablets (Diclofenac sodium, 50 mg gastroresistant test tablet or Voltarène, 50 mg gastroresistant tablets (Novartis) under high-fat conditions on two occasions in a randomised crossover order. Blood samples were taken at pre-dose and 1, 2, 2.5, 3, 3.5, 4 hours post-dose and from 4 hours after dosing onwards every 20 minutes until 15 hours after dosing. Thereafter 15.5, 16, 16.5, 17, 17.5, 18, 19, 20, 22 and 24 hours post-dose. Diclofenac in plasma was determined with a LC/MS/MS. Treatments were considered bioequivalent if the 90% confidence interval for AUCt was included within the bioequivalence range of 80-125%, and if the 90% confidence interval for Cmax was included within the range of 70-143%. The widened bioequivalence range for Cmax was considered justified, since Cmax levels reached are not expected to raise safety or efficacy problems. The results are described below.

Mean (SD) pharmacokinetic parameters for diclofenac (n=23).

Preparation	**C_{max} (ng/ml)**	**AUC_{0-t} (ng·h/ml)**	**t_{max} (h)**
Test	1330 (374)	1176 (238)	8.86 (3.54)
Reference	1630 (436)	1256 (245.2)	8.29 (3.23)
Ratio test/ref	80.90	93.60	
90% CI	72.27 - 90.58	88.98 – 98.41	

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.

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 testing of the package leaflet has been performed.

The risk/benefit ratio is considered positive and Diklofenak BMM Pharma 25 and 50 mg gastro-resistant tablets are recommended for approval.

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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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