Public Assessment Report
Scientific discussion

Eezeneo
(Diclofenac potassium)

Asp. no: 2005-0629 - 2005-0630

This module reflects the scientific discussion for the approval of Eezeneo. The procedure was finalised at 2008-09-12. For information on changes after this date please refer to the module ‘Update’.
I. INTRODUCTION

Antula Healthcare AB has applied for a marketing authorisation for Eezeneo film-coated tablets 25 mg and 50 mg with reference product Voltaren T, coated tablets, 25 and 50 mg marketed in Sweden by Novartis Sverige AB. The product contains diclofenac potassium as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Voltfast 50 mg marketed by Novartis Pharma in Italy.

II. QUALITY ASPECTS

II.1 Introduction

Eezeneo is presented in the form of film-coated tablets containing 25 and 50 mg of diclofenac potassium. The excipients are crospovidone, magnesium stearate, mannitol, potassium hydrogen carbonate, sodium laurilsulfate, hypromellose and macrogol. The film-coated tablets are packed in blister packs.

II.2 Drug Substance

Diclofenac potassium has a monograph in the Ph. Eur.

Diclofenac potassium is a white or slightly yellowish, slightly hygroscopic, crystalline powder which is 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

Eezeneo film-coated tablets are formulated using excipients described in the current Ph Eur. 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 particle size distribution.
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

Eezeneo film-coated tablets 25 mg and 50 mg contain diclofenac potassium, a substance with well-known pharmacological/toxicological profile. The excipients did not cause any concerns. Eezeneo showed a higher $C_{\text{max}}$ compared to the reference product in a bioequivalence study. However, from a non-clinical point of view, the higher exposure measured as $C_{\text{max}}$ is superseded by clinical data.

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.

Two bioequivalence studies have been submitted. The pivotal of the two, study (DIC-BESD-03) was a two-way randomised study of the 50 mg test product compared with the reference Voltfast, 50 mg, Novartis Pharma.

Bioequivalence was not shown for $C_{\text{max}}$, why the product was not approved as essentially similar. The applicant changed the application to a hybrid application and provided a discussion on the safety aspects of higher maximal concentrations. Given the combination of clinical and pharmaceutical data bridging the gastric tolerability safety data to the applied formulation, the product was accepted from a pharmacokinetic point of view.
IV.2 Discussion on the clinical aspects

To illustrate the gastric tolerability of Eezeneo, the Applicant has submitted a safety study comparing a diclofenac potassium oral solution with the same composition and buffering capabilities as the Eezeneo tablet with two commercial available diclofenac products; a diclofenac potassium tablet and a diclofenac sodium gastro-resistant tablet. The Eezeneo tablets have not been directly compared with the well-established diclofenac products described above. However it is concluded that the oral solution used in the safety study has the same properties as Eezeneo and, if anything, could have a more pronounced $C_{\text{max}}$ compared with the tablet, it is acceptable to bridge the submitted gastric tolerability safety data to the Eezeneo tablets.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has not been performed.

The submitted safety study has not directly compared Eezeneo with the widely approved diclofenac-K tablet (Voltaren-T, Cataflam etc). However, the oral solution used in the study is so similar in composition to the Eezeneo tablet that the results from the solution can bridge to this product.

With the Wilcoxon signed rank test appropriate in the evaluation of $T_{\text{max}}$ in a cross-over study, it has been shown that $T_{\text{max}}$ occurs earlier from a statistical point of view. However, the importance of the size of the difference in $T_{\text{max}}$ translated to a PD variable or efficacy variable has not been demonstrated, and no claims of an earlier time to onset of effect can be made.

No new safety signals for acute adverse events for the oral solution compared with widely used diclofenac-K tablets has been detected. However, safety data for administration longer than 24 hours are lacking. Yearly PSURs should be sufficient for monitoring any long term differences in the adverse event spectrum for this product compared with established diclofenac products with lower $C_{\text{max}}$.

The risk/benefit ratio is considered positive and Eezeneo 25 and 50 mg film-coated tablets are recommended for approval.

VI. APPROVAL

Eezeneo 25 mg and 50 mg film-coated tablets were approved in the national procedure on 2008-09-12.
## Public Assessment Report – Update

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