Public Assessment Report

Scientific discussion

Fenacta
(Diclofenac potassium)

DK/H/1385/001/MR

This module reflects the scientific discussion for the approval of Fenacta. The procedure was finalised at 7 April 2009. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

This assessment report concerns a generic application for diclofenac potassium film-coated tablets 12,5 mg approved through MRP (DK/H/1385/001/MR) on 7 April 2009 with Denmark acting as RMS.

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for the generic diclofenac potasium 12,5 mg film-coated tablets, indicated for " Mild to moderate pain such as rheumatic pain, headache, tooth pain, menstrual pain (primary dismenorrhoea), acute low back pain and muscular and joint pain. Relief of fever", could be approved. A national marketing authorisation was granted on 29 September 2006.

The application is submitted according to Article 10(1) of the European Directive 2001/83/EC as amended.

Essential similarity is claimed with the innovator product Zymamed 12,5 mg film-coated tablets, Novartis Healthcare A/S which was first authorised in Denmark on 25 August 1997.

Diclofenac potassium is a non-steroid anti-inflammatory drug with distinct analgetic, anti-inflammatory and anti-pyretic properties.
Diclofenac potassium works quickly, making it suitable for treating acute pain. Inhibition of prostaglandin synthesis is considered fundamental for the mechanism of action.
Prostaglandins play an important role against inflammation, pain and fever.
In vitro, the tissue proteoglycan synthesis is not reduced in the concentrations achieved in humans.

The recommended dose for adults and children from 14 years is initially 2 tablets, hereafter 1-2 tablets every 4 to 6 hour, however, maximum 6 tablets (75 mg) per 24 hours.
Duration of treatment: 3 days.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its National authorisation.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The PSUR cycle has been harmonised with the diclofenac potassium EU HBD. PSURs should be submitted in 3-yearly intervals (next DLP 200909).

II. QUALITY ASPECTS

II.1 Introduction

The finished product is presented as film-coated tablets in the strength of 12,5 mg packed in blister packs (aluminium/aluminium).

The excipients in the tablet core are: Colloidal silica, anhydrous; Maize starch; Sodium starch; glycolate type A; Povidone (K-29/32); Magnesium stearate; Calcium hydrogen phosphate, anhydrous.

The excipients in the coating are: Polyvinyl alcohol, partly hydrolysed; Titanium dioxide (E171); Talc; Lecithin soya (E322); Xanthan gum (E415).

II.2 2.2 Drug Substance

The product contains diclofenac potassium as active substance which is monographed in the Ph.Eur. The documentation is presented as a European Drug Master File in CTD format.
Synthesis, specifications and methods are all satisfactorily described. The applicant specification for diclofenac potassium is identical to that of the ASM, is satisfactory and complies with general ICH for drug substance specifications and the requirements of the Ph.Eur. monograph. All necessary analysis methods and validations are provided. A retest period of 3 years with no particular storage precautions is accepted.

II.3 Medicinal Product

The product composition is adequately described. The development of the product has been satisfactorily performed and explained and physical compatibility between API and excipients demonstrated. Excipients are common for manufacture of a tablet. The packaging materials are standard and shown suitable by the presented stability studies.

Product manufacture is by standard processing and employs an aqueous granulation process. Batch sizes are 7.5-75kg granulate yielding 100,000-1,000,000 tablets. Validation data are provided for 7.5kg granulate batches showing that there has been some difficulty with ensuring consistency of granulate blend potency. Modifications have been made and potency is now acceptable though tablet hardness requires adjustment. Scale up to 75kg will require careful watching. It is also proposed to mix two or more smaller batches to produce larger batches (up to a maximum of 75kg). Data on the suitability of mixing of batches should be provided to demonstrate suitability.

The finished product specification is standard for the pharmaceutical form and includes relevant physicochemical, ID, assay and purity tests. Separate release and shelf-life specifications are provided where the latter has widened limits for related substances. Batch analysis data on 5 batches of product (100,000 tablets) have been provided showing compliance with the release requirements.

Stability data are provided for 5 batches stored in the proposed market packagings (and two others). A shelf-life of 2 years stored below 25°C is approved.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of diclofenac potassium are well known and on this basis, the applicant has not provided additional studies and none are required. An overview based on a literature review, as presented, is therefore appropriate and acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

To support the application, the applicant has submitted a single bioequivalence study performed with the 12.5 mg strength under fasting conditions in a single dose crossover design. The pharmacokinetic variables evaluated were standard and were evaluated for diclofenac.

Bioequivalence was determined based on AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} as primary variables with limits of 80-125%. The results obtained demonstrate that the test product is bioequivalent with Voltaren Dolo 12.5mg tablets. Test product was tolerated equally well as reference product.

IV.2 Pharmacokinetics

The pharmacokinetics of diclofenac potassium are well known. Based on the available published literature including the brand leader's product information, a summary of pharmacokinetics is provided. In addition, the applicant has provided a bioequivalence study comparing their 12.5 mg film

coated tablets against the brand leader Voltaren Dolo 12.5 mg film coated tablets from Novartis, which is discussed in the clinical study sections.

Absorption
Diclofenac potassium is almost completely absorbed from the gastrointestinal tract following oral administration but undergoes significant first-pass metabolism. Bioavailability is approx. 50 to 60%. The pharmacokinetics are linear in the range 25-150 mg. Pharmacokinetics are unaltered following multiple administration and accumulation does not occur in the recommended dose range. Food intake delays t_{max} by 1 to 4.5 hours and reduces the peak plasma concentration. Bioavailability is not significantly affected.

Distribution
More than 99% diclofenac potassium is bound to plasma proteins and has a volume of distribution of 0.12-0.17 L/kg. Diclofenac is found in synovial fluid, with peak concentrations measured 2-4 hours following peak plasma levels. The elimination half-life from synovial fluid is 3-6 hours.

Metabolism
Diclofenac is extensively metabolised in the liver mainly by hydroxylation and subsequent conjugation. The major metabolite in man is 4'-hydroxydiclofenac which has little activity (about 1/130 of diclofenac).

Excretion
Approx. 50 – 70 % of the dose is eliminated in the urine and 30-35 % in the bile. Less than 1 % is eliminated unchanged. T½ under fasting conditions is 1.5 hours.

IV.3 Pharmacodynamics
The pharmacodynamics of diclofenac potassium are well established in the indications sought. In summary, there is good evidence for all claimed indications.

IV.4 Bioequivalence
To support the application, the applicant has submitted a single bioequivalence study performed under fasting conditions.

Study design
The study was an open-label, randomized, two-way crossover, single-dose bioavailability study conducted under fasting conditions with a wash out period of 7 days between the two administrations. 12.5mg was administered in each period with 240 ml water. The subjects reported to the study centre the evening before each dosing and fasted from at least 10 hours before until 4 hours after drug administration. Standardised meals were served on arrival predosing and at 4 and 9 hours after drug administration. Fluid intake was not allowed from 1 hour before until 1 hour after drug administration, otherwise no restrictions on water intake.
Blood samples were collected pre-dosing and at 0.167, 0.25, 0.333, 0.5, 0.667, 0.833, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8 and 10 hours post administration in each period.

Test and reference products:
Diclofenac potassium 12,5 mg film-coated tablets (batch no. 73230; batch size 100,000 tablets, EXP. Sept 2005) has been compared to Voltaren Dolo 12.5mg (batch no. B3083, from the German market, EXP. Sept. 2006). Satisfactory certificates of analysis of the test and reference product are presented.

Population(s) studied:
66 healthy subjects (44 males and 22 females, 58x Caucasian, 3xBlack, 5xHispanic; 18-45 years; 49-84kg) participated in the study. 65 subjects completed the study (43 males and 22 females). Drop-outs: Subject 64 was withdrawn prior to period 2 dosing due to positive urine screen. Data from subject 2 were not used in the statistical analysis as the subject has participated in another study at another CRO at the same time. Samples size is based on in house MDS data and literature suggesting intrasubject CV% of 40%. With a ratio between 0.95 and 1.05 and a power of 80%, subject number is calculated at 66.

Analytical methods:
The blood samples were analyzed by LC/MS/MS for detection of diclofenac. The method is shown validated within a range of 1-2000 ng/ml and has been satisfactorily validated for sensitivity and linearity, specificity, recovery, precision and accuracy, stability of samples and stock solutions and ruggedness. Within and between batch precision and accuracy has been established within acceptable values. Dilution integrity is acceptable up to 3-fold. The analyte has been shown to be stable in plasma samples following 5 freeze-thaw cycles, for up to 846 days stored at -20°C, for 48.5 hours at RT and processed for up to 47 hours at RT, 5°C and -20°C and 92.5 hours at RT (if re-injection is necessary). A bioanalytical report dated 21st April 2004 is provided together with an analytical validation report dated 15th April 2004.
Date of start and finish of the bio-analytical phase:
The study samples were analysed from 23rd February to 25th March 2004; the maximum sample storage period from the first blood draw was 44 days.
Reanalysis of samples:
A total of 2225 plasma samples (out of 2244 theoretical) were collected and analysed. Some reanalyses were necessary 45 for analytical reasons (primarily as the lowest standard had to be removed).

Pharmacokinetic Variables:
The parameters calculated were AUC_{0-t}, $AUC_{0-\infty}$, AUC_{0-t}/ $AUC_{0-\infty}$, C_{max}, t_{max}, K_{el} and $t_{½\ el}$. Primary variables: AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}.

Statistical methods:
ANOVA was performed on the ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. The ANOVA model (GLM procedure) included sequence, subject nested within sequence, period and treatment. Sequence and period effects were tested using an α error of 5%. Nonparametric test was carried out on t_{max} using methods of Koch and Hauschke.

Criteria for conclusion of bioequivalence:
90% CIs for the ratios (test/reference) for AUC_{0-t}, AUC_{0-inf} and C_{max} should be within 80-125%.
The PK parameters are standard and proposed limits within the normal acceptance range.

Results

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) - Diclofenac

N=64

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h	$T_{1/2}$ h
Test	310.8 (85.87)	314.9 (86.63)	317.34 (168.06)	0.51 (0.25-4.00)	1.74 (0.53)
Reference	308.6 (87.67)	313.2 (88.97)	308.38 (162.25)	- (1.50-4.50)	1.93 (0.72)
***Ratio (90% CI)**	101.1 (98.2-104.0)	100.9 (98.0-103.8)	105.5 (93.2-119.5)	-	-
CV (%)	9.7	9.8	43.9	-	-

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
T_{max} time for maximum concentration
$T_{1/2}$ half-life

*ln-transformed values

The extrapolated AUC is below 20% for all subjects and treatments. There were no measurable pre-dose concentrations of diclofenac at either period 1 or 2. All plasma concentrations are within the validated range of 1.0 ng/ml to 2000.0 ng/ml.
The 90% confidence intervals for the ln-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within 80-125%.

Acceptable plasma concentration-time curves (linear-linear and log-linear) are presented.
Plasma samples are extracted by liquid/liquid extraction.

Safety evaluation
No serious adverse events were reported during the study. A total of 39 adverse events were reported by 18 subjects (9 pre-dosing), 3 possibly related to the treatment (test product – nausea).

Pharmacokinetic conclusion
Based on the submitted bioequivalence study, Fenacta is considered bioequivalent with Zymamed.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Diclofenac has a well-recognised efficacy and an acceptable level of safety in the indications approved for Fenacta film coated tablets 12.5 mg, and corresponding products have been widely used in many countries. No new non-clinical or clinical safety concerns have been identified.
The bioequivalence study supports the claim that this generic product and the innovator are interchangeable. The benefit risk is therefore considered to be positive.