CBG MEB

Public Assessment Report

Scientific discussion

Areston 12.5 mg, film-coated tablets

(diclofenac potassium)

NL/H/3773/001/DC

Date: 12 March 2018

This module reflects the scientific discussion for the approval of Areston 12.5 mg, film-coated tablets. The procedure was finalised on 2 June 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Areston 12.5 mg, film-coated tablets, from Medochemie Limited.

The product is indicated for rheumatic pain, muscular pain, headache, dental pain, symptomatic treatment of primary dysmenorrhea, acute low back pain, cold and flu symptoms, including fever relief, sore throats and colds.

Areston is indicated for use in adults and children aged 14 years and over.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Voltaren K 12.5 mg, film-coated tablets (NL License RVG 20982) which has been registered in the Netherlands by GlaxoSmithKline Consumer Healthcare B.V since 8 September 1998.

The concerned member states (CMS) involved in this procedure were Bulgaria, Cyprus, Croatia, Estonia, Lithuania, Malta and Romania.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Areston is a white, capsule shaped, biconvex film-coated tablet and contains 12.5 mg diclofenac potassium..

The film-coated tablets are packed in cold forming aluminium/push through aluminium OPA-Al-PVC/Al blisters.

The excipients are:
tablet core – lactose monohydrate, calcium phosphate, sodium starch glycolate type A, maize starch, povidone K30, cellulose microcrystalline 101, silica colloidal anhydrous and magnesium stearate.
tablet coating – polyvinyl alcohol, titanium dioxide (E171), talc, lecithin (soya; E322) and xanthan gum.

II.2 Drug Substance

The active substance is diclofenac potassium, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or slightly yellowish, slightly hygroscopic, crystalline powder. Diclofenac potassium is sparingly soluble in water, freely soluble in methanol, soluble in ethanol and slightly soluble in acetone. The active substance shows polymorphism and the anhydrous and non-solvated polymorph is used. Diclofenac potassium does not exhibit potential for isomerism. The active substance is obtained from two manufacturers.

manufacturer 1 - The Active Substance Master File (ASMF) procedure is used. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

manufacturer 2 - The CEP procedure is used. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
manufacturer 1 – The manufacturing process is described in sufficient detail and is considered appropriate. It consist of three stages. The starting materials and solvents are considered acceptable.

manufacturer 2 - A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and is in line with the specification of both manufacturers and in line with the Ph. Eur. monograph of diclofenac potassium, with additional tests for particle size, microbiological purity and residual solvents. Batch analytical data demonstrating compliance with this specification have been provided for 4 batches.

Stability of drug substance
manufacturer 1 – Stability data on the active substance have been provided for 12 production scaled batches stored at 25°C/60%RH or 30°C/65% RH (up to 66 months) and 40°C/75% RH (6 months). Based on the data submitted, a retest period could be granted of 60 months with the storage condition: “Store in an airtight container, protected from light”

manufacturer 2 – The MAH provided stability data on the active substance from the second manufacturer as no re-test period is stated on the CEP. Stability data have been provided for 6 batches stored at 25°C/60% RH (3 batches up to 24 months and 3 batches up to 66 months) and 40°C/75%RH (6 months). Based on the data submitted, a retest period could be granted of 60 months without temperature restriction, though protected from light.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. Compared to the composition of the reference product, the test product additionally also contains calcium phosphate as a diluent. The function of the various excipients has been discussed.
The development of the dissolution method to be used for routine testing of the test product has been adequately discussed and the dissolution conditions have been justified. Comparative *in-vitro* dissolution profile data on test product Areston and reference product Volatren K 12.5mg in 0.1N Hydrochloric acid, pH 4.5 buffer and SIF pH 6.8 buffer (without enzymes) has been provided. The batches tested included the bio-batches. The in-vitro data provided show similar profiles in three media of different pH for the test product batches (including bio-batch) versus the reference product bio-batch tested since either more than 85% is dissolved in 15 minutes or the f2 similarity factor is more than 50. To support the application, the MAH has performed a bioequivalence study

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines and its provided description is considered sufficient. It is considered a standard process and consists of (pre-)blending, wet granulation, drying, blending, tabletting, film-coating and blistering. Process validation data on the product have been presented for 3 production scaled batches in accordance with the relevant European guidelines.

Control of excipients
All excipients, except for the film-coating, comply with the specifications of the Ph. Eur. monographs. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, average weight, identification of colorant, disintegration, hardness, uniformity of dosage units, dissolution, related compounds, assay, 2-propanol and micro-biological control. The release and shelf-life limits in the specification are similar and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from 4 production scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for 4 batches stored at in accordance with applicable European guidelines stored at 25°C/60%RH, 30°C/75% RH and 40°C/75%) in accordance with applicable European guidelines. The batches were stored in the proposed packaging. Considering the out-of-specification results at accelerated conditions and the data currently provided, a maximum shelf-life of 21 months can be assigned to the finished product with the storage condition ”Store below 30°C”. A photostability study, in accordance with ICH guideline on photostability testing, showed that the product is not sensitive to light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is of animal origin and magnesium stearate may be of animal origin. Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Areston has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Areston is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Voltaren K which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Diclofenac is a well-known active substance with established efficacy and tolerability.

A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Areston 12.5 mg, film-coated tablets (Medochemie Limited, Cyprus) is compared with the pharmacokinetic profile of the reference product Voltaren K 12.5 mg, film-coated tablets (GlaxoSmithKline Consumer Healthcare B.V., NL).

The choice of the reference product in the bioequivalence studies is accepted. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

A single-dose, randomised, four-period, two-sequence, fully replicated bioequivalence study was carried out under fasted conditions in 22 healthy male and female subjects, aged 18-44 years. Each subject received a single dose (12.5 mg) of one of the 2 active substance formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 8 hours. There were 4 dosing periods, separated by a washout period of 3 days.

Blood samples were collected pre-dose and at 0.167, 0.33, 0.5, 0.667, 0.833, 1, 1.25, 1.5, 1,75, 2, 2,5, 3, 4, 6, 8 and 10 hours after administration of the products.

The design of the study is acceptable, since diclofenac is a drug with a large intra-individual variability The wash-out period of 3 days is more than 5 elimination half-lives of diclofenac (elimination half-life of 1-2 hours) which is considered long enough to prevent carry-over effects. The sampling period was long enough and the sampling scheme was adequate to estimate the pharmacokinetic parameters.
The administration of 2×12.5 mg diclofenac is acceptable, since the first dose is 2×12.5 mg and the PK of diclofenac is linear over a dose range of 12.5 to 50 mg.
A bioequivalence study under fasted conditions is normally considered adequate as diclofenac may be taken regardless of food. It is known however, that the bioavailability under fasting and fed conditions may be differently affected by the type of oral formulation and a bioequivalence study under fasted and fed conditions may be needed. However, since both test and reference product are both film-coated tablets, a bioequivalence study under fasted conditions is considered sufficient. No bioequivalence study is needed under fed conditions..

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

During the study there were two withdrawn subjects and four drop-out subjects. Four subjects interrupted the study before Period 1 and two of them were replaced (by subjects standing-by). The two subjects withdrawn during the study were due to lost of interest for the study and not enough time to continue the study. Therefore, a total of 16 subjects completed all 4 periods and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of diclofenac under fasted conditions

Treatment N=16	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	599.42 (CV=30.04%)	612.24 (CV=29.73%)	567.30 (CV=52.21%)	0.74 (0.33-2.5)

Reference	584.77 (CV=33.12%)	597.99 (CV=32.84%)	574.51 (CV=36.16%)	0.77 (0.167-3.0)
***Ratio (90% CI)**	1.02 (0.98-1.07)	--	0.93 (0.75-1.16)	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence studies:
Since the within-subject CV for C_{max} was 35.52%, a widened range can be used to conclude bioequivalence. According to the EMA BE guideline, a lower limit of 0.76 and an upper limit of 1.31 can be used to conclude bioequivalence between the test and reference product. The MAH used acceptance limits of 0.71 to 1.41. The within-subject variability for C_{max} of the reference compound in the study is 47.57%. The widened CI limit was calculated as 0.71-1.41. The 90% CI for the test and reference was 75.21-115.92% and thus within the widened confidence intervals. Therefore, bioequivalence can be concluded for C_{max}. The AUC was inside the normal acceptance range of 80.00 to 125.00%. Thus, based on the submitted bioequivalence study Areston is considered bioequivalent with Voltaren K.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Areston.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Cardiovascular and cerebrovascular events (heart failure (NYHA class II-IV)) - Gastrointestinal bleeding, ulceration and perforations - Severe skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis) - Hepatic and renal disorders - Medication overuse headache (MOH) - Asthmatic patients and allergic reactions - Pregnancy and lactation
Important potential risks	None
Missing information	- Paediatric patients (under 14 years old)

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Voltaren K. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test followed by two rounds. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Areston 12.5 mg, film-coated tablets, have a proven chemical-pharmaceutical quality and is a generic form of Voltaren K 12.5 mg, film-coated tablets. Voltaren K is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Areston 12.5 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 2 June 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse