Public Assessment Report
Scientific discussion

Febuxostat PharOS 80 mg and 120 mg film-coated tablets

Febuxostat hemihydrate

ES/H/0442/001-002/DC

Applicant: PharOS-Pharmaceutical Oriented Services Ltd

This module reflects the scientific discussion for the approval of **Febuxostat Pharos 80 mg and 120 mg film-coated tablets**. The procedure was finalised on May 2017. For information on changes after this date please refer to the module ôUpdateô.

INTRODUCTION

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Adenuric film-coated tablets by pharmaceutical form as the reference product (Menarini International Operations Luxembourg S.A.). Adenuric film-coated tablets have been registered by centralised procedure (EMEA/H/C/000777) since April 21st, 2008.

The legal basis of the application is Article 10(1) of Directive 2001/83/EC.

The Concerned Member States involved in this procedure is MT.

The efficacy and safety of febuxostat hemihydrate has been demonstrated in several studies conducted with the reference product as well as with its use experience after placed in the market. Febuxostat Pharos 80 mg and 120 mg film-coated tablets are submitted under an abridged application and no studies regarding pharmacology, pharmacokinetic, safety and efficacy has been carried out besides the bioequivalence study against the reference product.

With Spain as the Reference Member State in this decentralised procedure, PharOS-Pharmaceutical Oriented Services Ltd. is applying for the Marketing Authorisations for Febuxostat PharOS 80 mg and 120 mg film-coated tablets in ES and MT.

Febuxostat is a 2-arylthiazole derivative that achieves its therapeutic effect of decreasing serum uric acid by selectively inhibiting xanthine oxidase (XO). Febuxostat is a potent, non-purine selective inhibitor of XO (NP-SIXO) with an in vitro inhibition K_i value less than one nanomolar. Febuxostat has been shown to potently inhibit both the oxidized and reduced forms of XO. At therapeutic concentrations febuxostat does not inhibit other enzymes involved in purine or pyrimidine metabolism, namely, guanine deaminase, hypoxanthine guanine phosphoribosyltransferase, orotate phosphoribosyltransferase, orotidine monophosphate decarboxylase or purine nucleoside phosphorylase.

Febuxostat is indicated in the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis) and for the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome (TLS).

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Member States have granted a marketing authorisation for **Febuxostat Pharos 80 mg and 120 mg film-coated tablets** for PharOS-Pharmaceutical Oriented Services Ltd.

I. SCIENTIFIC OVERVIEW AND DISCUSSION

II-1 Quality aspects

Drug substance

The drug substance is febuxostat hemihydrate. There is no Ph. Eur. monograph for this drug substance. The applicant has used the ASMF procedure.

Description of the manufacturing process is adequate. Elucidation and characterization of the drug substance are sufficient, including an acceptable proposal on impurities to control.

Specification for drug substance is considered adequate. Analytical methods are correctly described and their validation is performed according to ICH.

The proposed container for storage is similar than the one used in the stability studies.

Stability studies have been performed according to ICH/CPMP guidelines and guarantee the proposed retest period and storage conditions.

Drug Product

The drug product are pale yellow to yellow, film-coated, capsule shaped tablets, presented in two strengths: 80 mg (engraved with ñ80ò on one side and plain on the other, with dimensions 16.5 mm x 7.0 mm ± 5%) and 120 mg (engraved with ñ120ò on one side and plain on the other, with dimensions 18.5 mm x 9.0 mm ± 5%). Excipients are of Ph. Eur. quality and are commonly used in this dosage form.

All the manufacturers involved in the different steps of the drug product manufacture have been submitted. A flow chart of the manufacturing process, indicating critical steps and controls, is included. Industrial batch size is a range from 100,000 to 1,000,000 tablets.

Excipients specifications are according their respective Ph. Eur. monographs (with the exception of the colorant) and are adequate for their function in the formulation.

The specification proposed is acceptable. Analytical methods are adequately described and their validation is performed according to ICH. Number and size of the analysed batches are considered sufficient.

Proposed packaging material is adequate for the proposed dosage form and coincides with the one used in the stability studies.

Stability studies have been performed according to ICH. The proposed shelf-life and storage conditions can be accepted.

II-2 Non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology of the active substance has been provided, which is based on up-to-date and adequate scientific literature.

The submitted application concerns film coated tablets with the active substances in the same form as the reference product.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate and the Member States agreed that no further non-clinical studies are required.

Environmental Risk Assessment (ERA)

No ERA was submitted. The medicinal product has the same quantitative and qualitative composition in active substances and a similar pharmaceutical form to the reference product. The introduction on the market of this medicinal product will not mean an increased exposure to the environment, since the generic medicinal product is intended to substitute the reference medicinal product as well as other generic products in the market.

In accordance with the Guideline on the Environmental Risk Assessment for medicinal products for human use (CPMP/SWP/4447/00), the absence of this Environmental Risk Assessment is therefore justified.

II.3 Clinical aspects

Introduction

Fubuxostat hemihydrate is a well-known drug with established efficacy and safety.

No new clinical efficacy or safety studies were conducted, which is acceptable for this abridged application. A clinical overview has been provided, which is based on scientific literature. 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.

Biowaiver

The bioequivalence of test and reference products has been demonstrated for 120 mg strength (please refer to section of results). These data can be extrapolated (i.e., 80 mg) since all the requirements described in section 4.1.6 of the Bioequivalence Guideline are fulfilled.

Bioequivalence

To support the application, the Applicant has submitted a bioequivalence study ña single center, randomized, single dose, laboratory-blinded, 2-period, 2-sequence, crossover design in healthy male subjects under fasting conditions with a washout of 7 daysò.

The clinical part of the study was performed at Algorithme Pharma Inc., 1200 Beaumont Ave., Mount-Royal, Quebec, Canada, H3P 3P1.

The analytical portion was conducted at Algorithme Pharma Inc. 575 Armand-Frappier Blvd. Laval, Quebec, Canada H7V 4B3

The trial has been conducted in compliance with GCP requirements. Monitoring reports have been submitted. QA statement of audits assuring compliance to GCP was issued by Head-QA. The clinical, the analytical, the pharmacokinetic and the statistical sites were inspected by Regulatory Authorities of the European Union without critical findings.

Design

The study was a single center, randomized, single dose, laboratory-blinded, 2-period, 2-sequence, crossover design in healthy male subjects under fasting conditions with a washout of 7 days.

The innovator SmPC recommends that febuxostat can be taken without regard to food, therefore, a single dose study under fasting conditions with the highest strength is considered acceptable to demonstrate bioequivalence with the reference product.

Test Product: Febuxostat 120 mg film-coated tablet, manufactured by Rontis Hellas S.A., Greece for PharOS Generics Ltd, Cyprus. Batch number: TC150901. Batch size: 100,000 film-coated tablets. Expiry date (re-test date): March 2016. Assay (content): 98.0 % of label claim.

Reference Product: Adenuric® 120 mg film-coated tablet, manufactured by Menarini - Von Heyden GmbH, Germany (from the Dutch market). Batch number: 38008. Expiry date: August 2016. Assay (content): 100.4% of label claim.

A total of 40 subjects were included in this study and, after randomization, 37 subjects completed the study and were included in the pharmacokinetic and statistical analyses.

Analytical methods

The analytical method has been adequately validated before the conduct of the study and during the analysis of the subject samples. Therefore, the analytical method is considered acceptable for analysis of the plasma samples

Pharmacokinetic data analysis

Pharmacokinetic parameters were calculated using a non-compartmental method with acceptable software. AUC was calculated by the trapezoidal rule. The methods used in this study for the pharmacokinetic calculations are considered acceptable.

Statistical analysis

The statistical analyses using the GLM procedure were performed on ln-transformed AUC_{0-t} and C_{max}. The results are summarized in the table below.

PK Parameter	90% Confidence Intervals			
	Point estimate%	Lowe limit %	Upper Limit %	Intra-subject CV%
C_{max}	98.20%	84.96%	113.50%	38.1%
AUC_{0-t}	99.69%	95.71%	103.83%	10.4%

Based on the statistical analysis submitted by the Applicant the test product is equivalent to the reference with respect to the extent and rate of absorption/exposure as for febuxostat the 90% confidence intervals for the ln-transformed C_{max} and AUC_{0-t} are within the acceptance range of 80-125%.

Risk Management Plan

A risk management plan in accordance with the requirements of Directive 2001/83/EC as amended has been submitted.

No additional risk minimization activities were required beyond those included in the product information.

Discussion on the clinical aspects

Based on the statistical analysis submitted by the Applicant the test product is equivalent to the reference product.

Efficacy and safety of the active substance febuxostat hemihydrate are well documented for the reference medicinal product. The design of the submitted bioequivalence study is adequate and the results allow us to conclude bioequivalence with the reference.

III OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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

The SmPC, PIL and labelling are considered satisfactory and consistent with the information for the reference medicinal product. The user testing of the Package Information Leaflet has been tested in accordance with Article 59(3) of Directive 2001/83/EC, as amended by Directive 2004/27/EC.

The benefit/risk balance was considered to be positive.

Agreement between Member States was reached during the procedure. The decentralised procedure was finalised with a positive outcome in May 2017.