COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Feburik 80 mg, coated tablets

(febuxostat)

NL/H/4458/001/DC

Date: 17 September 2019

This module reflects the scientific discussion for the approval of Feburik 80 mg, coated tablets. The procedure was finalised at 20 February 2019. 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 Feburik 80 mg, coated tablets, from Laboratoires SMB S.A.

The product is indicated for the treatment of chronic hyperuricemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis) in adults.

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 Adenuric 80 mg, film-coated tablets which has been registered in the EEA by Menarini International Operations Luxembourg S.A. since 21 April 2008 trough a centralised procedure (EU/1/08/447).

The concerned member states (CMS) involved in this procedure were Belgium and Luxembourg.

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

II. QUALITY ASPECTS

II.1 Introduction

Feburik is an ochre, oblong, coated tablet with a score line. Each tablet contains 80 mg febuxostat and can be divided into equal doses.

The coated tablets are packed in transparent PCTFE/PVC/Aluminium blisters.

The excipients are:
Tablet core - lactose monohydrate, microcrystalline cellulose (E460), croscarmellose, hydroxypropylcellulose, colloidal anhydrous silica and magnesium stearate (E470b)
Tablet coating - hypromellose (E464), gelatine, red iron oxide (E172), black iron oxide (E172), yellow iron oxide (E172) and titanium dioxide (E171).

II.2 Drug Substance

The active substance is febuxostat (as hemihydrate), an established active substance, however not described in the European Pharmacopoeia (Ph.Eur.). The drug substance is a

white to off-white crystalline powder. It is soluble in dimethyl sulfoxide, slightly soluble in ethanol and practically insoluble in water. The febuxostat hemihydrate compound molecule does not contain a chiral centre and it does not exhibit optical isomerism. Several polymorphic forms are possible and form G is used.

The Active Substance Master File (ASMF) procedure is used for the active substance. 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.

Manufacturing process

The manufacturing process is adequately and sufficiently described in sufficient detail including operation conditions, quantity of reagent, solvents, auxiliaries and yield ranges. The flow chart of the manufacturing process is adequately pictured. The ASMF holder claims that no reworking is performed; no recovered solvents are used and that blending is not applied. Particle size is reduced using micronization. Overall, the manufacturing process is acceptable.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and comprises tests and limits for appearance, identification of the drug substance, water content, sulphated ash, heavy metals, related substances, assay, residual solvents contents, polymorphic form and polymorphic purity. Batch analytical data demonstrating compliance with this specification have been provided for six batches.

Stability of drug substance

Stability data on the active substance have been provided for six batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). No significant changes were observed in the tested parameters. The active substance is stable for 36 months when stored under the stated conditions.

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. The subdivision of the coated tablets has been adequately assessed; split tablets demonstrated equivalent performance to the whole tablets.

A bioequivalence study was carried with the 80 mg reference product. Comparative dissolution studies complementary to the bioequivalence study have been provided, with

comparative dissolution profiles (bio(test-) batch vs reference batch) generated in dissolution media pH 1.2, 4.5 and 6.8. Overall, the pharmaceutical development has been adequately performed.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. It is a standard, straightforward process. It consists of a wet granulation process, followed by tablet compression and film-coating. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients

The excipients, except iron oxide, used in the manufacturing comply with respective Ph. Eur. monographs. Iron oxide complies with EU Regulation 231/2012. 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 appearance, identification, uniformity of dosage units, water content, dissolution, assay, related substances, and microbiological quality. Limits in the specification have been justified 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 three batches per strength 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 three batches per strength 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The batches were stored in the proposed packaging. The conditions used in the stability studies are according to the ICH stability guideline. No significant change has been found in the tested parameters. A photostability study showed that the product is photo stable. On basis of the data submitted, a shelf life was granted of 24 months without any storage restriction.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The gelatin coating and lactose monohydrate are of animal origin. Adequate TSE/BSE free declarations/statements have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Feburik 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 Feburik 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 Adenuric 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

Febuxostat 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 Feburik 80 mg, coated tablets (Laboratoires SMB S.A., Belgium) is compared with the pharmacokinetic profile of the reference product Adenuric 80 mg, coated tablets (Menarini International Operations Luxembourg S.A., Luxembourg).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and composition of the EU reference product. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

A single-dose, open-label randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 44 healthy male and female subjects, aged 20-53 years. Each subject received a single dose (80 mg) of one of the 2 febuxostat formulations. The tablet was orally administered with water after an overnight fast. There were 2 dosing periods, separated by a washout period of 4 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.25, 1.5, 1.45, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 36 and 48 hours after administration of the products.

The design of the bioequivalence study is acceptable and in accordance with the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). Febuxostat may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption. Therefore, a food interaction study is not deemed necessary.

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

Five subjects were withdrawn from the study as they withdrew their consent or did not turn up for the second period. Therefore, 39 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=39	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	9832 ± 4889	10010 ± 4948	3983 ± 2230	0.68 (0.33 – 5.00)
Reference	9110 ± 3881	9290 ± 3936	3468 ± 1328	1.00 (0.67 – 5.00)
***Ratio (90% CI)**	1.02 (0.93 – 1.12)	--	1.05 (0.90 – 1.23)	--
CV (%)	25.6	--	45.6	--

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

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t}, and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Feburik is considered bioequivalent with Adenuric.

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 Feburik.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	- Serious skin/hypersensitivity reactions - Rhabdomyolysis - Drug-drug interactions with azathioprine or mercatopurine
Important potential risks	- Cardiovascular events - Hepatic events - Renal events - Neuropsychiatric events - Haematological/bleeding events - Thyroid events - Off label use in the paediatric population (TLS specific)
Missing information	- Children and adolescents - Subjects in whom the rate of serum urate formation is greatly increased (e.g. Lesch-Nyhan syndrome) - Organ transplantation - Severe hepatic impairment - Pregnancy and lactation - Limited experience in: severe renal impairment and moderate hepatic impairment - Interaction with standard therapy of haematological malignancies (TLS specific) - Off label use in patients with solid tumours (TLS specific)

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 Adenuric. 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 (PL) 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 with 4 participants followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

Feburik 80 mg, coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Adenuric 80 mg, film-coated tablets Adenuric 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 Feburik with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 February 2019.

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