COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Febuxostat Universal Farma 80 mg and 120 mg film-coated tablets

(febuxostat)

NL/H/4167/001-002/DC

Date: 20 August 2019

This module reflects the scientific discussion for the approval of Febuxostat Universal Farma 80 mg and 120 mg film-coated tablets. The procedure was finalised at 10 October 2018. 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 Febuxostat Universal Farma 80 mg and 120 mg film-coated tablets, from Universal Farma, S.L.

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

In addition, the 120 mg strength is also indicated 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).

The product is indicated 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 and 120 mg, film-coated tablets which has been registered in Luxembourg 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 Bulgaria, Czech Republic, Estonia, Hungary, Lithuania, Latvia, Poland, Romania, Slovenia and the Slovak Republic.

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

II. QUALITY ASPECTS

II.1 Introduction

Febuxostat Universal Farma is a pale yellow, coloured, oblong shaped, film-coated tablet. The product bears a score line on one side which is only to facilitate breaking for ease of swallowing and not to divide into equal doses. Each tablet contains 80 mg or 120 mg febuxostat (as hemihydrate).

The film-coated tablets are packed in transparent PVC/PVDC-Aluminum blister packs.

The excipients are:
Tablet core - lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, poloxamer 407 micronized, hydrated silicon dioxide and magnesium stearate
Tablet coating - polyvinyl alcohol, titanium dioxide (E171), polyethylene glycol/macrogol 4000, talc and yellow iron oxide (E172).

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 powder, 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 generally adequately described. The proposed starting materials for the drug substance manufacturing process are acceptable in view of ICH guidelines. Critical steps and corresponding in-process controls have generally been defined to ensure quality of the final substance. In-process controls performed during the synthesis are suitable to control the reaction progress. 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, contents of related substances, assay, residual solvents contents, polymorphic form, with additionally, limits for particle size distribution. Batch analytical data demonstrating compliance with this specification have been provided for at least five batches.

Stability of drug substance
Stability data on the active substance have been provided for three batches stored at 25°C/60% RH (48 months) and 45°C/75% RH (6 months). No significant changes were observed in the tested parameters. The active substance is stable for 48 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 objective of the development studies was to develop a solid oral dosage form essentially similar to the EU Reference product Adenuric. The EU reference product was used as prototype in the formulation development studies.
A bioequivalence study was carried with the 120 mg reference product, and a biowaiver of strength is claimed for the 80 mg product strength.
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. Of these three pH's, also comparative dissolution profiles between bio(test-) batch versus a 80 mg batch of the proposed product are presented.

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 to 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, 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 (12 months) and 45°C/75% RH (12 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

Lactose monohydrate is the only material of animal origin used in the manufacture of the film-coated tablets. Regarding lactose monohydrate it is declared that the substance has been produced from milk that has been sourced from healthy cows in the same conditions as milk collected for human consumption, and that the lactose has been prepared without the use of other ruminant material than calf rennet.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Febuxostat Universal Farma has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. The following post-approval commitment was made:

- The MAH will indicate the tablet strengths of both the 80 mg and 120 mg tablets on the tablets (or provide an alternative, additional distinguishing feature) post-approval, in the descriptions of tablet appearance in the appropriate module and in both the 80 mg and 120 mg SmPCs section 3, and in the product information.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Febuxostat Universal Farma 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 Febuxostat Universal Farma 120 mg film-coated tablets (Universal Farma, S.L., Spain) is compared with the pharmacokinetic profile of the reference product Adenuric 120 mg, film-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.

Biowaiver

The MAH has requested a biowaiver for the lower strength 80 mg febuxostat formulation. The biowaiver was based on the following conditions:

- the 80 mg and 120 mg formulation are manufactured by the same manufacturing process;
- the qualitative composition of the two strengths is the same and;
- the quantitative composition of the two strengths is dose proportional.

In-vitro dissolution tests were conducted by the MAH. The tablets are completely dose proportional and all biowaiver requirements are fulfilled. Therefore, the biowaiver has been granted.

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 68 healthy male/female subjects, aged 22-44 years. Each subject received a single dose (120 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 7 days.

Blood samples were collected pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 4.00, 6.00, 8.00, 10.00, 12.00, 16.00, 20.00, 24.00, 36.00 and 48.00 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 **). The washout period is sufficient. According to the study protocol, the mean apparent terminal elimination half-life was approximately 5 to 8 hours. Thus, a washout period of 7 days is more than 20 times the termination half life. The sampling scheme seems to be sufficient to estimate pharmacokinetic parameters of interest. The study is conducted at the highest strength under fasting conditions, which is in line with the above mentioned guideline.

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
All 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=68	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	24573.7 ± 7092.5	24853.3 ± 7140.0	6529.6 ± 2502	1.0 (0.5-6.0)
Reference	23753.1 ± 6880.6	24079.0 ± 6917.0	6247.4 ± 1891	2.5 (0.5 – 6.0)
***Ratio (90% CI)**	1.04 (1.00 – 1.08)	1.04 (1.00 – 1.07)	1.02 (0.9 – 1.12)	--
CV (%)	12.4	12.3	33.7	--

$AUC_{0-\infty}$ 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}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Febuxostat Universal Farma 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 Febuxostat Universal Farma.

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 (eg. malignant disease and its treatment, Lesch-Nyhan syndrome) - Organ transplantation - Severe hepatic impairment - Pregnancy and lactation - Limited experience in: female patients, elderly patients, severe renal impairment and moderate hepatic impairment - Interaction with standard therapy of haematological malignancies (TLS specific) - Off label use in patients with solid tumors (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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Adenuric. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Febuxostat Universal Farma 80 mg and 120 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Adenuric 80 mg and 120 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 Febuxostat Universal Farma with the reference product, and have therefore granted a marketing authorisation. The decentralized procedure was finalised with a positive outcome on 10 October 2018.

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
NL/H/4167 /IB/002/G	- Change in the (invented) name of the medicinal product; for nationally authorised products - Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use*	No	13-06-2019	Approved	-
NL/H/4167 /IB/003/G	Change in the (invented) name of the medicinal product; for nationally authorised products	No	26-06-2019	Approved	-
NL/H/4167 /IA/001/G	- Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Change in the shape or dimensions of the pharmaceutical form; immediate release tablets, capsules, suppositories and pessaries	-	26-06-2019	Invalid	The variation was submitted for both strengths, however the proposed changes did only apply to one strength
NL/H/4167 /IA/004/G	- Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance; up to 10-fold increase compared to the originally approved batch size - Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance; minor changes to an approved test procedure	No	17-07-2019	Approved	-
NL/H/4167 /IA/005/G	Change in the (invented) name of the medicinal product; for nationally authorised products of the active substance; minor changes to an approved test procedure	No	04-10-2019	Approved	-
NL/H/4167 /IA/006/G	- Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Change in the shape or	No	04-09-2019	Approved	-

	dimensions of the pharmaceutical form; immediate release tablets, capsules, suppositories and pessaries procedure				