COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Febuxostat Bausch 80 and 120 mg, film-coated tablets
(febuxostat hemihydrate)

NL/H/4869/001/DC

Date: 13 July 2021

This module reflects the scientific discussion for the approval of Febuxostat Bausch 80 and 120 mg, film-coated tablets. The procedure was finalised at 25 February 2021. 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 Bausch 80 and 120 mg, film-coated tablets, from Bausch Health Ireland Limited.

The product is indicated for:
- 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:
- Prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome (TLS).

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 and 120 mg, film-coated tablets which have been registered in the EEA by Menarini International Operations Luxembourg S.A. since 21 April 2008 by the centralised procedure (EU/1/08/447).

The concerned member states (CMS) involved in this procedure were Bulgaria, Czech Republic and Hungary.

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

II. QUALITY ASPECTS

II.1 Introduction

Febuxostat Bausch 80 mg is a pale yellow coloured round shaped film-coated tablet, debossed with “80” on one side. Each film-coated tablet contains 80 mg of febuxostat (as hemihydrate).
Febuxostat Bausch 120 mg is a pale yellow coloured oblong film-coated tablet, scored on one side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses. Each film-coated tablet contains 120 mg febuxostat (as hemihydrate).

The tablets are packed in transparent PVC/PVDC-Aluminium blisters.

The excipients are:

Tablet core - microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hydroxypropylcellulose, poloxamer 407 (containing BHT), colloidal hydrated silica and magnesium stearate.

Film-coating - polyvinyl alcohol, titanium dioxide (E171), macrogol 4000, talc and iron oxide yellow.

The tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is febuxostat hemihydrate, an established active substance, however not described in the European Pharmacopoeia (Ph. Eur.) or the United States Pharmacopeia (USP). The drug substance is febuxostat hemihydrate, which is a white to off-white powder, practically insoluble in water. The febuxostat molecule does not contain a chiral centre and it does not exhibit optical isomerism. The active substance shows polymorphism and the crystalline form G, which is the hemihydrate form, is consistently produced.

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

A detailed description of the manufacturing process has been provided. Adequate specifications have been adopted for starting materials, solvents and reagents. Critical steps and corresponding in-process controls have been defined to ensure quality of the final substance. In-process controls performed during the synthesis are suitable to control the reaction progress. The active substance has been adequately characterised.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and comprises tests and limits for appearance, identification , water content, sulfated ash, heavy metals, contents of related substances, assay, residual solvents contents, polymorphic form and additional tests for particle size distribution. A test for microbial purity is not included but its absence has been justified. 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 has been provided for three batches stored at 25°C/60% RH (60 months) and 45°C/75% RH (6 months). The proposed retest period of 48

months for the active drug substance, without special storage conditions, is justified as no clear trends or significant changes were observed for any of the tested parameters.

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 objective of the development studies was to develop a solid oral dosage form with essentially similar to the EU reference product, Adenuric. .
Adenuric 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 has been claimed for the 80 mg product strength.

Comparative dissolution studies complementary to the bioequivalence study have been provided, with comparative dissolution profiles (test batch versus reference batch) generated in dissolution media. In addition, comparative dissolution profiles between test batch (120 mg strength) versus a 80 mg strength batch of the proposed product are presented demonstrating similarity of dissolution profiles.

Manufacturing process

The manufacturing process consists of dry mixing, wet granulation, tablet compression and film-coating and has been validated according to relevant European guidelines. Process validation data on the product have been presented for two batches of each strength in accordance with the relevant European guidelines.

Control of excipients

The excipients, except the Opadry II Yellow, used in the manufacturing comply with respective Ph. Eur. monographs. The type and grade of several of the excipients has been stated and for several excipients functionality related characteristics have been included in the specification or the absence of such tests justified. The specification of Opadry Yellow has been included. Overall, the 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 five batches, two batches for the 80 mg strength and three batches for the 120 mg 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 from three batches per product strength stored at 25°C/60% RH (24 months), 30°C/75% RH (12 months) and 40°C/75% RH (6 months). The batches were stored in the proposed blister. The conditions used in the stability studies are according to the ICH stability guideline. On basis of the data submitted, a shelf life was granted of 24 months. No specific storage conditions need to be included in the SmPC or on the label.

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 Bausch 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 Febuxostat Bausch 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 hemihydrate 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 one 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 Bausch 120 mg, film-coated tablets (Bausch Health Ireland Limited, Ireland) is compared with the pharmacokinetic profile of the reference product Adenuric 120 mg, film-coated tablets (Menarini International Operations Luxembourg S.A., Luxemburg).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions 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 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.

Bioequivalence study

Design

An open label, balanced, randomised, two-treatment, two-sequence, single dose, crossover bioequivalence study was carried out under fasted conditions in 68 healthy male and 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 240 ml water after an overnight fast. Fasting was continued for 4 hours after dosing. There were two dosing periods, separated by a washout period of seven 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 study is acceptable. According to the SmPC, the tablet can be taken with or without food. As such, the fasting conditions applied in the study is acceptable.

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 68 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/ml/h)	**$AUC_{0-\infty}$** (ng/ml/h)	**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)	1.0 (0.92 – 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

**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 Bausch 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 Bausch.

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

Important identified risks	- Serious skin / hypersensitivity reactions - Rhabdomyolysis - Drug-drug interaction with azathioprine or mercaptopurine - Cardiovascular events
Important potential risks	- 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 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 2 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

Febuxostat Bausch 80 and 120 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Adenuric 80 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 Feburonix with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 February 2021.

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