COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Febuxostat MSN 80 mg and 120 mg, film-coated tablets

(febuxostat)

NL/H/4430/001-002/DC

Date: 15 October 2019

This module reflects the scientific discussion for the approval of Febuxostat MSN 80 mg and 120 mg, film-coated tablets. The procedure was finalised on 10 July 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 Febuxostat MSN 80 and 120 mg film-coated tablets, from Vivanta Generics s.r.o.

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.

The 120 mg product strength is also indicated for the prevention and treatment of hyperuricemia in adult patients undergoing chemotherapy for hematologic malignancies at intermediate to high risk of Tumour Lysis Syndrome (TLS) 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 and 120 mg, film-coated tablets which has been registered in the EEA by Menarini International Operations Luxembourg S.A. since 21 April 2008 through a centralised procedure (EU/1/08/447).

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

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

II. QUALITY ASPECTS

II.1 Introduction

Febuxostat MSN are yellow coloured, capsule shaped, biconvex film-coated tablets and are, according with the strength, debossed with “80” or “120” on one side and plain on the other side. Each tablet contains 80 mg or 120 mg febuxostat (as hemihydrate).

The film-coated tablets are packed in clear Aclar/PVC/Aluminium blisters.

The excipients are:
Tablet core - lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, colloidal hydrated silica and magnesium stearate
Tablet coating - polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, 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 yellowish crystalline powder. It is soluble in dimethyl formamide, slightly soluble in methanol and 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. 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 nine batches.

Stability of drug substance

Stability data on the active substance have been provided for four batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months). No significant changes were observed in the tested parameters. The active substance is stable for 60 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 vs 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 stored at 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 36 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 MSN 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 MSN 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 MSN 120 mg film-coated tablets (Vivanta Generics s.r.o., Czech Republic) is compared with the pharmacokinetic profile of the reference product Adenuric 120 mg, film-coated tablets (Menarini International Operations Luxembourg S.A., Luxembourg).

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing. The choice of the reference product in the bioequivalence study is justified, as it has been authorised through a centralised procedure.

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. 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 42 healthy male subjects, aged 18-44 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, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 20, 24 and 30 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
Two subjects were withdrawn from the study as they did not turn up for the second period. Therefore, 40 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=40	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	26772 ± 8035	26722 ± 8035	8142.7 ± 2725	1.25 (0.50 – 5.00)
Reference	25779 ± 7364	26091 ± 7456	7590.8 ± 2442	1.63 (0.50 – 4.00)
***Ratio (90% CI)**	1.03 (0.99 – 1.08)	1.03 (0.99 – 1.08)	1.07 (0.98 – 1.17)	--

$AUC_{0-\infty}$ 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 MSN 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 MSN.

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 - Patients 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 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

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 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 MSN 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 Febuxostat MSN with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 July 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