IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Febuxostat Rowa 120 mg film-coated tablets
Febuxostat
PA0074/085/002

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Febuxostat Rowa 80 milligram & 120 milligram Film-coated tablets, from Rowa Pharmaceuticals Limited on 30th April 2021 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 adults.

This application for a national marketing authorisation was submitted in accordance with Article 10(1) of Directive 2001/83/EC and is referred to as a "generic" application.

Febuxostat Rowa 80 milligram & 120 milligram Film-coated tablets are prescription only, for supply through pharmacy and for promotion to healthcare professionals only.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie.

Name of the product	Febuxostat Rowa 80 mg film-coated tablets Febuxostat Rowa 120 mg film-coated tablets
Name(s) of the active substance(s) (INN)	Febuxostat
Pharmacotherapeutic classification (ATC code)	M04AA -Preparations inhibiting uric acid production M04AA03 -febuxostat
Pharmaceutical form and strength(s)	Film-coated tablet; 80 mg, 120 mg
Marketing Authorisation Number(s) in Ireland (PA)	PA0074/085/001 PA0074/085/002
Marketing Authorisation Holder	Rowa Pharmaceuticals Limited
MRP/DCP No.	CRN008KNG

II. QUALITY ASPECTS

II.1. Introduction

This application is for Febuxostat Rowa 80 mg and 120 mg film-coated tablets.

II.2 Drug substance

The active substance is Febuxostat hemihydrate; an established active substance not described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality of the active substance. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at a suitably qualified manufacturing site.

The manufacturing process has been validated according to relevant European guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.7 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.8 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical and Pharmaceutical Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Febuxostat Rowa 80 and 120 mg film-coated tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is the same as that present in Adenuric 80 mg tablets on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Ecotoxicity/environmental risk assessment

An Environmental Risk Assessment has not been performed as this product is intended for generic substitution and therefore will not result in an increase of risk to the environment during use, storage and disposal.

IV. CLINICAL ASPECTS

IV.1 Introduction

This is a generic application submitted under article 10(1) of Directive 2001/83/EC.

Febuxostat is a well-known active substance with established efficacy and tolerability.

The content of the SmPCs approved during the national procedure are in accordance with those accepted for the reference product Adenuric marketed by Menarini International Operations Luxembourg S.A.

This application concerns the 80 mg and 120 mg strengths. To support the application, the applicant has submitted the report of a bioequivalence study with the highest strength and a justification for waiver of a bioequivalence study with the 80mg strength.

Bioequivalence study: 120mg strength
An open label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, crossover, oral bioequivalence study was carried out in normal healthy adult human subjects under fasting conditions. Febuxostat Tablets 120 mg of Laboratorios Liconsa S.A., Spain was compared to the reference product Adenuric (Febuxostat) 120 mg film-coated tablets of Menarini International Operations Luxembourg S.A. The results of this study indicate that based on the pharmacokinetic parameters of active substance febuxostat, the reference tablet and test tablet are bioequivalent.

Biowaiver: 80mg strength
A justification for waiver of a study with the 80 mg strength is presented:

1. Febuxostat 80 mg and 120 mg film-coated tablets strengths are manufactured by the same manufacturing process
2. The qualitative composition of Febuxostat 80 mg and 120 mg film-coated tablets strengths is the same
3. The composition of Febuxostat 80 mg and 120 mg film-coated tablets is quantitatively proportional
4. Appropriate in-vitro dissolution data have been submitted.

Based on the bioequivalence study done with the 120mg strength and the above justification, a biowaiver of a bioequivalence study with the 80mg strength was accepted as per CHMP Guideline on the Investigation of Bioequivalence.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Absorption
Febuxostat is rapidly (tmax of 1.0-1.5 h) and well absorbed (at least 84%). After single or multiple oral 80 and 120 mg once daily doses, Cmax is approximately 2.8-3.2 µg/mL, and 5.0- 5.3 µg/mL, respectively. Absolute bioavailability of the febuxostat tablet formulation has not been studied.

Distribution
The apparent steady state volume of distribution (Vss/F) of febuxostat ranges from 29 to 75 L after oral doses of 10-300 mg. The plasma protein binding of febuxostat is approximately 99.2%, (primarily to albumin), and is constant over the concentration range achieved with 80 and 120 mg doses. Plasma protein binding of the active metabolites ranges from about 82% to 91%.

Biotransformation
Febuxostat is extensively metabolized by conjugation via uridine diphosphate glucuronosyltransferase (UDPGT) enzyme system and oxidation via the cytochrome P450 (CYP) system.

Elimination
Febuxostat is eliminated by both hepatic and renal pathways.

IV.3 Pharmacodynamics

Mechanism of action
Febuxostat is a 2-arylthiazole derivative that achieves its therapeutic effect of decreasing serum uric acid by selectively inhibiting XO. Febuxostat is a potent, non- purine selective inhibitor of XO (NP-SIXO) with an in vitro inhibition Ki value less than one nanomolar. Febuxostat has been shown to potently inhibit both the oxidized and reduced forms of XO.

IV.4 Clinical Efficacy

The clinical efficacy of febuxostat is well established. No additional efficacy clinical studies to demonstrate efficacy have been included in the application. This is appropriate for this type of application. The summary of product characteristics for the Febuxostat 80mg and 120mg film-coated tablets are in line with those of the reference product Adenuric 80mg and 120mg film-coated tablets.

IV.5 Clinical Safety

The clinical safety of febuxostat is well established. No additional safety clinical studies to demonstrate safety have been included in the application. The summary of product characteristics claims for the proposed Febuxostat 80mg and 120mg film-coated tablets are in line with those of the reference product Adenuric 80mg and 120mg film-coated tablets. Hence there are no differences from the reference product in the undesirable effects, contraindications, precautions and warnings.

Risk Management Plan

The Applicant submitted a Risk Management Plan to support this application. The following table outlines the approved summary of safety concerns:

Table 1: Safety specification

Summary of safety concerns	
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 tumors (TLS specific)

Routine risk minimisation measures and routine pharmacovigilance activities were proposed to address the safety concerns outlined above and this is considered acceptable.

The Applicant should submit Periodic Safety Update Reports (PSUR) Periodic Safety Update Reports (PSUR) in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal

Pharmacovigilance System

The Marketing Authorisation Holder submitted a set of documents describing the Pharmacovigilance System, including information on the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

IV.6 Discussion on the clinical aspects

As this is a generic application under Article 10(1) of Directive 2001/83/EC, additional non-clinical and clinical studies to demonstrate efficacy and safety are not required. The applicant has submitted the results of a suitable bioequivalence study, which has demonstrated the similarity of the test products against the reference products, in accordance with the relevant guidance. No additional tests are required for this application.

The applicant has also submitted a clinical overview and summary of the evidence demonstrating the efficacy and safety of this product in clinical practice.

V. OVERALL CONCLUSIONS

Febuxostat Rowa 80 milligram & 120 milligram Film-coated tablets is a generic form of Adenuric 80 milligram & 120 milligram film-coated tablets (Menarini International Operations Luxembourg S.A.). Adenuric 80 milligram & 120 milligram film-coated tablets is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown for the 120mg strength and a biowaiver for the 80mg strength has been accepted in accordance with CHMP bioequivalence guidance documents. The SmPCs are consistent with those of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

From a quality, non-clinical and clinical perspective, the overall assessment outcome of Febuxostat Rowa 80 milligram & 120 milligram Film-coated tablets, is positive.

The HPRA, on the basis of the data submitted considered that Febuxostat Rowa 80 milligram & 120 milligram Film-coated tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE