IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Febuxostat Tillomed 120 mg film-coated tablets
Febuxostat
PA2321/004/002

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.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Febuxostat Tillomed 80mg & 120 mg Film coated Tablets, from Laboratorios Tillomed Spain, S.L.U. on 26th June 2020 for the following indications in adults:

Febuxostat Tillomed 80mg Film-coated Tablets 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).

Febuxostat Tillomed 120mg Film-coated Tablets 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). Febuxostat Tillomed 120mg Film-coated Tablets 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).

This application for a marketing authorisation was submitted under Article 10(1) of Directive 2001/83/EC as amended and via the decentralised procedure whereby Ireland (IE) was the Reference Member State and Germany, Italy, Spain and the Netherlands were the Concerned Member States.

The reference products, ADENURIC 80 mg and 120 mg film-coated tablets developed by Menarini International Operations Luxembourg S.A., have been authorised in the European Economic Area since 21/04/2008.

The applicant's product Febuxostat Tillomed 80 mg and 120 mg film-coated tablets are of the same indication, strength and route of administration as that of the reference medicinal product ADENURIC 80 mg and 120 mg film-coated tablets.

Febuxostat Tillomed 80 mg and 120 mg film-coated tablets are subject to prescription which may be renewed.

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 Tillomed 80 mg film-coated tablets Febuxostat Tillomed 120 mg film-coated tablets
Name(s) of the active substance(s) (INN)	Febuxostat Hemihydrate
Pharmacotherapeutic classification (ATC code)	M04AA03 Febuxostat
Pharmaceutical form and strength(s)	Film-coated tablet; 80 mg, 120 mg
Marketing Authorisation Number(s) in Ireland (PA)	PA2321/004/001-002
Marketing Authorisation Holder	Laboratorios Tillomed Spain, S.L.U
MRP/DCP No.	IE/H/0917/001-002/DC
Reference Member State	IE
Concerned Member State	DE ES IT NL

II. QUALITY ASPECTS

II.1. Introduction

This application is for Febuxostat Tillomed 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 and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The excipients in this medicinal product is 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 suitably qualified manufacturing sites.

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 these products 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 Tillomed 80 mg and 120 mg film-coated tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Adenuric 80 mg film-coated 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

Since Febuxosat Tillomed 80mg & 120 mg Film coated Tablets 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.3 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of febuxostat are well known. As febuxostat is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

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 decentralised procedure is in accordance with that accepted for the reference product Adenuric 80 mg and 120 mg film-coated tablets marketed by Menarini International Operations Luxembourg S.A.

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

Bioequivalence study: 120mg strength
The applicant submitted a bioequivalence study in which the pharmacokinetic profile of the test product Febuxostat 120 mg film-coated tablets of Emcure Pharmaceuticals Ltd is compared with the pharmacokinetic profile of the reference product Adenuric (febuxostat) 120 mg film-coated tablets of Menarini International Operations Luxemborg S.A.

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Febuxostat 120 mg film-coated tablets of Emcure Pharmaceuticals Ltd was compared to the reference product Adenuric (febuxostat) 120 mg film-coated tablets of Menarini International Operations Luxemborg S.A.. Based on the pharmacokinetic parameters of active substance febuxostat, the reference tablet Adenuric 120 mg film-coated tablets marketed by Menarini International Operations Luxemborg S.A. and test tablet Febuxostat Tillomed 120 mg Film coated Tablets are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Biowaiver: 80mg strength
A justification for waiver of a study with the 80 mg strength was provided in accordance with recommendations in the bioequivalence guideline:
- Both strengths are manufactured by the same manufacturer and process
- The qualitative composition of the two strengths are the same
- Composition of strengths are quantitatively proportional
- The dissolution profiles are comparable over the pH range 1 to 6.8 under appropriate conditions
- The pharmacokinetics is linear in the therapeutic dosage range

Based on the above, waiver of a bioequivalence study with the 80 mg strength is acceptable and the results of the bioequivalence study performed with the 120 mg film-coated tablets therefore apply to the 80 mg film-coated tablet strength.

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, nonpurine 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.

No new pharmacodynamic studies have been provided and none are required.

IV.4 Clinical Efficacy

The efficacy of febuxostat in the proposed indications is established in clinical use. No new clinical efficacy studies are provided and none are required.

IV.5 Clinical Safety
The overall safety profile of febuxostat is established and generally known. No new safety studies are provided and none are required.

The safety information in the SmPC and Package Leaflet are in line with those of the reference product.

Risk Management Plan
The applicant 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 Tillomed 80mg & 120mg film-coated tablets. The revised RMP (version 0.3 dated final sign off 12/03/2020) is acceptable. Routine risk minimization activities are considered sufficient. The applicant is requested to ensure it maintains the RMP in line with the latest SmPC updates and maintains regular reviews.

Summary table of safety concerns as approved in RMP

Important identified risks	• Serious skin/hypersensitivity reactions; • Rhabdomyolysis; • Drug-drug interactions 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	• Use in children and adolescents; • Use in subjects in whom the rate of serum urate formation is greatly increased (e.g. Lesch-Nyhan syndrome); • Use during organ transplantation; • Use in patients with severe hepatic impairment; • Use during pregnancy and lactation; • Limited experience in severe renal impairment & moderate hepatic impairment; • Interaction with standard therapy of haematological malignancies (TLS specific) *; • Off-label use in patients with solid tumours (TLS specific)*;

*Safety concerns specific for Febuxostat 120mg film-coated tablets

Periodic Safety Update Report (PSUR)
With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted 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. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

Common renewal date
Common renewal date will be 5 years after the finalisation of the procedure.

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 product Febuxostat 120 mg film-coated tablets of Emcure Pharmaceuticals Ltd against the reference product Adenuric (Febuxostat) 120 mg film-coated tablets of Menarini International Operations Luxemborg S.A., in accordance with the relevant guidance. A justification for waiver of a study with the 80 mg strength has been provided. 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 Tillomed 80mg & 120 mg Film coated Tablets, from Laboratorios Tillomed Spain, S.L.U. are generic forms of ADENURIC 80 mg and 120 mg film-coated tablets developed by Menarini International Operations Luxembourg S.A.. ADENURIC 80 mg and 120 mg 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 to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

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

The HPRA, on the basis of the data submitted considered that Febuxostat Tillomed 80mg & 120 mg 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

07.05.2025