LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Urogerolan
(febuxostat)

SE/H/1634/01-02/DC

This module reflects the scientific discussion for the approval of Urogerolan. The procedure was finalised on 2017-06-21. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Urogerolan, 80 mg and 120 mg, film-coated tablets, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, G.L. Pharma GmbH applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, CZ and HU as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Adenuric 80 mg and 120 mg film-coated tablets authorised in the Community since 2008, with Menarini International Operations Luxembourg S.A. as marketing authorisation holder.

The reference product used in the bioequivalence study is Adenuric 120 mg film-coated tablets from Germany with Menarini-Von Heyden GmbH as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Pharmacokinetics
Febuxostat has an oral bioavailability of at least 84 %. Following an oral dose of febuxostat maximal plasma concentrations occur at approximately 1-1.5 hours. Concomitant food intake decreases the C_{max} and AUC of febuxostat to an extent that is not considered clinically relevant and therefore there are no restrictions with respect to food in the SmPC of the originator. The pharmacokinetics of febuxostat is linear within the dose range 10-120 mg. For doses between 120 mg and 300 mg, a greater than dose proportional increase in AUC is observed. The terminal half-life is approximately 5-8 hours.

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 60 healthy volunteers, comparing Febuxostat, 120 mg, film-coated tablets with Adenuric, 120 mg, film-coated tablets under fasting conditions. The study was conducted at Syngene International Limited, Bangalore, India between 25th September and 5th October 2015. Blood samples were collected pre-dose and up to 48 hours post-dose. The study design is considered acceptable. Plasma concentrations of febuxostat were determined with an adequately validated LC/MS/MS method. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for febuxostat, n=59.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**21747±3862**	**6120±1597**	**1.50 (0.33-5.50)**
Reference	**22065±4071**	**6650±1899**	**1.00 (0.33-4.67)**
***Ratio (90% CI)**	**98.76 (96.14-101.45)**	**92.63 (86.36-99.35)**	**-**

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 plasma concentration

**calculated based on ln-transformed data*

From a pharmacokinetic point of view, absence of studies with the additional strength 80 mg is acceptable, as the pharmacokinetics of febuxostat is linear between 10 mg and 120 mg.

Based on the submitted bioequivalence study, Urogerolan is considered bioequivalent with Adenuric.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

IV.3 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 Urogerolan.

The risk management plan (RMP) for the Urogerolan (Febuxostat film-coated tablets; 80 mg and 120 mg), version 1.0, with data lock point 2016-04-27, was initially submitted; and the RMP had been updated (version 1.1) with date of final sign off (2017-01-10) inserted.

Safety specification
The following summary of safety concerns have been proposed by the Applicant.

Summary of safety concerns	
Important identified risks	• Serious skin / hypersensitivity reactions (1) • Rhabdomyolysis (2) • Drug-drug interaction with azathioprine or mercaptopurine (3)
Important potential risks	• Cardiovascular events (4) • Hepatic events (5) • Renal events (6) • Neuropsychiatric events (7) • Haematological/Bleeding events (8) • Thyroid events (9) • Off label use in the paediatric population (TLS specific) (10)
Missing information	• Children and adolescents (11) • Subjects in whom the rate of serum urate formation is greatly increased (eg, malignant disease and its treatment, Lesch-Nyhan syndrome) (12) • Organ transplantation (13) • Severe hepatic impairment (14) • Pregnancy and lactation (15) • Limited experience in: female patients, elderly patients, severe renal impairment, moderate hepatic impairment (16) • Interaction with standard therapy of haematological malignancies (TLS specific) (17) • Off label use in patients with solid tumors (TLS specific) (18)

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the Applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the Applicant, which is endorsed.

Summary of the RMP
The RMP is approved.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to ADENURIC, film-coated tablets, EMEA/H/C/777 (content) and Ceolat 1 mg/ml-Lösung zum Einnehmen, MA no. 135599 (AT) (layout). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Urogerolan, is found adequate. There are no objections to approval of Urogerolan, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable.
The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Urogerolan, 80 mg and 120 mg, film-coated tablets was positively finalised on 2017-06-21.

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MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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