LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Allopurinol Mylan
(allopurinol)

SE/H/1588/01-02/DC

This module reflects the scientific discussion for the approval of Allopurinol Mylan. The procedure was finalised on 2017-10-04. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Allopurinol Mylan, 100 mg and 300 mg, tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Mylan AB applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and CZ, DK, ES, FI, FR, HU, IT, NL, NO, PT as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Zyloric, 100 mg, tablet authorised in SE since 1967 and Zyloric, 300 mg, tablet authorised in SE since 1976 with Aspen Pharma Trading Limited as marketing authorisation holder.
The reference product used in the bioequivalence study is Zyloric, 300 mg, tablet from DE with Aspen Pharma Trading Limited 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

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 32 healthy volunteers, comparing Allopurinol Mylan, 300 mg tablets with Zyloric®, 300 mg tablets under fasting conditions. The study was conducted at Accutest Research Lab (I) Pvt. Ltd., (Unit-II) Opposite The Grand Bhagwati Hotel, Sarkhej-Gandhinagar Highway, Bodakdev, Ahmedabad -380054, INDIA, between 17th of December 2010 and 5th of January 2011. Blood samples were collected pre-dose and up to 96 hours post-dose. The study design is considered acceptable. Plasma concentrations of allopurinol were determined with an adequately validated LC/MS/MS method.

The results are presented below.

Table 1. Pharmacokinetic parameters (non-transformed values; geometric mean) for Allopurinol Mylan, n=31.

Treatment	**AUC_{0-t}** **ng*h/ml**	**C_{max}** **ng/ml**
Test	**7807.30**	**2250.03**
Reference	**8854.33**	**2545.03**
***Ratio (90% CI)**	**88.1749 (81.37- 95.55)**	**88.4089 (81.46- 95.95)**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration		

**calculated based on ln-transformed data*

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%.

Based on the submitted bioequivalence study, Allopurinol Mylan is considered bioequivalent with Zyloric®. Absence of studies with the additional strength is acceptable since all conditions for biowaiver for additional strength have been fulfilled.

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 MAH has submitted a risk management plan (RMP), 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 Allopurinol Mylan.

The RMP for the Allopurinol Mylan 100 mg and 300 mg tablets (version 1.0) was valid from 25-Jan-2016 with data lock point 31-July-2015. The RMP was updated (version 2.0), with date of final sign off on 07-Nov-2016.

Safety specification

The following summary of safety concerns have been proposed by the MAH.

Summary of safety concerns	
Important identified risks	• Serious hypersensitivity reactions
Important potential risks	• Concomitant administration of ampicillin/amoxicillin • Administration during pregnancy and lactation
Missing information	• None

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 approvable.

Periodic Safety Update Report (PSUR)
Active substance is currently listed in the published EURD list

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.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

V. USER CONSULTATION

The package leaflet 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 language used for the purpose of user testing the PIL was english.
The results show that the package leaflet 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

The quality of the generic product, Allopurinol Mylan, is found adequate. There are no objections to approval of Allopurinol Mylan, 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 Allopurinol Mylan, 100 mg and 300 mg, tablet was positively finalised on 2017-10-04.

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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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