Public Assessment Report

Decentralised Procedure

ALLOPURINOL 100MG TABLETS
ALLOPURINOL 200MG TABLETS
ALLOPURINOL 300MG TABLETS

Procedure No: UK/H/1313/001-3/DC

UK Licence No: PL 00289/1093-5

TEVA UK LIMITED
LAY SUMMARY

Allopurinol 100mg, 200mg and 300mg Tablets

(allopurinol)

This is a summary of the Public Assessment Report (PAR) for Allopurinol 100mg, 200mg and 300mg Tablets (PL 00289/1093-5; UK/H/1313/001-3/DC). It explains how Allopurinol 100mg, 200mg and 300mg Tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Allopurinol 100mg, 200mg and 300mg Tablets.

For practical information about using Allopurinol 100mg, 200mg and 300mg Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Allopurinol 100mg, 200mg and 300mg Tablets and what are they used for?
Allopurinol 100mg, 200mg and 300mg Tablets are ‘generic medicines’. This means that Allopurinol 100mg, 200mg and 300mg Tablets are similar to ‘reference medicines’ already authorised in the European Union (EU) called Zyloric 100mg, 200mg and 300mg Tablets, which were originally granted licences in 1980 to The Wellcome Foundation Limited, UK (100mg and 300mg strengths) and in 1984 to Laboratoire Glaxosmithkline, France (200mg strength).

Allopurinol 100mg, 200mg and 300mg Tablets are used for the long term, preventative treatment of gout and may be used in other conditions associated with an excess of uric acid in the body, including kidney stones and other types of kidney disease.

How do Allopurinol 100mg, 200mg and 300mg Tablets work?
This medicine contains the active ingredient allopurinol, which belongs to a group of medicines called enzyme inhibitors, which act to control the speed at which special chemical changes occur in the body.

How are Allopurinol 100mg, 200mg and 300mg Tablets used?
The pharmaceutical form of this medicine is a tablet and the route of administration is oral (by mouth). The patient should swallow the tablets whole, preferably with a drink of water. The patient should take their tablets after a meal. They should drink plenty of fluids (2-3 litres a day) while they are taking this medicine.

The patient should always take this medicine exactly as their doctor or pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

The usual dose is:
Adults (including the elderly)
Starting dose: 100 - 300 mg/day.
When the patient starts treatment, their doctor may also prescribe an anti-inflammatory medicine or colchicine for a month or more, to prevent attacks of gouty arthritis.
The patient’s dose of allopurinol may be adjusted depending on the severity of the condition. The maintenance dose is:
• mild conditions, 100-200 mg/day
• moderately severe conditions, 300-600 mg/day
• severe conditions, 700-900 mg/day.
The patient’s dose may also be altered by their doctor if the patient has reduced kidney and liver function, particularly if they are elderly.
If the daily dose exceeds 300 mg/day and the patient is suffering from gastro-intestinal side effects such as nausea or vomiting (see section 4 of the package leaflet), their doctor may prescribe allopurinol in divided doses to reduce these effects.

If the patient has a serious kidney problem
• they may be asked to take less than 100 mg each day
• or they may be asked to take 100 mg at longer intervals than one day
If the patient has dialysis two or three times a week, their doctor may prescribe a dose of 300 or 400 mg which is to be taken straight after their dialysis.

Children (under 15 years)
100 - 400 mg/day.
Treatment may be started together with an anti-inflammatory medicine or colchicine, and the dose adjusted if the patient has reduced kidney and liver function, or divided to reduce gastro-intestinal side effects, as for adults above.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

For further information on how Allopurinol 100mg, 200mg and 300mg Tablets are used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

What benefits of Allopurinol 100mg, 200mg and 300mg Tablets have been shown in studies?
Allopurinol 100mg, 200mg and 300mg Tablets are generic medicines therefore studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicines Zyloric 100mg, 200mg and 300mg Tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Allopurinol 100mg, 200mg and 300mg Tablets?
Allopurinol 100mg, 200mg and 300mg Tablets are generic medicines and are bioequivalent to the reference medicines Zyloric 100mg, 200mg and 300mg Tablets therefore their benefits and possible side effects are taken as being the same as the reference medicines.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Allopurinol 100mg, 200mg and 300mg Tablets, see section 4 of the package leaflet available on the MHRA website.

Why were Allopurinol 100mg, 200mg and 300mg Tablets approved?
It was concluded that, in accordance with EU requirements, Allopurinol 100mg, 200mg and 300mg Tablets have been shown to have comparable quality and to be bioequivalent to Zyloric 100mg, 200mg and 300mg Tablets. Therefore, the MHRA decided that, as for Zyloric 100mg, 200mg and 300mg Tablets, the benefits are greater than the risks and recommended that they can be approved for use.
What measures are being taken to ensure the safe and effective use of Allopurinol 100mg, 200mg and 300mg Tablets?
Safety information has been included in the Summaries of Product Characteristics (SmPCs) and the package leaflet for Allopurinol 100mg, 200mg and 300mg Tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Allopurinol 100mg, 200mg and 300mg Tablets

For Allopurinol 100mg and 300mg Tablets (PL 00289/1093 & 5; UK/H/1313/001 & 3/DC):
Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Spain, France, Ireland, Italy, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Sweden and Slovakia and the UK agreed to grant Marketing Authorisations for Allopurinol 100mg and 300mg Tablets on 10 June 2010. Marketing Authorisations were granted in the UK on 20 July 2010.

For Allopurinol 200mg Tablets (PL 00289/1094; UK/H/1313/002/DC):
Austria, Bulgaria, Cyprus, Czech Republic, Germany, France, Ireland, Netherlands, Poland and Romania and the UK agreed to grant Marketing Authorisations for Allopurinol 200mg Tablets on 10 June 2010. A Marketing Authorisation was granted in the UK on 20 July 2010.

The full PAR for Allopurinol 100mg, 200mg and 300mg Tablets follows this summary.
For more information about treatment with Allopurinol 100mg, 200mg and 300mg Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in March 2018.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>I</th>
<th>Introduction</th>
<th>Page 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Quality aspects</td>
<td>Page 8</td>
</tr>
<tr>
<td>III</td>
<td>Non-clinical aspects</td>
<td>Page 9</td>
</tr>
<tr>
<td>IV</td>
<td>Clinical aspects</td>
<td>Page 10</td>
</tr>
<tr>
<td>V</td>
<td>User consultation</td>
<td>Page 12</td>
</tr>
<tr>
<td>VI</td>
<td>Overall conclusion, benefit/risk assessment and recommendation</td>
<td>Page 12</td>
</tr>
<tr>
<td></td>
<td>Table of content of the PAR update</td>
<td>Page 24</td>
</tr>
</tbody>
</table>
I  INTRODUCTION

Please note that the below scientific discussion consists of the original assessment of this product licence, plus a summary of key post approval changes at the end of this introduction section to improve the accuracy of this Public Assessment Report.

Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Allopurinol 100mg, 200mg and 300mg Tablets (PL 00289/1093-5; UK/H/1313/001-3/DC) could be approved. These applications were submitted by the decentralised procedure, with the UK as Reference Member State (RMS), and Austria, Bulgaria, Cyprus, Czech Republic, Germany, France, Ireland, Netherlands, Poland, Romania, (UK/H/1313/001-3) and Belgium, Denmark, Spain, Italy, Luxembourg, Norway, Portugal, Sweden and Slovakia (UK/H/1313/001 and 003 only) as Concerned Member States (CMS).

The products are prescription-only medicines for the treatment of:

Adults
- All forms of hyperuricaemia not controllable by diet including secondary hyperuricaemia of differing origin and in clinical complications of hyperuricaemic states, particularly manifest gout, urate nephropathy and for the dissolution and prevention of uric acid stones
- The management of recurrent mixed calcium oxalate stones in concurrent hyperuricaemia, when fluid, dietary and similar measures have failed.

Children and adolescents
- Secondary hyperuricaemia of differing origin
- Uric acid nephropathy during treatment of leukaemia
- Hereditary enzyme deficiency disorders, Lesch-Nyhan syndrome (partial or total hypoxanthin-guanin phosphoribosyl transferase deficiency) and adenine phosphoribosyl transferase deficiency.

These are applications made according to Article 10.1 of 2001/83/EC, as amended, claiming to be generic medicinal products of Zyloric 100mg, 200mg and 300mg Tablets, which were originally granted licences in 1980 to The Wellcome Foundation Limited, UK (100mg and 300mg strengths) and in 1984 to Laboratoire Glaxosmithkline, France (200mg strength).

Allopurinol is a xanthine-oxidase inhibitor. Allopurinol and its main metabolite oxipurinol lower the level of uric acid in plasma and urine by inhibition of xanthine oxidase, the enzyme catalyzing the oxidation of hypoxanthine to xanthine and xanthine to uric acid. In addition to the inhibition of purine catabolism in some, but not all, hyperuricaemic patients, de novo purine biosynthesis is depressed via feedback inhibition of hypoxanthine-guanine phosphoribosyltransferase. Other metabolites of allopurinol include allopurinol-riboside and oxipurinol-7 riboside.

No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 210) on 10 June 2010. After a subsequent national phase, the licences were granted in the UK on 20 July 2010.

Summary of key post-approval changes:
The following post-approval variations have been granted for these licences:

1. To add a HDPE container (35 ml and 100 ml) primary packaging material (beside the currently approved transparent PVC/PVdC-Alu blister), pack sizes: 30 & 100. Sections 6.4 & 6.5 of the SmPC has been updated granted on 22/03/2013 (PL 00289/1093-0012 & PL 00289/1095-0012).

2. To register a change in the number of units in a pack within the range of the currently approved pack sizes, too add pack size of 105 tablets for blister for strengths 100 mg and 300 mg only. Consequentially, the PIL, label and section 6.5 of the SPC has been updated granted on 15/01/2016 (PL 00289/1093-0019 & PL 00289/1095-0020).
II QUALITY ASPECTS

II.1 Introduction
Each tablet contains 100mg, 200mg or 300mg of allopurinol as the active ingredient. Other ingredients consist of the pharmaceutical excipients lactose monohydrate, silica colloidal anhydrous, maize starch, powdered cellulose, sodium starch glycolate (Type A), sodium laurilsulfate, povidone K30 and magnesium stearate (E470b).

All strengths of finished product are packaged in polyvinylchloride/polyvinylidene chloride/aluminium blisters, in pack sizes of 20, 28, 30, 50 (including a hospital pack), 60 and 100. Additional pack sizes of 90, 98 and 500 tablets are available for the 100mg and 300mg strengths, and there is an additional pack size of 25 tablets for the 100mg alone.

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance
INN: Allopurinol
Chemical name: 1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one Structure:

```
\begin{center}
\includegraphics[width=0.5\textwidth]{structure.png}
\end{center}
```

Molecular formula: C₉H₄N₄O
Molecular mass: 136.1
Appearance: Allopurinol is a white to almost white powder. It is very slightly soluble in water and in alcohol, and dissolves in a dilute solution of alkali hydroxide. Allopurinol has no chiral centres and has no stereo isomers. Allopurinol is known to exist as only one polymorphic form.

Allopurinol is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance allopurinol are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

II.3 Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious tablets, containing 100, 200 and 300mg allopurinol, that could be considered generic medicinal products of Zyloric Tablets.

A satisfactory account of the pharmaceutical development has been provided.
Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

All excipients comply with their respective European Pharmacopoeia monograph. Suitable batch analysis data have been provided for each excipient.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the lactose is sourced from healthy animals under the same conditions as milk for human consumption.

These products do not contain or consist of genetically modified organisms (GMO).

**Manufacture of the product**

Satisfactory batch formulae have been provided for the manufacture of all strengths of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

**Finished Product Specification**

The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

**Stability of the product**

Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years, with no special storage conditions.

**Bioequivalence/bioavailability**

Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

**MAA forms**

The MAA forms are pharmaceutically satisfactory.

**Expert report**

The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**

There are no objections to the approval of these products from a pharmaceutical viewpoint.

**III NON-CLINICAL ASPECTS**

**III.1 Introduction**

As the pharmacodynamic, pharmacokinetic and toxicological properties of allopurinol are well-known, no new non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ pharmacology and toxicology.
III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
A suitable justification has been provided for non-submission of an environmental risk assessment.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of these products from a non-clinical viewpoint.

IV CLINICAL ASPECTS
IV.1 Introduction
The clinical pharmacology of allopurinol is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of allopurinol.

IV.2 Pharmacokinetics
In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open-label, randomised, single-dose, two–way, two-treatment, crossover, single-centre study to compare the pharmacokinetics of the test product Allopurinol 300mg Tablets versus the reference product Zyloric 300mg Tablets (Laboratoires Wellcome, France) in healthy adult male volunteers under fasted conditions.

All volunteers were dosed in a fasted state in two treatment periods. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 96 hours post dose. The washout period between treatment periods was at least 10 days.

The pharmacokinetic results for allopurinol and its active metabolite oxipurinol are presented below:

Table 1: Pharmacokinetic parameters allopurinol (non-transformed values; arithmetic mean ± SD, tmax median, range)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC0-t ng/ml/h</th>
<th>AUC0-∞ ng/ml/h</th>
<th>Cmax ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (mean)</td>
<td>4148.19</td>
<td>4306.47</td>
<td>1800</td>
</tr>
<tr>
<td>Standard dev.</td>
<td>2006.26</td>
<td>2065.59</td>
<td>727</td>
</tr>
<tr>
<td>Reference</td>
<td>3732.89</td>
<td>3907.91</td>
<td>1697</td>
</tr>
<tr>
<td>Standard dev.</td>
<td>1047.75</td>
<td>1070.68</td>
<td>678</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>97.5-117.22%</td>
<td>97.3-115.7%</td>
<td>90.7-123.4%</td>
</tr>
</tbody>
</table>
The 90% confidence intervals for AUC and C\text{max} were within the predefined acceptance range for both allopurinol and its active metabolite oxipurinol. Bioequivalence was demonstrated for the parent compound (allopurinol) and the active metabolite (oxipurinol) for both products. Therefore, the proposed product is bioequivalent to the reference product.

As the 100, 200 and 300mg strengths of the product meet the criteria specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 300mg strength can be extrapolated to the 100mg and 200mg strengths.

**IV.3 Pharmacodynamics**

No new pharmacodynamic data were submitted and none were required for these applications.

**IV.4 Clinical efficacy**

No new efficacy data were submitted and none were required for these applications.

**IV.5 Clinical safety**

With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for these applications. No new or unexpected safety issues were raised by the bioequivalence data.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**

The SmPC, PIL and labels are medically acceptable. The SmPCs are consistent with those for the originator products. The PIL is consistent with the SmPC and in-line current guidelines. The labelling is in-line with current guidelines.

**Clinical Expert Report**

The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.
IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a Risk Management Plan for these products.

IV.7 Discussion on the clinical aspects
There are no objections to the approval of these products from a clinical viewpoint.

V User consultation
A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

VI Overall conclusion, benefit/risk assessment and recommendation
QUALITY
The important quality characteristics of Allopurinol 100, 200 and 300mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Allopurinol 300mg Tablets and its respective reference product (Zyloric 300mg Tablets). As the 100mg and 200mg strengths of the product meet the biowaiver criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 300mg strength can be extrapolated to the other strength tablets.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products, where appropriate.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the originator products are interchangeable. Extensive clinical experience with allopurinol is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The following text is the approved label text for Allopurinol 100mg Tablets, no label mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained:
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Allopurinol 100 mg Tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg of allopurinol.

3. LIST OF EXCIPIENTS

Also contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Allopurinol 100 mg Tablets
28 Tablets,
100 mg.

20, 25, 30, 50, 60, 90, 98, 100, 105 and 500 tablets
50 hospital pack

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Please read the enclosed package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.

9. SPECIAL STORAGE CONDITIONS
This medicinal product does not require any special storage conditions.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

   MA Holder:
   TEVA UK Limited, Eastbourne, BN22 9AG

12. **MARKETING AUTHORISATION NUMBER(S)**

   PL 00289/1093

13. **BATCH NUMBER**

   LOT:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

   POM

15. **INSTRUCTIONS ON USE**

   **DOSAGE:**
   Use as directed by the doctor.

16. **INFORMATION IN BRAILLE**

   Allopurinol 100 mg Tablets
The current approved mock-up labelling for Allopurinol 200mg Tablets is presented below:
The following text is the approved label text for Allopurinol 300mg Tablets, no label mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained:

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING CARTON</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARTON</td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

Allopurinol 300 mg Tablets

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 300 mg of allopurinol

3. **LIST OF EXCIPIENTS**

Also contains lactose. See leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**

Allopurinol 300 mg Tablets
300 mg
28 Tablets
20, 30, 50, 60, 90, 98, 100, 105 and 500 tablets.
50 hospital pack

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use
Please read the enclosed package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP:

9. **SPECIAL STORAGE CONDITIONS**

This medicinal product does not require any special storage conditions
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MA Holder: TEVA UK Limited, Eastbourne, BN22 9AG

12. MARKETING AUTHORISATION NUMBER(S)

PL 00289/1095

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

**DOSAGE**: Use as directed by the doctor.

16. INFORMATION IN BRAILLE

Allopurinol 300mg Tablets
Annex 1

Table of content of the PAR update
Steps taken after the initial procedure with an influence on the Public Assessment Report
(Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
</tr>
</thead>
<tbody>
<tr>
<td>To register an update to the additional clinical and non-clinical studies, including the Bioequivalence study</td>
<td>UK/H/1313/001-3/II/020</td>
<td>None</td>
<td>31/08/2017</td>
<td>05/01/2018</td>
<td>Approved</td>
<td>Yes-see Annex 1</td>
</tr>
</tbody>
</table>
ANNEX 1

Our Reference: PL 00289/1093-0026
               PL 00289/1094-0024
               PL 00289/1095-0027

Product: Allopurinol 100mg Tablets
          Allopurinol 200mg Tablets
          Allopurinol 300mg Tablets

Marketing Authorisation Holder: Teva UK Limited
Active Ingredient(s): Allopurinol

Type of Procedure: Mutual recognition
Submission Type: Variation
Submission Category: Type II
Submission Complexity: Complex
EU Procedure Number (if applicable): UK/H/1313/001-3/II/020

RECOMMENDATION

Based on the review of the data on safety and efficacy, the RMS considers that the variations for Allopurinol 100mg, 200mg and 300mg Tablets (allopurinol), in the treatment of:

Adults

- All forms of hyperuricaemia not controllable by diet including secondary hyperuricaemia of differing origin and in clinical complications of hyperuricaemic states, particularly manifest gout, urate nephropathy and for the dissolution and prevention of uric acid stones
- The management of recurrent mixed calcium oxalate stones in concurrent hyperuricaemia, when fluid, dietary and similar measures have failed.

Children and adolescents

- Secondary hyperuricaemia of differing origin
- Uric acid nephropathy during treatment of leukaemia
- Hereditary enzyme deficiency disorders, Lesch-Nyhan syndrome (partial or total hypoxanthin-guanin phosphoribosyl transferase deficiency) and adenine phosphoribosyl transferase deficiency.

For the following proposed changes: To inform the health authorities involved in the DCP about a recent biostudy undertaken. The bioequivalence study was done in order to fulfil current regulatory requirements ahead of an intended repeat use procedure from the approved DCP.

is approvable.

EXECUTIVE SUMMARY

Scope of the variation
The marketing authorisation holder (MAH) is submitting a Type II variation to inform the member states involved in the decentralised procedure (DCP) about the results of a recent
Bioequivalence study, conducted to fulfil current regulatory requirements ahead of an intended repeat use procedure from the approved DCP.

No product information changes are proposed by the MAH.

**Background**

This product was approved in 2010 (UK/H/1313/001-003/DC) under Article 10.1. The originator products in the UK are Zyloric 100 mg tablet, 200 mg tablet and 300 mg tablet by GlaxoSmithKline, UK. The application was supported by a bioequivalence study of a single dose of the 300 mg strength tablet in fasted healthy volunteers. A biowaiver for the lower strengths was accepted. The results of the allopurinol analysis of the study are summarised in the following table:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$\text{AUC}_{0-t}$ (ng/ml/h)</th>
<th>$\text{AUC}_{0-\infty}$ (ng/ml/h)</th>
<th>$\text{C}_{\text{max}}$ (ng/ml)</th>
<th>$t_{\text{max}}$ (h)</th>
<th>$T_{1/2}$ (terminal) (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (mean)</td>
<td>4148.19 ± 2006.26</td>
<td>4306.47 ± 2065.59</td>
<td>1800 ± 727</td>
<td>1.25</td>
<td>1.12</td>
</tr>
<tr>
<td>Reference</td>
<td>3732.89 ± 1048.1</td>
<td>3907.91 ± 1073.3</td>
<td>1697 ± 678</td>
<td>1.00</td>
<td>1.14</td>
</tr>
</tbody>
</table>

*A Ratio (90% CI) (ln-transformed values)

$\text{AUC}_{0-t}$ area under the plasma concentration-time curve from time zero to infinity

$\text{AUC}_{0-\infty}$ area under the plasma concentration-time curve from time zero to $\infty$ hours

$\text{C}_{\text{max}}$ maximum plasma concentration

$T_{\text{max}}$ time for maximum concentration

$T_{1/2}$ half-life

During the marketing authorisation application (MAA) procedure, the applicant was asked to justify the lack of fed data, since the following recommendation is stated in section 4.2 of the SmPC:

**Allopurinol may be taken orally once a day. To increase gastrointestinal tolerability, it should be taken after a meal.**

The applicant argued that the recommendation to take with food is intended only to improve tolerability. According to the Pharmacokinetics Working Party (PKWP) questions and answers (Q&A) document published at that time, fasted bioequivalence data was considered acceptable under these circumstances. The argumentation was accepted by the RMS and CMSs, and the products were approved based on fasted data only.

According to the *Guideline on the investigation of bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) which came into force in 2010, ‘For products where the SmPC recommends intake of the reference medicinal product only in fed state, the bioequivalence study should generally be conducted under fed conditions.’ In view of this, the MAH has conducted a bioequivalence study in the fed state, to support a repeat use mutual recognition procedure.

Allopurinol is a xanthine oxidase inhibitor. It acts upon purine metabolism without disruption of the biosynthesis of vital purines. The drug reduces the production of uric acid by inhibition of the biochemical reactions preceding its formation. Allopurinol reduces the production of uric acid by inhibiting xanthine oxidase, the enzyme responsible for conversion of hypoxanthine to xanthine and of xanthine to uric acid, resulting in reductions in plasma
and urinary concentrations of uric acid. Allopurinol is metabolised to oxipurinol which is also an inhibitor of xanthine oxidase.

**SCIENTIFIC DISCUSSION**

**Quality aspects**

*Assessor’s comment:*
The changes made to the test product over the years have been described and it is agreed that these would be unlikely to affect bioequivalence. These changes were supported by adequate comparative dissolution data and were accepted without the need for further bioequivalence studies.

Regarding the history of the reference product, the MAH discusses the potential for divergence from the original product used in the original bioequivalence study as a result of various divestments. A tabulated summary of the reference products available across the EU is presented; however, it is not clear whether there are any differences in the products. Information in the referenced public assessment reports do not clarify the situation any further. The excipients in all of the products are stated to be the same.

Dissolution data for the reference product from different markets are presented. The data indicate that there are differences in the rate and extent of release of allopurinol from the batches from different markets; however, these data are inconclusive and there is no proven *in vivo* correlation. The data do not appear to be predictive of *in vivo* performance.

**Non clinical aspects**

N/A

**Clinical aspects**

**III.3.1 Clinical pharmacology**

The MAH has submitted the clinical study report of a bioequivalence study: ‘An open labelled, randomised, single dose, two-way crossover, bioequivalence study of Allopurinol 300 mg tablets in healthy human, adult subjects under fed conditions.’

The primary objective of the study was to assess the bioequivalence of Allopurinol Teva 300 mg Tabletter (Teva Pharmaceutical Works), compared to that of Zyloric® 300, Tabletten (Mibe GmbH Arzneimittel, Germany) following a single oral dose (1 × 300 mg tablet) in healthy human adult subjects when administered under fed conditions. The secondary objective of the study was to assess the safety and tolerability of the test and reference products in healthy human adult subjects.

The applicant has stated that the bioequivalence study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

**Methods**

**Study design**

This was an open-label, randomised, single-dose, 2-treatment, 2-period, 2-sequence, crossover bioequivalence study under fed conditions. There was a supervised fast of 10 hours prior to dosing and 4 hours post-dose. Subjects were served a high calorie high fat breakfast exactly 30 minutes prior to dosing. Subjects received a single oral 300mg dose of either test or reference product with 240mL of water, according to the randomisation schedule.
Compliance was confirmed by mouth check. Meals, fluid intake, posture and activity were standardised during the study. Subjects were housed until 24 hours post-dose. The washout period was 7 days.

Blood samples were collected pre-dose and up to 24.00 hours post-dose. Plasma was analysed for allopurinol and its major active metabolite oxipurinol by a validated LC-MS/MS method.

**Assessor’s comment**
The study design is acceptable taking into account the study objectives. The sampling schedule is acceptable in view of an expected $T_{max}$ of 1.5 hours, and plasma half-life of 1-2 hours. The washout period is adequate.

The analysis of oxipurinol was included as a protocol amendment after study completion, once the Sponsor had reviewed the allopurinol analyses. The sampling schedule is insufficient to fully characterise the concentration-time profile of oxipurinol which has a $T_{max}$ of 3-5 hours and a half-life of 13-30 hours; however the washout period may be adequate.

**Test and reference products**
**Test product**: Allopurinol Teva 300 mg Tablett (Teva Pharmaceutical Works)
**Reference product**: Zyloric 300 mg Tableten (Mibe GmbH Arzneimittel, Germany)

**Assessor’s comment**
The test and reference product are acceptable.

**Population(s) studied**
Healthy non-smoking adult male subjects were enrolled and dosed, according to standard eligibility criteria for this type of study. Two additional subjects were enrolled in case of drop-outs prior to dosing, but were checked out after completion of dosing activity for the other subjects. All subjects completed both periods and were eligible for analysis.

**Assessor’s comment**
The study population was appropriate. There were no drop-outs.

**Analytical methods**
Concentrations of allopurinol and oxipurinol in plasma were measured using a validated LC-MS/MS technique.

**Assessor’s comment**
Analytical and method validation reports are provided for the original bioequivalence study from 1996, for the initial 2017 evaluation (looking at allopurinol only) and for the final evaluation (looking at allopurinol and the major metabolite, oxipurinol). The methods for the study have been validated in accordance with the Guideline on bioanalytical method validation. Back conversion has been considered and determined to be unlikely and insignificant.

**Pharmacokinetic Variables**
The chosen PK variable included: $AUC_0-t$, $AUC_0-inf$, $C_{max}$, $T_{max}$, $K_{el}$ and half-life. $AUC_0-t$ and $C_{max}$ were the primary pharmacokinetic (PK) variables. Actual sampling time-points were used for the PK analysis. PK analysis was conducted using a non-compartmental method.
**Assessor's comment**  
The PK variables are appropriate.

**Statistical methods**  
The randomisation schedule was generated, and the statistical analysis conducted, ANOVA was performed on the log-transformed pharmacokinetic parameters AUC0-t, AUC0-∞ and C\text{max} of allopurinol and oxipurinol. The ANOVA model included sequence, subjects nested within sequence, period and treatment as the fixed effects. 90% confidence intervals for the difference between the least square means was calculated for the log-transformed pharmacokinetic parameters AUC0-t, AUC0-∞ and C\text{max} of allopurinol and oxipurinol. The bioequivalence criteria of 80.00-125.00% were prospectively defined.

**Assessor's comment**  
The statistical methods are appropriate.

**Results**

There were several sampling time-point deviations. However, the majority were less than 3 minutes. Larger deviation of up to 6 minutes were recorded for the 24.00 hour time-point.

**Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t\text{max} median, range) for ALLOPURINOL**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC\text{0-t}</th>
<th>AUC\text{0-∞}</th>
<th>C\text{max}</th>
<th>t\text{max}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>5194.23 ± 1491.008</td>
<td>5243.09 ± 1499.225</td>
<td>2164.93 ± 885.112</td>
<td>2.00 (0.67-5.00)</td>
</tr>
<tr>
<td>Reference</td>
<td>5239.81 ± 1617.290</td>
<td>5290.72 ± 1622.613</td>
<td>1829.40 ± 693.514</td>
<td>2.00 (0.67-6.00)</td>
</tr>
</tbody>
</table>

*Ratio (90% CI)  

99.98 (96.84-103.22) 99.93 (96.82-103.13) 117.56 (108.88-126.95)

AUC\text{0-t}  
Area under the plasma concentration curve from administration to last observed concentration at time t.  
AUC\text{0-72h} can be reported instead of AUC\text{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products.

AUC\text{0-∞}  
Area under the plasma concentration curve extrapolated to infinite time.

C\text{max}  
Maximum plasma concentration.

T\text{max}  
Time until C\text{max} is reached.

*ln-transformed values
Figure 1: The Linear plot of Mean Plasma Allopurinol plasma concentrations versus. Time

![Image of linear plot](image)

The extrapolated AUC was <20% for all subjects after both test and reference product. \( T_{\text{max}} \) was not observed in any subject during the first sample time. No carryover was observed. The maximum observed plasma concentration was within the validated range of the analytical method for allopurinol.

**Assessor's comment**
Sampling time-point deviations were not of concern, since actual sampling time-points were used in the PK analysis.

Bioequivalence has not been demonstrated after a single dose in the fed state. The upper bound of the 90% confidence interval for \( C_{\text{max}} \) is 126.95% which is outside the pre-specified bioequivalence criteria.

**Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, \( t_{\text{max}} \) median, range) for OXIPURINOL**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( \text{AUC}_{0-t} ) ng/ml/h</th>
<th>( \text{AUC}_{0-\infty} ) ng/ml/h</th>
<th>( C_{\text{max}} ) ng/ml</th>
<th>( t_{\text{max}} ) h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>87038.21 ± 13456.668</td>
<td>225103.94 ± 68373.410</td>
<td>5040.23 ± 934.042</td>
<td>5.00 (0.67-10.00)</td>
</tr>
<tr>
<td>Reference</td>
<td>86887.79 ± 13860.163</td>
<td>227137.64 ± 77374.862</td>
<td>4922.93 ± 785.312</td>
<td>6.00 (3.00-16.00)</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>100.17 (98.70-101.66)</td>
<td>98.89 (94.20-103.80)</td>
<td>101.97 (99.57-104.43)</td>
<td></td>
</tr>
</tbody>
</table>

\( \text{AUC}_{0-t} \) Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC<sub>0-72h</sub> can be reported instead of AUC<sub>0-t</sub> in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products

AUC<sub>∞</sub> Area under the plasma concentration curve extrapolated to infinite time.

C<sub>max</sub> Maximum plasma concentration

t<sub>max</sub> Time until C<sub>max</sub> is reached

*ln-transformed values

A pre-dose concentration >5% of C<sub>max</sub> was observed for one subject in period II. This subject was excluded from the PK analysis per protocol. For all observations, the extrapolated AUC was >20% (mean AUC<sub>0-72</sub>/AUC<sub>0-inf</sub> was 41.31% after test and 40.94% after reference). The maximum observed plasma concentration was within the validated range of the analytical method for oxipurinol.

**Assessor’s comment**
The the sampling schedule was insufficient to characterise the concentration-time profile of oxipurinol, which has a longer half-life than allopurinol. In addition, the parent drug is considered more sensitive than metabolites when evaluating bioequivalence. Therefore, the results of the oxipurinol analysis can only be considered supportive.

Safety results
A total of three adverse events (AEs) were reported in the study and all were considered by the Investigator to be unrelated to study drug: pain at cannula (2 reports), headache (one report after dosing of reference product). Laboratory values were within clinically acceptable range.

**Assessor’s comment**
There are no new safety concerns.

### III.3.2 Clinical efficacy

No efficacy data is submitted.

### III.3.3 Clinical safety

See section III.3.1.

### Product information

No product information changes are proposed by the MAH.

**Assessor’s comment**
The new bioequivalence data does not need to be reflected in the product information.

ASSESSMENT OF THE RESPONSES TO THE MEMBER STATE(S) REQUEST FOR SUPPLEMENTARY INFORMATION

**Quality aspects**

N/A

**Non-clinical aspects**

N/A
Clinical aspects

IV.3.1 Major objections

N/A

IV.3.2 Other concerns

Question (Ireland (IE))

IE agrees with the RMS regarding approval of the variation, but would like further clarification on the study.

In light of the negative result of the study, whereby the study did not meet bioequivalence criteria in terms of the $C_{\text{max}}$ of allopurinol, please ask the MAH to provide a safety summary outlining any AE reporting for patients taking Allopurinol Teva with a high fat diet compared to those taking a low fat diet.

Summary of the MAH’s response

To compare the safety summary of Allopurinol in patients following a high-fat diet versus a low-fat diet, data from bioequivalence studies and post-marketing were reviewed.

Bioequivalence studies

In 1996 the MAH has submitted the clinical study report of a bioequivalence study: ‘A comparative bioavailability study with Allopurinol Tablets (1 x 300 mg)’. This was an open labelled, randomised, single dose, two-way crossover bioequivalence study of Allopurinol 300 mg tablets in healthy volunteer subjects, conducted under fasting conditions. The subjects were instructed to have a late evening meal on the evening preceding dose administration (Day 1 of each study period) and then to fast for 10 hours. A total of 16 adverse events were reported (35%) of the subjects during the study periods. Approximately equal numbers of events were reported following dosing with the Teva Allopurinol tablet (n=9) and the reference product (n=7). The events reported for Allopurinol Teva are summarised in Table 1.

Table 1. Adverse events reported for Allopurinol Teva in bioequivalence study under fasting conditions

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Outcome of adverse event</th>
<th>Seriousness assessment</th>
<th>Relatedness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive thirst</td>
<td>Recovered</td>
<td>Non-serious</td>
<td>Possible</td>
</tr>
<tr>
<td>Aching limbs</td>
<td>Recovered</td>
<td>Non-serious</td>
<td>Possible</td>
</tr>
<tr>
<td>Rash</td>
<td>Recovered</td>
<td>Non-serious</td>
<td>Probable</td>
</tr>
<tr>
<td>Nausea</td>
<td>Recovered</td>
<td>Non-serious</td>
<td>Possible</td>
</tr>
<tr>
<td>Flatulence</td>
<td>Recovered</td>
<td>Non-serious</td>
<td>Possible</td>
</tr>
</tbody>
</table>
In 2017 the MAH has submitted the clinical study report of a bioequivalence study: ‘An open labelled, randomised, single dose, two way crossover, bioequivalence study of Allopurinol 300 mg tablets in healthy human, adult subjects under fed conditions.’ Subjects were served high calorie high fat breakfast exactly 30 min prior dosing. A total of three adverse events were reported in the study and all were considered unrelated to the study products. Of those, one adverse event (catheter site pain) occurred following administration of Allopurinol Teva.

In the bioequivalence studies Allopurinol Teva exhibited a safety profile similar to the reference product. More adverse events were reported in the subjects under fasting conditions compared to the subjects under fed conditions, especially gastrointestinal adverse events. Therefore, the following recommendation is stated in the Section 4.2 of the SmPC: To increase gastrointestinal tolerability, it should be taken after a meal.

Post-marketing cases
A search was performed to retrieve the cases received cumulatively through 31 October 2017 for Allopurinol Teva. A total of 1,546 cases describing 3,402 events were retrieved. The cases were manually reviewed to identify information on patients’ diet. In a single case the patient acknowledged that they were on a ‘high-protein diet’. This patient experienced an allergic reaction and rash following administration of Allopurinol. None of the cases reported information regarding patients’ caloric intake or distribution of the main nutrients, including fat/lipids.

A surrogate analysis was used to compare the safety profile of Allopurinol in patients following a high-fat diet versus a low-fat diet. The analysis was based on the fact that food choice is influenced by many interrelating factors ranging from biological mechanism and genetic profiles to social and cultural factors. Cultural influences lead to the difference in the habitual consumption of certain foods, including fats.

For the purpose of this analysis the following data were used:
- Distribution of adverse events in the MAH’s Pharmacovigilance Database per MedDRA System Organ Class (SOC) and per occurrence country
- Daily supply of fats per country and per capita
- Average daily supply of calories per country and per capita.

According to World Health Organization (WHO) recommendations, a healthy diet contains less than 30% of total energy intake from fats. For the countries for which at least one case was identified in the Pharmacovigilance Database, data on the daily fat supply (g/person/day) and average daily supply of calories (kilocalories /person/day) were collected. Considering that 1 g fat provides 9 calories per gram, the percentage of total energy intake from fats was calculated and it ranged from 27.85 to 41.14% (average 36.93%). It is considered that the patients from countries with a percentage less than average were more likely to follow a low-

<table>
<thead>
<tr>
<th>Vomiting</th>
<th>Recovered</th>
<th>Non-serious</th>
<th>Possible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal discomfort</td>
<td>Recovered</td>
<td>Non-serious</td>
<td>Possible</td>
</tr>
<tr>
<td>Headache</td>
<td>Recovered</td>
<td>Non-serious</td>
<td>Possible</td>
</tr>
<tr>
<td>Generalised weakness</td>
<td>Recovered</td>
<td>Non-serious</td>
<td>Unlikely</td>
</tr>
</tbody>
</table>
fat diet whereas the patients from countries with a percentage greater than average were more likely to follow a high-fat diet. These data are summarised in Table 2.

Table 2. Estimated percentage of fats in diet per occurrence country

<table>
<thead>
<tr>
<th>Occurrence country</th>
<th>Number of cases in Pharmacovigilance Database</th>
<th>Daily fat supply (g/person/day)</th>
<th>Average daily supply of calories (kilocalories/person/day)</th>
<th>Estimated percentage of fats in diet (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>6</td>
<td>162.32</td>
<td>3,733</td>
<td>39.13</td>
</tr>
<tr>
<td>Denmark</td>
<td>8</td>
<td>134.54</td>
<td>3,367</td>
<td>35.96</td>
</tr>
<tr>
<td>France</td>
<td>145</td>
<td>159.2</td>
<td>3,482</td>
<td>41.14</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>20</td>
<td>95.87</td>
<td>3,098</td>
<td>27.85</td>
</tr>
<tr>
<td>Ireland</td>
<td>1</td>
<td>125.84</td>
<td>3,600</td>
<td>31.46</td>
</tr>
<tr>
<td>Italy</td>
<td>787</td>
<td>154.74</td>
<td>3,579</td>
<td>38.91</td>
</tr>
<tr>
<td>Netherlands</td>
<td>38</td>
<td>125.63</td>
<td>3,228</td>
<td>35.02</td>
</tr>
<tr>
<td>Spain</td>
<td>27</td>
<td>143.71</td>
<td>3,173</td>
<td>40.76</td>
</tr>
<tr>
<td>Sweden</td>
<td>117</td>
<td>130.19</td>
<td>3,179</td>
<td>38.85</td>
</tr>
<tr>
<td>Switzerland</td>
<td>58</td>
<td>153.59</td>
<td>3,391</td>
<td>40.76</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>339</td>
<td>138.42</td>
<td>3,417</td>
<td>36.45</td>
</tr>
</tbody>
</table>

The cases in the Pharmacovigilance database correspond to the known safety profile of Allopurinol. Most frequently reported events included MedDRA Preferred terms under SOC ‘Skin and subcutaneous tissue disorders’, as follows: ‘Pruritus’ (n=186), ‘Rash’ (n=160) and ‘Erythema’ (n=110). The distribution of cases in the Pharmacovigilance Database per SOC is shown in Figure 1.
Five countries had an estimated percentage of fats in the diet below the average, as follows: Denmark, Hong Kong, Ireland, Netherlands and United Kingdom. The cases originating from these countries concern patients who were more likely to follow a low-fat diet. The distribution of events in these cases is shown in Figure 2.

Six countries had an estimated percentage of fats in the diet above the average, as follows: Belgium, France, Italy, Spain, Sweden and Switzerland. The cases originating from these countries concern patients who were more likely to follow a high-fat diet. The distribution of events in these cases is shown in Figure 3.
There is a similar pattern when comparing the distribution of cumulative data with the distribution of events occurring in countries where the estimated percentage of fats in the diet was below and, respectively, above the average. No conclusion regarding the safety profile of Allopurinol taken with a low-fat diet or a high-fat diet can be drawn based on the post-marketing data.

Assessment of the MAH’s response

The MAH has compared the safety results of the single dose fasted bioequivalence study and the single dose fed study. More AEs were reported for the fasted study compared to the fed study. Although numbers are small, this comparison provides some reassurance that a marginally higher $C_{\text{max}}$ of allopurinol is not associated with a worse safety outcome.

Using the MAH’s Pharmacovigilance Database, post-marketing cases were retrieved for Allopurinol Teva. None of the cases reported information regarding patients’ caloric or fat intake. A descriptive analysis of the distribution of events was conducted according to % fats in diet for country of origin. No clear difference was evident.

In conclusion, the MAH has provided the requested safety summary, outlining any AE reporting for patients taking Allopurinol Teva with a high fat diet compared to those taking a low fat diet. There is no evidence of any difference in safety according to diet.

Conclusion

Point resolved

Product information

N/A
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The MAH has submitted the results of a recently-conducted single dose bioequivalence study in fed healthy volunteers, against the German reference product. However, the upper bound of the 90% confidence interval for $C_{\text{max}}$ was 126.95% which exceeds acceptance criteria of 90.00-125.00%.

The main active metabolite oxipurinol was also measured, as a post-hoc analysis. Bioequivalence is demonstrated for this analyte, which provides support for a safety profile comparable to the reference product. However, it should be noted that due to longer $T_{\text{max}}$ and half-life, the sampling schedule was not adequate to fully characterise the concentration-time profile.

The MAH points out that the allopurinol arithmetic mean $C_{\text{max}}$ of 2.16 mg/mL for the test product corresponds to the $C_{\text{max}}$ of 2 mg/mL described in literature after an oral 300 mg dose. There is extensive post-marketing experience with the Teva formulation; reported adverse drug reactions are in-line with the known safety profile of allopurinol. There is no evidence that the safety profile of the Teva formulation is worse in the fed state, or in patients on a high fat diet.

Allopurinol has a wide therapeutic window, and can be used at daily doses up to 900 mg, although in general, most patients receive up to 300 mg daily. The marginally higher $C_{\text{max}}$ in the fed state is unlikely to be clinically relevant for an allopurinol product. Therefore, the benefit risk of Allopurinol 100mg, 200mg, 300mg tablets remains positive.

REQUEST FOR SUPPLEMENTARY INFORMATION AS PROPOSED BY THE RMS

None

Decision: Approved on 02 February 2018.