Public Assessment Report

ALLOPURINOL 100 and 200 MG TABLETS

(Allopurinol)

UK Licence No: PL 00289/0951-2

TEVA UK Limited
LAY SUMMARY
Allopurinol 100 and 200 mg Tablets
(Allopurinol)

This is a summary of the Public Assessment Report (PAR) for Allopurinol 100 and 200 mg Tablets (PL 00289/0951-2). It explains how Allopurinol 100 and 200 mg Tablets (PL 00289/0951-2) 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 these medicines.

The products will collectively be referred to as Allopurinol Tablets throughout the remainder of this Lay summary.

For practical information about using Allopurinol Tablets, the patient should read the package leaflet or contact their doctor or pharmacist.

What are Allopurinol Tablets and what are they used for?
Allopurinol Tablets are generic medicines. This means that they are similar to a ‘reference medicine’ already authorised in the UK called Zyloprim® 300mg Tablets (The Wellcome Foundation Limited, UK).

Allopurinol 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 Tablets work?
Allopurinol Tablets contain 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. This medicinal product works by reducing the production of uric acid in the body.

How are Allopurinol Tablets used?
Allopurinol Tablets are taken by mouth. The whole tablet should be swallowed, 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.

Patients must take this medicine exactly as a doctor or pharmacist has told them. They must 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 patients start 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 dose may also be altered by their doctor if a patient has reduced kidney and liver function, particularly if they are elderly.
If the daily dose exceeds 300 mg/day and patients are suffering from gastro-intestinal side effects such as nausea or vomiting, a doctor may prescribe allopurinol in divided doses to reduce these effects.

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

Allopurinol Tablets can only be obtained on prescription from a doctor.

For further information on how Allopurinol Tablets are used, please see the Summaries of Product Characteristics and package leaflet available on the MHRA website.

**How have Allopurinol Tablets been studied?**
Because Allopurinol Tablets are generic medicines, studies have been limited to tests to determine that they are bioequivalent to the reference medicines, Zyloric® 300 mg Tablets (Mibe GmbH Arzneimittel, Germany). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the benefits and risks of Allopurinol Tablets?**
As Allopurinol Tablets are generic medicines of the reference medicine, Zyloric® 300mg Tablets their benefits and risks are taken as being the same as those for the reference medicine.

**Why are Allopurinol Tablets approved?**
It was concluded that, in accordance with EU requirements, Allopurinol Tablets have been shown to have comparable quality and to be bioequivalent to Zyloric® 300mg Tablets. Therefore, the view was that, as for the reference product, the benefits outweigh the identified risks.

**What measures are being taken to ensure the safe and effective use of Allopurinol Tablets?**
Safety information has been included in the summaries of Product Characteristics (SmPCs) and the package leaflet for Allopurinol 100 mg and 200 mg tablets including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about Allopurinol Tablets**
Marketing Authorisations were granted in the UK on 16 October 2008.

The full PAR for Allopurinol Tablets follows this summary.

This summary was last updated in April 2018.
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I INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted TEVA UK Limited, Marketing Authorisations for the medicinal products Allopurinol 100 and 200 mg Tablets (PL 00289/0951-2) on 16 October 2008. These products are prescription-only medicines (POM).

Allopurinol is indicated for reducing urate/uric acid formation in conditions where urate/uric acid deposition has already occurred (e.g. skin tophi, gouty arthritis, and nephrolithiasis) or is a predictable clinical risk (e.g. treatment of malignancy potentially leading to acute uric acid nephropathy). The main clinical conditions where urate/uric acid deposition may occur are: uric acid lithiasis; idiopathic gout; acute uric acid nephropathy; neoplastic disease and myeloproliferative disease with high cell turnover rates, in which high urate levels occur either spontaneously, or after cytotoxic therapy; certain enzyme disorders which lead to overproduction of urate, for example: hypoxanthine-guanine phosphoribosyltransferase, including Lesch-Nyhan syndrome; glucose-6-phosphatase including glycogen storage disease; phosphoribosylpyrophosphate synthetase; phosphoribosylpyrophosphate amidotransferase; adenine phosphoribosyltransferase. Allopurinol is also indicated for the management of 2,8-dihydroxyadenine (2,8-DHA) renal stones related to deficient activity of adenine phosphoribosyltransferase. Allopurinol is also indicated for the management of recurrent mixed calcium oxalate renal stones in the presence of hyperuricosuria, when fluid, dietary and similar measures have failed.

These applications were submitted as abridged national applications, according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products. The applicant has cross-referred to Zyloric® 300mg Tablets granted to The Wellcome Foundation Limited (now part of GlaxoSmithKline). The originator product licence has been granted in the EU for more than 10 years and hence the period of data exclusivity has expired.

Allopurinol and its primary metabolite, oxipurinol is an inhibitor of the enzyme xanthine oxidase. In man, uric acid is formed primarily by the oxidation of hypoxanthine and xanthine, a reaction which is catalysed by xanthine oxidase.

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

A bioequivalence study was submitted to support these applications comparing the applicant’s test product Allopurinol 300 mg Tablets and the reference product, Zyloric® 300, Tablets (Mibe GmbH Arzneimittel) in healthy adult, human subjects under fed conditions. The applicant has stated that the bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new clinical data were submitted, which is acceptable given that these applications were based on products being generic medicinal products of an originator product that has been in clinical use for over 10 years.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacturing and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Allopurinol 100 and 200 mg Tablets outweigh the risks and Marketing Authorisations were granted.
II QUALITY ASPECTS

II.1 Introduction
Each tablet contains 100 or 200 mg allopurinol as active ingredient. Other ingredients consist of the pharmaceutical excipients lactose monohydrate, colloidal anhydrous silica, maize starch, powdered cellulose, sodium starch glycolate (Type A), sodium lauryl sulfate, povidone (E1201) and magnesium stearate (E572).

All excipients used comply with their respective Ph.Eur monograph.

Appropriate justification for the inclusion of each excipient has been provided. Satisfactory certificates of analysis have been provided for all excipients.

With the exception of lactose monohydrate, none of the excipients used contain material of animal or human origin. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. Confirmation has also been given that the magnesium stearate used in the tablets is of vegetable origin.

The finished product is packaged in Transparent polyvinylchloride (PVC), polyvinylidenechloride (PVdC) aluminium (Al) blister strips in packs of 7, 10, 14, 21, 28, 30, 50, 56, 60, 84, 90, 100, 110, 112, 120, 150, 160 and 168 tablets.

The marketing authorisation holder has stated that not all pack sizes are intended for marketing. However, they have committed to submitting mock-ups for all packaging for assessment before they are commercially marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

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

Molecular formula: C$_5$H$_4$N$_4$O
Molecular weight: 136.1 g/mol
Appearance: Allopurinol is a white to almost white powder. It is very slightly soluble in water and in alcohol, it dissolves in dilute solution of alkali hydroxide.

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 and Healthcare (EDQM) Certificate of Suitability.
II.3. Medicinal Product  
Pharmaceutical Development  
The objective of the development programme was to formulate a safe, efficacious, tablets containing allopurinol that is comparable in performance to the reference product, Zyloric® 300mg Tablets (The Wellcome Foundation Limited).

Suitable pharmaceutical development data have been provided for these applications.

Dissolution profiles for both strengths of drug product were found to be similar to the originator products marketed in various European countries. The data demonstrates that the dissolution specification is acceptable. The impurity profiles for the drug product are the same as those described for the drug substance.

Manufacture of the products  
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on two batches of each strength. The results are satisfactory.

Finished Product Specifications  
The finished product specifications proposed are acceptable. The test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Products  
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 24 months has been set, which is satisfactory. Storage conditions are “Do not store above 25 degrees” and “Store in the original package”. A post approval commitment has been given by the applicant to provide data from the first three full-scale production batches of both strengths of the product.

II.4 Discussion on chemical, pharmaceutical and biological aspects  
There are no objections to the approval of these applications 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. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics 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)**
Since Allopurinol 100 and 200 mg Tablets are intended for generic substitution, the use of these products will not lead to an increased exposure of the environment. An environmental risk assessment is therefore not deemed necessary.

**III.6 Discussion on the non-clinical aspects**
No new non-clinical studies were conducted or necessary for this type of applications.

There are no objections to the approval of these applications 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 studies detailed below, no new pharmacodynamic or pharmacokinetic data are provided or required for these applications.

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

Based on the data provided, the test product Allopurinol 100 and 200 mg Tablets can be considered bioequivalent to Zyloric® 300mg Tablets (Mibe GmbH Arzneimittel).

**IV.2 Pharmacokinetics**
In support of these applications, the applicant submitted a comparative bioavailability study of the test product, allopurinol 300 mg tablets and the reference product, Zyloric 300 mg Tablets (Laboratories Wellcome S.A). The study was performed in accordance with Good Clinical Practice and was approved by Pinewood Independent Ethics Committee.

The study was an open, randomized, single oral dose, two-way crossover, single centre study in healthy volunteer subjects. The study consisted of two study periods of five days with a washout period of ten days. Blood samples were collected prior to dosing and at 20 minutes, 40 minutes, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 10, 13, 24, 48, 72 and 96 hours after dosage. Plasma samples were analysed by HPLC for both allopurinol and the main metabolite oxypurinol. Plasma concentrations showed a wide variability across subjects. The primary determinants were logarithmically transformed peak plasma concentration data and area under the curve data. 24 subjects completed the study and no serious adverse events were recorded. One subject was withdrawn from the study due an adverse event. The subject had dermographism and expert opinion suggested that allopurinol may have been the antigenic stimulus. This adverse event was reported to have resolved following a period of 2 months. Nine subjects experienced a total of 16 events during the study period. None of the events were considered related to either of the study drugs and the most common event was headache.

**Results**
**Results for main pharmacokinetic parameters:**

<table>
<thead>
<tr>
<th></th>
<th>Test (APS)</th>
<th>Reference (Zyloric)</th>
<th>Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (h.μg/l)</td>
<td>2079-12454</td>
<td>2102-6471</td>
<td>97.3-115.7%</td>
</tr>
<tr>
<td>(Allopurinol)</td>
<td>(Mean 4309)</td>
<td>(Mean 3908)</td>
<td></td>
</tr>
<tr>
<td>AUC (h.μg/l)</td>
<td>142182-269274</td>
<td>120227-283087</td>
<td>94.6-101.9%</td>
</tr>
<tr>
<td>(Oxypurinol)</td>
<td>(Mean 194242)</td>
<td>(Mean 198975)</td>
<td></td>
</tr>
<tr>
<td>Cmax (μg/l)</td>
<td>828-3904</td>
<td>888-3488</td>
<td>90.7-123.4%</td>
</tr>
</tbody>
</table>
Bioavailability was assessed by measuring plasma concentrations of allopurinol and its major metabolite oxypurinol. Based on the 90% confidence interval data for AUC and $C_{\text{max}}$, the Test product (300 mg allopurinol tablet) and reference product (300 mg Zyloric tablet) were shown to be bioequivalent.

The applicant has provided justification for exemption from carrying out bioavailability/bioequivalence studies for the 100 mg and 200 mg line extension tablets. Firstly, these pharmaceutical products are manufactured by the same manufacturer and by the same process. Secondly, they provide evidence (published literature) which demonstrates that the steady state plasma concentration of oxypurinol increased linearly over a dose range of 50-600 mg (Graham et al., 1996). The exemption is in keeping with CPMP guidelines on bioavailability/bioequivalence (Section 5.4 Dose proportionality in immediate release dosage forms).

According to the latest CPMP guidelines, the Test and Reference product are bioequivalent and the applicant provided evidence to support linearity of the product over the range of 50-600 mg.

### IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for an application of this type.

### IV.4 Clinical efficacy
No new data are provided or required for this application.

### IV.5 Clinical safety
No new data are provided or required for this application. The applicant has provided a brief review of the published literature, confirming the efficacy and safety of allopurinol.

### IV.6 Pharmacovigilance System
Safety information has been included in the summaries of Product Characteristics (SmPCs) and the package leaflet for Allopurinol 100 mg and 200 mg tablets including the appropriate precautions to be followed by healthcare professionals and patients.

### IV.7 Discussion on the clinical aspects
The grant of marketing authorisation is recommended for these applications from a clinical point of view.

### V User consultation
The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL 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
The quality of the products is acceptable, and no new non-clinical or clinical concerns have been identified. The bioequivalence study supports the claim that the applicant’s test product (Allopurinol 300mg Tablets) and the innovator product (Zyloric® 300mg Tablets) are interchangeable. Based on

<table>
<thead>
<tr>
<th>(Allopurinol)</th>
<th>(Mean 1800)</th>
<th>(Mean 1697)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (μg/l) (Oxypurinol)</td>
<td>3974-6577 (Mean 5520)</td>
<td>4383-7180 (Mean 5540)</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hours) (Allopurinol)</td>
<td>1.25</td>
<td>1.0</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hours) (Oxypurinol)</td>
<td>2.5-7</td>
<td>1-7</td>
</tr>
</tbody>
</table>
consideration of composition, method of manufacture, supporting development data and pharmacokinetics, Allopurinol 100mg and 200mg Tablets are approvable as additional strengths within the approved posology. Extensive clinical experience with allopurinol is considered to have been demonstrated the therapeutic value of the active substance. 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 approved labelling for Allopurinol 100 and 200 mg Tablets is presented below:
PAR Allopurinol 100 and 200 mg Tablets

Allopurinol 200 mg Tablets

Each tablet contains 200 mg of allopurinol. Also includes lactose, some package leaflet for further information.

DOSAGE:
Use as directed by the physician. Read the package leaflet before use.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Do not store above 25°C. Store in the original package.
Please note this variation only concerns Allopurinol 100 mg Tablets (PL 00289/0951)

Annex 1

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

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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>outcome</th>
</tr>
</thead>
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<tr>
<td>13/09/2017</td>
<td>Type II</td>
<td>To register a bioequivalence study of Allopurinol 300 mg tablets in healthy human, adult subjects under fed conditions.</td>
<td>Approved</td>
</tr>
</tbody>
</table>
Annex 1

Reference:  PL 00289/0951-0028

Product:  Allopurinol 100 mg Tablets

Marketing Authorisation Holder: TEVA UK Limited

Active Ingredient:  Allopurinol

Type of Procedure: National

Submission category: Type II variation

Reason:
To register a bioequivalence study of Allopurinol 300 mg tablets in healthy human, adult subjects under fed conditions.

RECOMMENDATION
Based on the review of the data on safety and efficacy, the RMS considers that the variation for Allopurinol 100mg 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.

is approvable.

EXECUTIVE SUMMARY
Scope of the variation
The marketing Authorisation holder (MAH) is submitting a Type II variation to inform the MHRA 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.

This national variation is being run in parallel with a mutual recognition (MR) variation: Allopurinol 100mg, 200mg and 300mg Tablets; UK/H/1313/001-003/II/020 (PL 00289/1093-1095).
Background
This product was approved in 2008 (100 mg strength). The originator products in the UK are Zyloric 100 mg and 300 mg tablet by GlaxoSmithKline, UK. The DCP for the same products (UK/H/1313/001-003/DC) was supported by a bioequivalence study of a single dose of the 300 mg strength tablet in 26 fasted healthy volunteers, of which 24 completed the study and were analysed. A biowaiver for the lower strengths was accepted. The results of the allopurinol analysis of study are summarised in the following table:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} (ng/mL/h)</th>
<th>AUC_{0-\infty} (ng/mL/h)</th>
<th>C_{max} (ng/mL)</th>
<th>t_{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>
<tr>
<td>*Ratio (90% CI)</td>
<td>106.91 (95.70-117.22)</td>
<td>105.76 (90.66-123.38)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{0-\infty} area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
T_{max} time for maximum concentration
T_{1/2} half-life

*In-transformed values

During the DCP 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 in vitro* correlation. The data do not appear to be predictive of *in vivo* performance.

**Clinical aspects**

**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, compared to that of Zyloric® 300, Tabletten, 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 under yellow monochromatic light, 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 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 $T_{\text{max}}$ of 1.5 hours, and plasm 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 $T_{\text{max}}$ of 3-5 hours and a half-life of 13-30 hours; however the washout period may be adequate.

Test and reference products
Test: Allopurinol Teva 300 mg Tabletter
Reference: Zyloric® 300 mg Tabletten (Mibe GmbH Arzneimittel, Germany)

**Assessor's comment**
The test and reference product are acceptable. Since the test product is also marketed, the batch size is not relevant.

**Population (s) studied**
A 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 (PK) Variables**
The chosen PK variable included: $\text{AUC}_{0-t}$, $\text{AUC}_{0-\infty}$, $C_{\text{max}}$, $T_{\text{max}}$, $K_{el}$ and half-life. $\text{AUC}_{0-t}$ and $C_{\text{max}}$ were the primary 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, using SAS® version 9.4.
ANOVA was performed on the log-transformed pharmacokinetic parameters $\text{AUC}_{0-t}$, $\text{AUC}_{0-\infty}$ and $C_{\text{max}}$ of allopurinol and oxipurinol using PROC GLM procedure of SAS®. 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 $\text{AUC}_{0-t}$, $\text{AUC}_{0-\infty}$ 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>( \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>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>
<tr>
<td>*Ratio (90% CI)</td>
<td>99.98 (96.84-103.22)</td>
<td>99.93 (96.82-103.13)</td>
<td>117.56 (108.88-126.95)</td>
<td></td>
</tr>
</tbody>
</table>

\( \text{AUC}_{0-t} \) Area under the plasma concentration curve from administration to last observed concentration at time \( t \).

\( \text{AUC}_{0-72\text{h}} \) can be reported instead of \( \text{AUC}_{0-t} \), in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products

\( \text{AUC}_{0-\infty} \) 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 vs. Time

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 4928.01 ng/mL, which 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>AUC$_{0-t}$ ng/ml/h</th>
<th>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>

AUC$_{0-t}$ Area under the plasma concentration curve from administration to last observed concentration at time $t$.

AUC$_{0-72h}$ can be reported instead of AUC$_{0-t}$ in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products.

AUC$_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.

AUC$_{0-\infty}$ does not need to be reported when AUC$_{0-72h}$ is reported.

$C_{\text{max}}$ Maximum plasma concentration

$t_{\text{max}}$ Time until $C_{\text{max}}$ is reached

*A ln-transformed values

A pre-dose concentration >5% of $C_{\text{max}}$ was observed for subject 46 in period II. This subject was excluded from the PK analysis per protocol. For all observation, the extrapolated AUC was >20% (mean AUC$_{0-t}$/AUC$_{0-\infty}$ was 41.31% after test and 40.94% after reference). The maximum observed plasma concentration was 8552.86 ng/mL, which was within the validated range of the analytical method for oxipurinol.

Assessor’s comment

As commented in the methods section, the sampling schedule was insufficient to characterize 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 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.

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 MHRA Request for FURTHER information

Clinical aspects

Major objections
N/A

Other concerns

Question 1
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, the MAH is asked to provide a safety summary outlining any adverse events (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 by nine (35%) of the 26 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
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 minutes 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 he was 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:

<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>
<tr>
<td>Vomiting</td>
<td>Recovered</td>
<td>Non-serious</td>
<td>Possible</td>
</tr>
<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>
• Distribution of adverse events in 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-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.

Fig 1. Distribution of cases in the Pharmacovigilance Database per SOC
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.

Fig 2. Distribution of events from countries with estimated percentage of fats in the diet below the average

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.
Fig 3. Distribution of events from countries with estimated percentage of fats in the diet above the average

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 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 Cmax 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

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 not considered to be clinically relevant for an allopurinol product. Therefore, the benefit risk of Allopurinol 100mg Tablets remains positive.

**Decision**: Approved on 27 March 2018