ALLOPURINOL 100MG TABLETS
PL 00289/0951

ALLOPURINOL 200MG TABLETS
PL 00289/0952

UKPAR

TABLE OF CONTENTS

Lay Summary Page 2
Scientific discussion Page 3
Steps taken for assessment Page 13
Steps taken after authorisation – summary Page 14
Summary of Product Characteristics Page 15
Product Information Leaflet Page 31
Labelling Page 41
LAY SUMMARY

The MHRA granted TEVA (UK) Limited Marketing Authorisations (licences) for the medicinal products Allopurinol 100mg Tablets (PL 00289/0951) and Allopurinol 200mg Tablets (PL 00289/0952). These are prescription-only medicines (POM) used for the long term, preventative treatment of gout as well as in other conditions associated with an excess of uric acid in the body, including kidney stones and other types of kidney diseases.

Allopurinol Tablets contain the active ingredient allopurinol, which is an enzyme inhibitor, which acts to control the speed at which special chemical changes occur in the body.

Allopurinol 300mg Tablets (PL 00289/0175) was approved on 24th March 1992 to TEVA (UK) Limited and was considered to be a generic version of the reference product Zyloric® 300mg Tablets (PL 00003/0092R, GlaxoSmithKline) based on data submitted by TEVA UK Limited. Data for the Allopurinol 300mg Tablets were extrapolated to the Marketing Authorisations applied for Allopurinol 100mg and 200mg Tablets.

This application is based on a reference product with a valid UK licence. No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Allopurinol 100mg and 200mg Tablets outweigh the risk; hence Marketing Authorisations have been granted.
SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction .......................................................... Page 4
Pharmaceutical assessment ........................................ Page 5
Preclinical assessment ............................................... Page 8
Clinical assessment (including statistical assessment) .... Page 9
Overall conclusions and risk benefit assessment .......... Page 12
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Allopurinol 100mg (PL 00289/0951) and Allopurinol 200mg Tablets (PL 00289/0952) on 16th December 2008. The products are prescription-only medicines.

These are two strengths of Allopurinol, submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, and have been shown to be generic medicinal products of the original, Zyloric® 300 mg 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.

The products are used as a treatment for a range of clinical conditions where reduction of urate/uric acid formation is desired. These conditions include uric acid lithiasis, idiopathic gout, acute uric acid nephropathy and certain neoplastic and myeloproliferative diseases.

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. At low concentrations, allopurinol is a substrate for and competitive inhibitor of the enzyme. At high concentration it is a non-competitive inhibitor. Allopurinol thus reduces the plasma concentration and urinary excretion of uric acid and increases the plasma concentration and renal excretion of the more soluble oxypurine precursors.

These applications depend upon the bioequivalence study presented by the applicant comparing the TEVA UK Limited product Allopurinol 300mg Tablets (PL 00289/0175) with the reference product Zyloric® 300mg Tablets (PL 00003/0092R, GlaxoSmithKline). As the test products, Allopurinol 100mg and 200mg Tablets, were deemed to meet the criteria specified in the Note 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 were extrapolated to the 100mg and 200mg strength tablets.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Allopurinol

INN: Allopurinol

Chemical names: 1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

CAS No. – 315-30-0

STRUCTURE

Molecular formula – C₅H₄N₄O
Relative molecular mass – 136.1

GENERAL PROPERTIES

Allopurinol is a white to almost white powder. It is very slightly soluble in water and in alcohol, it dissolve in dilute solution of alkali hydroxide.

TSE statement

A TSE declaration has been provided for the drug substance allopurinol from the drug substance manufacturers.

Manufacture

All aspects of the manufacture, in-process controls, validation and active substance specification are covered by certificates of suitability for both the active substance manufacturers.

An appropriate specification is provided for the active substance allopurinol. The specification is according to the current Ph Eur monograph with supplementary testing as required by the certificate of suitability for the drug substance manufacturers.

Batch analysis data are provided and comply with the proposed specification. Certificates of analysis have been provided for any working standards used.

An impurity profile for the drug substance has been provided and the impurities described are identical to those in the Ph.Eur.monograph for allopurinol.

Active allopurinol is stored in appropriate packaging material. The specifications and typical analytical test reports are provided and are satisfactory.
Batch analysis data are provided and comply with the proposed specification. Certificates of analysis have been provided for any working standards used.

Appropriate stability data have been generated supporting a retest period of five years.

**DRUG PRODUCT**

**Other Ingredients**

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, maize starch, sodium starch glycolate Type A, cellulose powdered, colloidal anhydrous silica, povidone K30, sodium lauryl sulphate, magnesium stearate and purified water. 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.

**Dissolution and impurity profiles**

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**

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 specification**

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

**Container Closure System**

The product is packaged in transparent blisters composed of aluminium foil and polyvinyl chloride (PVC) and polyvinylidene chloride (PVdC). Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with Ph Eur monograph and the EU food directive 2002/72/EC regarding contact with food. The product is packaged in sizes 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.

**Stability**

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 original container”. 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.

**Conclusion**

It is recommended that Marketing Authorisations are granted for these applications.

Considering the bioequivalence data provided, the applicant’s claim that Allopurinol 300mg Tablets is a generic medicinal product of Zyloric® 300mg Tablets is justified. The results of the bioequivalence study can be extrapolated to the 100mg and 200mg strength tablets.

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. Marketing Authorisations may be granted.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for an application of this type.
CLINICAL ASSESSMENT

1.1 CLINICAL BACKGROUND
Allopurinol is an isomer of hypoxanthine. Allopurinol inhibits the production of uric acid, the metabolite responsible for gout, by inhibiting the enzyme xanthine oxidase. Allopurinol is metabolised by xanthine oxidase to oxypurinol (alloxanthine). Allopurinol is used in the treatment and management of a range of clinical conditions where a reduction of urate/uric acid formation is desired. These conditions include prophylaxis of gout, uric acid renal stones and prophylaxis of hyperuricaemia associated with cancer chemotherapy for haematological malignancy (Tumour Lysis Syndrome). The use of allopurinol is contraindicated in episodes of acute gout as it may cause an acute exacerbation. Allopurinol is generally well tolerated, with the most common side effect being skin reactions.

1.2 INDICATIONS
The indications are in line with the UK approved reference drug SPC.

1.3 DOSE AND DOSE REGIMEN
The dose and dose regimen are in line with the UK approved reference drug SPC.

2 CLINICAL PHARMACOLOGY
2.1 PHARMACOKINETICS
No new data are provided or required for this application.

2.2 PHARMACODYNAMICS
No new data are provided or required for this application.

2.3 BIOEQUIVALENCE
The applicant has submitted a comparative bioavailability study with allopurinol tablets (1 X 300 mg), Test (Approved Prescription Service Limited, TEVA UK Limited) and Reference (Zyloprim, Laboratories Wellcome S.A). The objective of the study was to compare the bioavailability of allopurinol from tablets marketed by APS Ltd and from Zyloprim tablets marketed by 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>Parameter</th>
<th>Test (APS)</th>
<th>Reference (Zyloric)</th>
<th>Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC (h.µg/l)</strong> (Allopurinol)</td>
<td>2079-12454 (Mean 4309)</td>
<td>2102-6471 (Mean 3908)</td>
<td>97.3-115.7%</td>
</tr>
<tr>
<td><strong>AUC (h.µg/l)</strong> (Oxypurinol)</td>
<td>142182-269274 (Mean 194242)</td>
<td>120227-283087 (Mean 198975)</td>
<td>94.6-101.9%</td>
</tr>
<tr>
<td><strong>C_{max} (µg/l)</strong> (Allopurinol)</td>
<td>828-3904 (Mean 1800)</td>
<td>888-3488 (Mean 1697)</td>
<td>90.7-123.4%</td>
</tr>
<tr>
<td><strong>C_{max} (µg/l)</strong> (Oxypurinol)</td>
<td>3974-6577 (Mean 5520)</td>
<td>4383-7180 (Mean 5540)</td>
<td>96.1-103.2%</td>
</tr>
<tr>
<td><strong>T_{max} (hours)</strong> (Allopurinol)</td>
<td>1.25</td>
<td>1.0</td>
<td>-</td>
</tr>
<tr>
<td><strong>T_{max} (hours)</strong> (Oxypurinol)</td>
<td>2.5-7</td>
<td>1-7</td>
<td>-</td>
</tr>
</tbody>
</table>

2.3.1 Assessor's Comment
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_{max}, the Test product (300 mg APS 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).
2.3.2 Assessor's Conclusion on Bioequivalence
According to the latest CPMP guidelines, the Test and Reference product are bioequivalent and the applicant provides evidence to support linearity of the product over the range of 50-600 mg.

3 CLINICAL EFFICACY
No new data are provided or required for this application.

4 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.

5 EXPERT REPORTS
A satisfactory Clinical Expert Report has been submitted with appropriate CV.

The clinical overview and summary were well-constructed and cross-referenced with appropriate supporting literature. The clinical overview provides details of the product development rationale, overview of the biopharmaceutics, the clinical pharmacology, efficacy, safety and benefits & risks. The clinical summary provided a summary of the biopharmaceutical studies.

6 PRODUCT LITERATURE
This is satisfactory. The text of the SPC is essentially the same as that of the cross-reference product licence.

6.1 PATIENT INFORMATION LEAFLET
This is satisfactory.

6.2 LABEL
These are satisfactory.

6.3 APPLICATION FORM
The application forms comply with the procedures set out in EU directive ‘Notice to Applicants’.

7 CONCLUSION
The applicant appears to have demonstrated bioequivalence. Marketing authorisations should be granted for these products.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Allopurinol 100mg and 200mg 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.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between Allopurinol 300mg Tablets (PL 00289/0175) and the reference product Zyloric® 300mg Tablets (GlaxoSmithKline). This supports the applicant’s claim that Allopurinol 100mg & 200mg Tablets are hybrid versions of Zyloric® 300mg Tablets. The results and conclusions of the bioequivalence study on the 300mg strength were extrapolated to the 100mg and 200mg strengths. Separate bioequivalence studies were not considered necessary for Allopurinol 100mg and 200mg Tablets as exemption criteria, detailed in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), have been fulfilled.

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The approved SPC, PIL and labelling are satisfactory and consistent with that of the reference product.

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.

The approved labelling artwork complies with statutory requirements.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety 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 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 risk: benefit is, therefore considered to be positive.
ALLOPURINOL 100MG TABLETS  
PL 00289/0951  

ALLOPURINOL 200MG TABLETS  
PL 00289/0952  

**STEPS TAKEN FOR ASSESSMENT**

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<thead>
<tr>
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<th>Description</th>
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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 10th April 2006.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 7th June 2006.</td>
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<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 17th November 2006, and further information relating to the quality dossiers on 8th September 2006 and 18th September 2007.</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 18th April 2007 for the clinical sections, and again on 23rd April 2007 and 2nd July 2008 for the quality sections.</td>
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<tr>
<td>5</td>
<td>The applications were determined on 16th October 2008.</td>
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ALLOPURINOL 100MG TABLETS
PL 00289/0951

ALLOPURINOL 200MG TABLETS
PL 00289/0952

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Allopurinol 100 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 100 mg Allopurinol.
Excipients: lactose monohydrate
Each tablet Allopurinol 100 mg contains 60 mg lactose monohydrate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet
White, biconvex tablets, debossed: 4K1, plain on reverse.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
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.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
For oral administration.
Dosage should be modified by monitoring serum urate concentrations and urinary urate/uric acid levels at appropriate intervals.

Dose frequency:
Allopurinol may be taken orally once a day after a meal. It is well tolerated, especially after food. If the daily dosage exceeds 300 mg and gastrointestinal intolerance is evident, a divided dosage regimen may be appropriate.

Adults:
2 - 10 mg/kg bodyweight/day or 100 - 200 mg daily in mild conditions, 300 - 600 mg daily in moderately severe conditions, or 700 - 900 mg daily in severe conditions. The initial dose should be in the range of 100 to 300 mg per day which may be taken as a single dose preferably after food.

Children under 15 years:
10 - 20 mg/kg bodyweight/day, or 100 to 400 mg daily. Use in children is rarely indicated except in malignant conditions, especially in leukaemia and certain enzyme disorders, for example Lesch-Nyhan syndrome.
Elderly:
No specific dosage recommendations, the lowest dosage which produces satisfactory urate reduction should be used. Also refer to dosage advice under Dosage recommendations in renal disorders and section 4.4 Special warnings and precautions for use.

Treatment of high urate turnover conditions e.g. neoplasia, Lesch-Nyhan syndrome:
It is advisable to correct existing hyperuricaemia and/or hyperuricosuria with allopurinol before commencing cytotoxic therapy. It is important to ensure adequate hydration to maintain optimum diuresis and to attempt alkalinisation of urine to increase solubility of urinary urate/urate acid. The dose of allopurinol should be in the lower range.

If urate nephropathy or other pathology has compromised renal function, advice provided in Dosage recommendations in renal disorder should be followed.

These steps may reduce the risk of xanthine and/or oxipurinol deposition complicating the clinical situation. See also sections 4.5 Interaction with other medicinal products and other forms of interaction and 4.8 Undesirable effects.

Dosage recommendations in renal disorders:
Allopurinol and its metabolites are excreted by the kidney, therefore impairment of renal function may lead to retention of the drug and/or its metabolites. The plasma half lives may as a consequence be prolonged. Serious consideration should be given in the presence of impaired renal function, to initiating treatment with a maximum dose of 100 mg/day and increasing it only if the serum and/or urinary rate response is unsatisfactory. In severe renal insufficiency, it may be advisable to use less than 100 mg/day or to use single doses of 100 mg at longer intervals than one day.

Dosage in hepatic impairment:
Reduced doses should be used in patients with hepatic impairment. Periodic liver function tests are recommended during the early stages of therapy.

Alternative schedules based on creatinine clearances are unsatisfactory, because of inaccuracy of low clearance values.

If plasma oxipurinol concentration monitoring is available, the dose should be adjusted to maintain plasma oxipurinol levels below 100 micromol/Litre (15.2 microgram/ml).

Dose recommendations in renal dialysis:
Allopurinol and its metabolites are removed by renal dialysis. If frequent dialysis is required an alternative schedule of 300 - 400 mg allopurinol after each dialysis with none in the interim should be considered.

4.3 CONTRAINDICATIONS
Allopurinol is contraindicated where there is known intolerance, where there is hypersensitivity to any of the excipients and in cases of acute gout. However, prophylactic therapy may be started when the acute attack has completely subsided, provided that anti-inflammatory therapy is also taken.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Treatment should not be started during or immediately after an acute attack of gout (see section 4.3 Contraindications).

As with other uricosuric agents, in the early stages of treatment with allopurinol, an acute attack of gouty arthritis may be precipitated. Therefore it is advisable to employ prophylactic therapy with a suitable anti-inflammatory agent or colchicine (0.5 mg three times a day) for at least a month.

The dosage of allopurinol should be reduced in patients with renal or hepatic diseases.
Particular care should be taken in the elderly where renal function may be reduced thus leading to a retention of the drug and its metabolites with the consequent prolongation of action.

Allopurinol should be withdrawn immediately when a skin rash or other evidence of hypersensitivity occurs. It should be withdrawn immediately and permanently at the first sign of intolerance.

Patients under treatment for cardiac insufficiency or hypertension, for example with ACE inhibitors or diuretics, may have some concomitant impairment of renal function and allopurinol should be used with care in this group.

Asymptomatic hyperuricaemia _per se_ is not an indication for allopurinol therapy. Fluid and dietary modification with modification of the underlying cause may correct the condition. If other clinical conditions suggest a need for allopurinol, it must be introduced at a low dosage (50 to 100 mg/day) to reduce the risk of adverse reactions. The dose should only be increased if the serum urate response is unsatisfactory.

### 4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

The therapeutically active major metabolite of allopurinol, oxipurinol, is excreted by the kidney in a similar way to urate. Therefore drugs with uricosuric activity e.g. probenecid, or large doses of salicylate, may accelerate oxipurinol excretion. This may have the effect of decreasing the therapeutic activity of allopurinol, however the significance needs to be assessed in every case.

There have been rare reports of increased effect of warfarin and other coumarin anticoagulants when co-administered with allopurinol therefore, all patients receiving anticoagulants must be carefully monitored.

When 6-mercaptopurine or azathioprine is given by mouth concurrently with allopurinol, only one quarter of the usual dose of those drugs should be given because inhibition of xanthine oxidase will prolong their activity. If allopurinol is given concomitantly with chlorpropamide when renal function is poor, there may be an increased risk of prolonged hypoglycaemic activity.

There is evidence to suggest that the plasma half-life of vidarabine (adenine arabinoside) is increased in the presence of allopurinol. Extra vigilance is required during concomitant use of the two products to recognise enhanced toxic effects.

Allopurinol may inhibit the hepatic oxidation of phenytoin, however the clinical significance of this has not been established.

Inhibition of the metabolism of theophylline has been reported. The mechanism of the interaction may be explained by xanthine oxidase being involved in the biotransformation of theophylline in man. Theophylline levels should be monitored in patients increasing or starting allopurinol therapy.

An increase in the frequency of skin rash has been reported among patients receiving amoxicillin or ampicillin concurrently with allopurinol compared to patients who are not receiving both drugs. The cause of the association has not been established. However, it is recommended that in patients receiving allopurinol an alternative to amoxicillin or ampicillin is used where available.

Enhanced bone marrow suppression by cyclophosphamide and other cytotoxic agents has been reported among patients with neoplastic disease (other than leukaemia), in the presence of allopurinol. However, in a well-controlled study of patients treated with doxorubicin, bleomycin, cyclophosphamide, procarbazine and/or mechloethamine (mustine hydrochloride) allopurinol did not appear to increase the toxic reaction of these cytotoxic agents.

There have been reports suggesting that the plasma concentration of ciclosporin may be increased during concomitant treatment with allopurinol. The possibility of enhanced ciclosporin toxicity should be considered if the drugs are to be co-administered.
4.6 PREGNANCY AND LACTATION

There is insufficient evidence of the safety of allopurinol in human pregnancy, although it has been widely used for many years without apparent ill consequence.

Allopurinol should be used in pregnancy only where there is no safer alternative and when the disease itself carries risks for the mother or child.

One study in mice receiving intraperitoneal doses of 50 or 100 mg/kg on days 10 or 13 of gestation resulted in foetal abnormalities; however, in a similar study in rats at 120 mg/kg on day 12 of gestation no abnormalities were observed. Extensive studies of high oral doses of allopurinol in rats up to 200 mg/kg/day, mice up to 100 mg/kg/day and rabbits up to 150 mg/kg/day during days 8 to 16 of the gestation period produced no teratogenic effects.

An in vitro study using foetal mouse salivary gland in culture to detect embryotoxicity indicated that allopurinol would not be expected to cause embryotoxicity without also causing maternal toxicity.

Reports indicate that allopurinol is excreted in human breast milk. However, there are no data concerning the effects of allopurinol or its metabolites on the breast-fed baby.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Since adverse reactions such as vertigo, somnolence and ataxia have been reported in patients receiving allopurinol, patients should exercise caution before driving, using machinery or participating in dangerous activities until they are sure that allopurinol does not adversely affect performance.

4.8 UNDESIRABLE EFFECTS

For this product there is no modern clinical documentation which can be used as support for determining the frequency of undesirable effects. Undesirable effects may vary in their incidence depending on the dose received and also when given in combination with other therapeutic agents.

The frequency categories assigned to the adverse drug reactions below are estimates: for most reactions, suitable data for calculating incidence are not available. Adverse drug reactions identified through post-marketing surveillance were considered to be rare or very rare. The following convention has been used for the classification of frequency:

Very common (≥1/10);
Common (≥1/100 to <1/10);
Uncommon (≥1/1000 to ≤1/100);
Rare (≥1/10,000 to ≤1/1000);
Very rare (≤1/10,000), not known (cannot be estimated from the available data).

Adverse reactions in association with allopurinol are rare in the overall treated population and mostly of a minor nature. The incidence is higher in the presence of renal and/or hepatic disorder.

Cardiac disorders

Very rare: angina, bradycardia.

Blood and lymphatic system disorders

Very rare: agranulocytosis, aplastic anaemia, thrombocytopenia

Very rare reports have been received of thrombocytopenia, agranulocytosis and aplastic anaemia, particularly in individuals with impaired renal and/or hepatic function, reinforcing the need for particular care in this group of patients.

Nervous system disorders

Very rare: coma, paralysis, ataxia, neuropathy, paraesthesiae, somnolence, headache, taste perversion.
Eye disorders
Very rare: cataract, visual disorder, macular changes.

Ear and labyrinth disorders
Very rare: vertigo.

Gastrointestinal disorders
Uncommon: vomiting, nausea.
Very rare: recurrent haematemesis, steatorrhoea, stomatitis, changed bowel habit.
In early clinical studies, nausea and vomiting were reported. Further reports suggest that this reaction is not a significant problem and can be avoided by taking allopurinol after meals.

Renal and urinary disorders
Very rare: haematuria, uraemia.

Skin and subcutaneous tissue disorders
Common: rash.
Very rare: angioedema, fixed drug eruption, alopecia, discoloured hair.
Skin reactions are the most common reactions and may occur at any time during treatment. They may be pruritic, maculopapular, sometimes scaly, sometimes purpuric and rarely exfoliative. Allopurinol should be withdrawn immediately should such reactions occur. After recovery from mild reactions, Allopurinol may, if desired, be re-introduced at a small dose (e.g. 50mg/day) and gradually increased. If the rash recurs, Allopurinol should be permanently withdrawn as more severe hypersensitivity may occur (see Immune system disorders).
Angioedema has been reported to occur with and without signs and symptoms of a more generalised hypersensitivity reaction.

Metabolism and nutrition disorders
Very rare: diabetes mellitus, hyperlipidaemia.

Infections and infestations
Very rare: furunculosis.

Vascular disorders
Very rare: hypertension.

General disorders and administration site conditions
Very rare: oedema, general malaise, asthenia, fever.
Fever has been reported to occur with and without signs and symptoms of a more generalised Allopurinol hypersensitivity reaction (see Immune system disorders).

Immune system disorders
Uncommon: hypersensitivity reactions.
Very rare: angioimmunoblastic lymphadenopathy.
Serious hypersensitivity reactions, including skin reactions associated with exfoliation, fever, lymphadenopathy, arthralgia and/or eosinophilia including Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis occur rarely (see Skin and subcutaneous tissue disorders). Associated vasculitis and tissue response may be manifested in various ways including hepatitis, renal impairment and very rarely, seizures. Very rarely acute anaphylactic shock has been reported. If such reactions do occur, it may be at any time during treatment, allopurinol should be withdrawn immediately and permanently.
Corticosteroids may be beneficial in overcoming hypersensitivity skin reactions. When generalised hypersensitivity reactions have occurred, renal and/or hepatic disorder has usually been present particularly when the outcome has been fatal.
Angioimmunoblastic lymphadenopathy has been described very rarely following biopsy of a generalised lymphadenopathy. It appears to be reversible on withdrawal of allopurinol.

**Hepatobiliary disorders**
Uncommon: asymptomatic increases in liver function tests.
Rare: hepatitis (including hepatic necrosis and granulomatous hepatitis).
Hepatic dysfunction has been reported without overt evidence of more generalised hypersensitivity.

**Reproductive system and breast disorders**
Very rare: male infertility, erectile dysfunction, gynaecomastia.

**Psychiatric disorders**
Very rare: depression.

4.9 **OVERDOSE**
There have been reports of accidental or deliberate ingestion of up to 5 g, (or very rarely 20 g), of allopurinol. Symptoms or signs have included nausea, vomiting, diarrhoea and dizziness. Recovery followed general supportive measures. Massive absorption of allopurinol may lead to considerable inhibition of xanthine oxidase activity. This should have no untoward effect unless 6-mercaptopurine and/or azothiaprine is being taken concomitantly. Adequate hydration to maintain optimum diuresis will facilitate excretion of allopurinol and its metabolites. If it is considered necessary, haemodialysis may be used.

5 **PHARMACOLOGICAL PROPERTIES**
5.1 **PHarmacodynamic PROPERTIES**
ATC Code: M04A A01 Preparations inhibiting uric acid production.
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.
At low concentrations, allopurinol is a substrate for and competitive inhibitor of the enzyme. At high concentration it is a non-competitive inhibitor.
Allopurinol thus reduces the plasma concentration and urinary excretion of uric acid and increases the plasma concentration and renal excretion of the more soluble oxypurine precursors.

5.2 **PHarmacokinetic PROPERTIES**
Allopurinol is active when given orally and is rapidly absorbed from the upper gastrointestinal tract. Studies have detected allopurinol in the blood 30-60 minutes after dosing. Estimates of bioavailability vary from 67% to 90%. Peak plasma levels of allopurinol generally occur approximately 1.5 hours after oral administration of Allopurinol, but fall rapidly and are barely detectable after 6 hours. Peak levels of oxipurinol generally occur after 3-5 hours after oral administration of Allopurinol and are much more sustained.
Allopurinol is negligibly bound by plasma proteins and therefore variations in protein binding are not thought to significantly alter clearance. The apparent volume of distribution of allopurinol is approximately 1.6 litre/kg, which suggests relatively extensive uptake by tissues. Tissue concentrations of allopurinol have not been reported in humans, but it is likely that allopurinol and oxipurinol will be present in the highest concentrations in the liver and intestinal mucosa where xanthine oxidase activity is high.
Approximately 20% of the ingested allopurinol is excreted in the faeces in 48 - 72 hours. Elimination of allopurinol is mainly by metabolic conversion to oxipurinol by xanthine oxidase and aldehyde oxidase, with less than 10% of the unchanged drug excreted in the urine. Allopurinol has a plasma half-life of about 1 to 2 hours.
Oxipurinol is a less potent inhibitor of xanthine oxidase than allopurinol, but the plasma half-life of oxipurinol is far more prolonged. Estimates range from 13 to 30 hours in man. Therefore effective inhibition of xanthine oxidase is maintained over a 24 hour period with a single daily dose of Allopurinol. Patients with normal renal function will gradually accumulate oxipurinol until a steady-state plasma oxipurinol concentration is reached. Such patients, taking 300 mg of allopurinol per day will generally have plasma oxipurinol concentrations of 5-10 mg/litre.

Oxipurinol is eliminated unchanged in the urine but has a long elimination half-life because it undergoes tubular reabsorption. Reported values for the elimination half-life range from 13.6 hours to 29 hours. The large discrepancies in these values may be accounted for by variations in study design and/or creatinine clearance in the patients.

Pharmacokinetics in patients with renal impairment.

Allopurinol and oxipurinol clearance is greatly reduced in patients with poor renal function resulting in higher plasma levels in chronic therapy. Patients with renal impairment, where creatinine clearance values were between 10 and 20ml/min, showed plasma oxipurinol concentrations of approximately 30mg/litre after prolonged treatment with 300 mg allopurinol per day. This is approximately the concentration which would be achieved by doses of 600 mg/day in those with normal renal function. A reduction in the dose of Allopurinol is therefore required in patients with renal impairment.

Pharmacokinetics in elderly patients.

The kinetics of the drug are not likely to be altered other than due to deterioration in renal function (see Pharmacokinetics in patients with renal impairment).

5.3 PRECLINICAL SAFETY DATA

Mutagenicity

Cytogenetic studies show that allopurinol does not induce chromosome aberrations in human blood cells in vitro at concentrations up to 100 micrograms/ml and in vivo at doses up to 600 mg/day for mean period of 40 months.

Allopurinol does not produce nitrato compounds in vitro or affect lymphocyte transformation in vitro.

Evidence from biochemical and other cytological investigations strongly suggests that allopurinol has no deleterious effects on DNA at any stage of the cell cycle and is not mutagenic.

Carcinogenicity

No evidence of carcinogenicity has been found in mice and rats treated with allopurinol for up to 2 years.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose Monohydrate
Colloidal Anhydrous Silica
Maize Starch
Powdered cellulose
Sodium Starch Glycolate (Type A)
Sodium Lauryl Sulphate
Povidone (E1201)
Magnesium Stearate (E572)
6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
24 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 25°C. Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER
Transparent PVC/PVdC/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.
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Not applicable.

7 MARKETING AUTHORISATION HOLDER
TEVA UK Limited
Brampton Road
Hampden Park
Eastbourne
East Sussex
BN22 9AG.
Trading address:
Leeds LS27 OJG
England.

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/0951

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION
16/10/2008

10 DATE OF REVISION OF THE TEXT
16/10/2008

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Allopurinol 200 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 200 mg Allopurinol.
Excipients: lactose monohydrate
Each tablet Allopurinol 200 mg contains 120 mg lactose monohydrate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet
White, biconvex tablets, debossed: 3K1, plain on reverse.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
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.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
For oral administration.
Dosage should be modified by monitoring serum urate concentrations and urinary urate/uric acid levels at appropriate intervals.

Dose frequency:
Allopurinol may be taken orally once a day after a meal. It is well tolerated, especially after food. If the daily dosage exceeds 300 mg and gastrointestinal intolerance is evident, a divided dosage regimen may be appropriate.

Adults:
2 - 10 mg/kg bodyweight/day or 100 - 200 mg daily in mild conditions, 300 - 600 mg daily in moderately severe conditions, or 700 - 900 mg daily in severe conditions. The initial dose should be in the range of 100 to 300 mg per day which may be taken as a single dose preferably after food.
Children under 15 years:
10 - 20 mg/kg bodyweight/day, or 100 to 400 mg daily. Use in children is rarely indicated except in malignant conditions, especially in leukaemia and certain enzyme disorders, for example Lesch-Nyhan syndrome.
Elderly:
No specific dosage recommendations, the lowest dosage which produces satisfactory urate reduction should be used. Also refer to dosage advice under Dosage recommendations in renal disorders and section 4.4 Special warnings and precautions for use.

Treatment of high urate turnover conditions e.g. neoplasia, Lesch-Nyhan syndrome:
It is advisable to correct existing hyperuricaemia and/or hyperuricosuria with allopurinol before commencing cytotoxic therapy. It is important to ensure adequate hydration to maintain optimum diuresis and to attempt alkalisation of urine to increase solubility of urinary urate/uric acid. The dose of allopurinol should be in the lower range.

If urate nephropathy or other pathology has compromised renal function, advice provided in Dosage recommendations in renal disorder should be followed.

These steps may reduce the risk of xanthine and/or oxipurinol deposition complicating the clinical situation. See also sections 4.5 Interaction with other medicinal products and other forms of interaction and 4.8 Undesirable effects.

Dosage recommendations in renal disorders:
Allopurinol and its metabolites are excreted by the kidney, therefore impairment of renal function may lead to retention of the drug and/or its metabolites. The plasma half lives may as a consequence be prolonged. Serious consideration should be given in the presence of impaired renal function, to initiating treatment with a maximum dose of 100 mg/day and increasing it only if the serum and/or urinary rate response is unsatisfactory. In severe renal insufficiency, it may be advisable to use less than 100 mg/day or to use single doses of 100 mg at longer intervals than one day.

Dosage in hepatic impairment:
Reduced doses should be used in patients with hepatic impairment. Periodic liver function tests are recommended during the early stages of therapy.

Alternative schedules based on creatinine clearances are unsatisfactory, because of inaccuracy of low clearance values.

If plasma oxipurinol concentration monitoring is available, the dose should be adjusted to maintain plasma oxipurinol levels below 100 micromol/Litre (15.2 microgram/ml).

Dose recommendations in renal dialysis:
Allopurinol and its metabolites are removed by renal dialysis. If frequent dialysis is required an alternative schedule of 300 - 400 mg allopurinol after each dialysis with none in the interim should be considered.

4.3 CONTRAINDICATIONS
Allopurinol is contraindicated where there is known intolerance, where there is hypersensitivity to any of the excipients and in cases of acute gout. However, prophylactic therapy may be started when the acute attack has completely subsided, provided that anti-inflammatory therapy is also taken.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Treatment should not be started during or immediately after an acute attack of gout (see section 4.3 Contraindications).

As with other uricosuric agents, in the early stages of treatment with allopurinol, an acute attack of gouty arthritis may be precipitated. Therefore it is advisable to employ prophylactic therapy with a suitable anti-inflammatory agent or colchicine (0.5 mg three times a day) for at least a month.

The dosage of allopurinol should be reduced in patients with renal or hepatic diseases.
Particular care should be taken in the elderly where renal function may be reduced thus leading to a retention of the drug and its metabolites with the consequent prolongation of action.

Allopurinol should be withdrawn immediately when a skin rash or other evidence of hypersensitivity occurs. It should be withdrawn immediately and permanently at the first sign of intolerance.

Patients under treatment for cardiac insufficiency or hypertension, for example with ACE inhibitors or diuretics, may have some concomitant impairment of renal function and allopurinol should be used with care in this group.

Asymptomatic hyperuricaemia per se is not an indication for allopurinol therapy. Fluid and dietary modification with modification of the underlying cause may correct the condition. If other clinical conditions suggest a need for allopurinol, it must be introduced at a low dosage (50 to 100 mg/day) to reduce the risk of adverse reactions. The dose should only be increased if the serum urate response is unsatisfactory.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

The therapeutically active major metabolite of allopurinol, oxipurinol, is excreted by the kidney in a similar way to urate. Therefore drugs with uricosuric activity e.g. probenecid, or large doses of salicylate, may accelerate oxipurinol excretion. This may have the effect of decreasing the therapeutic activity of allopurinol, however the significance needs to be assessed in every case.

There have been rare reports of increased effect of warfarin and other coumarin anticoagulants when co-administered with allopurinol therefore, all patients receiving anticoagulants must be carefully monitored.

When 6-mercaptopurine or azathioprine is given by mouth concurrently with allopurinol, only one quarter of the usual dose of those drugs should be given because inhibition of xanthine oxidase will prolong their activity. If allopurinol is given concomitantly with chlorpropamide when renal function is poor, there may be an increased risk of prolonged hypoglycaemic activity.

There is evidence to suggest that the plasma half-life of vidarabine (adenine arabinoside) is increased in the presence of allopurinol. Extra vigilance is required during concomitant use of the two products to recognise enhanced toxic effects.

Allopurinol may inhibit the hepatic oxidation of phenytoin, however the clinical significance of this has not been established.

Inhibition of the metabolism of theophylline has been reported. The mechanism of the interaction may be explained by xanthine oxidase being involved in the biotransformation of theophylline in man. Theophylline levels should be monitored in patients increasing or starting allopurinol therapy.

An increase in the frequency of skin rash has been reported among patients receiving amoxicillin or ampicillin concurrently with allopurinol compared to patients who are not receiving both drugs. The cause of the association has not been established. However, it is recommended that in patients receiving allopurinol an alternative to amoxicillin or ampicillin is used where available.

Enhanced bone marrow suppression by cyclophosphamide and other cytotoxic agents has been reported among patients with neoplastic disease (other than leukaemia), in the presence of allopurinol. However, in a well-controlled study of patients treated with doxorubicin, bleomycin, cyclophosphamide, procarbazine and/or mechloretamine (mustine hydrochloride) allopurinol did not appear to increase the toxic reaction of these cytotoxic agents.

There have been reports suggesting that the plasma concentration of ciclosporin may be increased during concomitant treatment with allopurinol. The possibility of enhanced ciclosporin toxicity should be considered if the drugs are to be co-administered.
4.6 PREGNANCY AND LACTATION

There is insufficient evidence of the safety of allopurinol in human pregnancy, although it has been widely used for many years without apparent ill consequence.

Allopurinol should be used in pregnancy only where there is no safer alternative and when the disease itself carries risks for the mother or child.

One study in mice receiving intraperitoneal doses of 50 or 100 mg/kg on days 10 or 13 of gestation resulted in foetal abnormalities; however, in a similar study in rats at 120 mg/kg on day 12 of gestation no abnormalities were observed. Extensive studies of high oral doses of allopurinol in rats up to 200 mg/kg/day, mice up to 100 mg/kg/day and rabbits up to 150 mg/kg/day during days 8 to 16 of the gestation period produced no teratogenic effects.

An in vitro study using foetal mouse salivary gland in culture to detect embryotoxicity indicated that allopurinol would not be expected to cause embryotoxicity without also causing maternal toxicity.

Reports indicate that allopurinol is excreted in human breast milk. However, there are no data concerning the effects of allopurinol or its metabolites on the breast-fed baby.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Since adverse reactions such as vertigo, somnolence and ataxia have been reported in patients receiving allopurinol, patients should exercise caution before driving, using machinery or participating in dangerous activities until they are sure that allopurinol does not adversely affect performance.

4.8 UNDESIRABLE EFFECTS

For this product there is no modern clinical documentation which can be used as support for determining the frequency of undesirable effects. Undesirable effects may vary in their incidence depending on the dose received and also when given in combination with other therapeutic agents.

The frequency categories assigned to the adverse drug reactions below are estimates: for most reactions, suitable data for calculating incidence are not available. Adverse drug reactions identified through post-marketing surveillance were considered to be rare or very rare. The following convention has been used for the classification of frequency:

Very common (≥1/10);
Common (≥1/100 to <1/10);
Uncommon (≥1/1000 to ≤1/100);
Rare (≥1/10,000 to ≤1/1000);
Very rare (≤1/10,000), not known (cannot be estimated from the available data).

Adverse reactions in association with allopurinol are rare in the overall treated population and mostly of a minor nature. The incidence is higher in the presence of renal and/or hepatic disorder.

Cardiac disorders

Very rare: angina, bradycardia.

Blood and lymphatic system disorders

Very rare: agranulocytosis, aplastic anaemia, thrombocytopenia

Very rare reports have been received of thrombocytopenia, agranulocytosis and aplastic anaemia, particularly in individuals with impaired renal and/or hepatic function, reinforcing the need for particular care in this group of patients.

Nervous system disorders

Very rare: coma, paralysis, ataxia, neuropathy, paraesthesiae, somnolence, headache, taste perversion.
Eye disorders
Very rare: cataract, visual disorder, macular changes.

Ear and labyrinth disorders
Very rare: vertigo.

Gastrointestinal disorders
Uncommon: vomiting, nausea.
Very rare: recurrent haematemesis, steatorrhoea, stomatitis, changed bowel habit.
In early clinical studies, nausea and vomiting were reported. Further reports suggest that this reaction is not a significant problem and can be avoided by taking allopurinol after meals.

Renal and urinary disorders
Very rare: haematuria, uraemia.

Skin and subcutaneous tissue disorders
Common: rash.
Very rare: angioedema, fixed drug eruption, alopecia, discoloured hair.
Skin reactions are the most common reactions and may occur at any time during treatment. They may be pruritic, maculopapular, sometimes scaly, sometimes purpuric and rarely exfoliative. Allopurinol should be withdrawn immediately should such reactions occur. After recovery from mild reactions, Allopurinol may, if desired, be re-introduced at a small dose (e.g. 50mg/day) and gradually increased. If the rash recurs, Allopurinol should be permanently withdrawn as more severe hypersensitivity may occur (see Immune system disorders).

Angioedema has been reported to occur with and without signs and symptoms of a more generalised hypersensitivity reaction.

Metabolism and nutrition disorders
Very rare: diabetes mellitus, hyperlipidaemia.

Infections and infestations
Very rare: furunculosis.

Vascular disorders
Very rare: hypertension.

General disorders and administration site conditions
Very rare: oedema, general malaise, asthenia, fever.
Fever has been reported to occur with and without signs and symptoms of a more generalised Allopurinol hypersensitivity reaction (see Immune system disorders).

Immune system disorders
Uncommon: hypersensitivity reactions.
Very rare: angioimmunoblastic lymphadenopathy.
Serious hypersensitivity reactions, including skin reactions associated with exfoliation, fever, lymphadenopathy, arthralgia and/or eosinophilia including Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis occur rarely (see Skin and subcutaneous tissue disorders). Associated vasculitis and tissue response may be manifested in various ways including hepatitis, renal impairment and very rarely, seizures. Very rarely acute anaphylactic shock has been reported. If such reactions do occur, it may be at any time during treatment, allopurinol should be withdrawn immediately and permanently.
Corticosteroids may be beneficial in overcoming hypersensitivity skin reactions. When generalised hypersensitivity reactions have occurred, renal and/or hepatic disorder has usually been present particularly when the outcome has been fatal.
Angioimmunoblastic lymphadenopathy has been described very rarely following biopsy of a
generalised lymphadenopathy. It appears to be reversible on withdrawal of allopurinol.

**Hepatobiliary disorders**
Uncommon: asymptomatic increases in liver function tests.
Rare: hepatitis (including hepatic necrosis and granulomatous hepatitis).
Hepatic dysfunction has been reported without overt evidence of more generalised
hypersensitivity.

**Reproductive system and breast disorders**
Very rare: male infertility, erectile dysfunction, gynaecomastia.

**Psychiatric disorders**
Very rare: depression.

**4.9 OVERDOSE**
There have been reports of accidental or deliberate ingestion of up to 5 g, (or very rarely 20 g),
of allopurinol. Symptoms or signs have included nausea, vomiting, diarrhoea and dizziness.
Recovery followed general supportive measures. Massive absorption of allopurinol may lead
to considerable inhibition of xanthine oxidase activity. This should have no untoward effect
unless 6-mercaptopurine and/or azothiaprine is being taken concomitantly. Adequate
hydration to maintain optimum diuresis will facilitate excretion of allopurinol and its
metabolites. If it is considered necessary, haemodialysis may be used.

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 PHARMACODYNAMIC PROPERTIES**
ATC Code: M04A A01 Preparations inhibiting uric acid production.

Allopurinol and its primary metabolite, oxipurinol is an inhibitor of the enzyme xanthine
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a reaction which is catalysed by xanthine oxidase.

At low concentrations, allopurinol is a substrate for and competitive inhibitor of the enzyme.
At high concentration it is a non-competitive inhibitor.

Allopurinol thus reduces the plasma concentration and urinary excretion of uric acid and
increases the plasma concentration and renal excretion of the more soluble oxypurine
precursors.

**5.2 PHARMACOKINETIC PROPERTIES**
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tract. Studies have detected allopurinol in the blood 30-60 minutes after dosing. Estimates of
bioavailability vary from 67% to 90%. Peak plasma levels of allopurinol generally occur
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oral administration of Allopurinol and are much more sustained.

Allopurinol is negligibly bound by plasma proteins and therefore variations in protein binding
are not thought to significantly alter clearance. The apparent volume of distribution of
allopurinol is approximately 1.6 litre/kg, which suggests relatively extensive uptake by tissues.
Tissue concentrations of allopurinol have not been reported in humans, but it is likely that
allopurinol and oxipurinol will be present in the highest concentrations in the liver and
intestinal mucosa where xanthine oxidase activity is high.

Approximately 20% of the ingested allopurinol is excreted in the faeces in 48 - 72 hours.
Elimination of allopurinol is mainly by metabolic conversion to oxipurinol by xanthine
oxidase and aldehyde oxidase, with less than 10% of the unchanged drug excreted in the urine.
Allopurinol has a plasma half-life of about 1 to 2 hours.
Oxipurinol is a less potent inhibitor of xanthine oxidase than allopurinol, but the plasma half-life of oxipurinol is far more prolonged. Estimates range from 13 to 30 hours in man. Therefore effective inhibition of xanthine oxidase is maintained over a 24 hour period with a single daily dose of Allopurinol. Patients with normal renal function will gradually accumulate oxipurinol until a steady-state plasma oxipurinol concentration is reached. Such patients, taking 300 mg of allopurinol per day will generally have plasma oxipurinol concentrations of 5-10 mg/litre.

Oxipurinol is eliminated unchanged in the urine but has a long elimination half-life because it undergoes tubular reabsorption. Reported values for the elimination half-life range from 13.6 hours to 29 hours. The large discrepancies in these values may be accounted for by variations in study design and/or creatinine clearance in the patients.

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Pharmacokinetics in elderly patients.

The kinetics of the drug are not likely to be altered other than due to deterioration in renal function (see Pharmacokinetics in patients with renal impairment).

5.3 PRECLINICAL SAFETY DATA

Mutagenicity

Cytogenetic studies show that allopurinol does not induce chromosome aberrations in human blood cells in vitro at concentrations up to 100 micrograms/ml and in vivo at doses up to 600 mg/day for mean period of 40 months.

Allopurinol does not produce nitrascos compounds in vitro or affect lymphocyte transformation in vitro.

Evidence from biochemical and other cytological investigations strongly suggests that allopurinol has no deleterious effects on DNA at any stage of the cell cycle and is not mutagenic.

Carcinogenicity

No evidence of carcinogenicity has been found in mice and rats treated with allopurinol for up to 2 years.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose Monohydrate

Colloidal Anhydrous Silica

Maize Starch

Powdered cellulose

Sodium Starch Glycolate (Type A)

Sodium Lauryl Sulphate

Povidone (E1201)

Magnesium Stearate (E572)
6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
24 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 25°C. Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER
Transparent PVC/PVdC/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.
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
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East Sussex
BN22 9AG.
Trading address:
Leeds LS27 OJG
England.

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PL 00289/0952

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16/10/2008

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16/10/2008

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)
PATIENT INFORMATION LEAFLET
PACKAGE LEAFLET: INFORMATION FOR THE USER

Allopurinol 100 & 300 mg Tablets

Read all of this leaflet carefully before you start using this medicine.
• Keep this leaflet. You may need to read it again.
• If you have any further questions, ask your doctor or pharmacist.
• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
• If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

IN THIS LEAFLET:
1. What Allopurinol is and what it is used for
2. Before you take Allopurinol
3. How to take Allopurinol
4. Possible side effects
5. How to store Allopurinol
6. Further information

1. What Allopurinol is and what it is used for

• Allopurinol belongs to a group of medicines called enzyme inhibitors, which act to control the speed at which special chemical changes occur in the body.
• 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.

2. Before you take Allopurinol

Do NOT take Allopurinol:
• If you are allergic (hypersensitive) to Allopurinol or any of the other ingredients of this medicine
• If you are currently having an attack of gout.

Take special care with Allopurinol:
• If you are suffering from, or have previously suffered from any form of liver or kidney disease
• If you are pregnant or trying to become pregnant
• If you are taking other medication to treat gout e.g. probenecid
• If you are taking large doses of aspirin-type drugs (salicylates)
• If you are taking medicines for high blood pressure or heart disease
• If you are taking any diuretics (water tablets)
• If you are taking any medicines used to thin your blood (anticoagulants) e.g. warfarin
• If you are taking mercaptopurine (used to treat leukaemia)
• If you are taking ciclosporin or azathioprine (used to suppress the immune system)
• If you are taking Didanosine (used to treat HIV infections)
• If you are taking chlorpropamide (used to treat diabetes)
• If you are using vidarabine (adenine arabinoside), used in the treatment of herpes
• If you are taking phenytoin (used to treat epilepsy)
• If you are taking theophylline (used for respiratory problems)
• If you are taking the antibiotics amoxicillin or ampicillin
• If you are taking cyclophosphamide or any other anti-cancer medication.

Taking other medicines

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Allopurinol Tablets can cause drowsiness, giddiness and can affect your coordination. If you are affected do not drive, operate machinery or participate in dangerous activities.

Important information about some of the ingredients of Allopurinol

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Allopurinol

Always use Allopurinol exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

You should take your tablets after a meal.

The usual dose is:

Adults (including the elderly):

Starting dose: 100 - 300 mg/day; this may be increased depending on the severity of the condition.

Your dosage may be altered by your doctor if you have reduced kidney and liver function particularly if you are elderly.

Children (under 15 years):

100 - 400 mg/day.

If the daily dose exceeds 300 mg/day, your doctor may prescribe allopurinol in divided doses.
If you take more Allopurinol than you should

If you (or someone else) swallow a lot of the tablets all together, or if you think a child has swallowed any of the tablets, contact your nearest hospital casualty department or your doctor immediately.

If you forget to take Allopurinol

Do not take a double dose to make up for a forgotten dose. You should continue to take these tablets for as long as your doctor tells you to. If you forget to take a tablet, take one as soon as you remember, unless it is nearly time to take the next one. Never take two doses together. Take the remaining doses at the correct time.

Ask your doctor or pharmacist if you have any further questions on the use of this product.

4. Possible side effects

Like all medicines, Allopurinol can cause side effects, although not everybody gets them.

Skin rashes are the most common side effect with allopurinol (affecting fewer than one person in 10 but more than one person in 100). If you suffer from an unexpected skin reaction (possibly in association with fever, swollen glands, joint pain, unusual blistering or bleeding, kidney problems or a sudden onset of fits), you should stop taking Allopurinol and contact your doctor immediately.

A few people may develop a severe allergic reaction to allopurinol, this is an uncommon side effect (affecting less than one person in 100 but more than one person in 1,000) but is a very serious side effect. If you experience any of the following symptoms tell your doctor immediately or go to your nearest hospital casualty department:

- Swelling of the face, hands, lips, tongue or throat
- Difficulty swallowing or breathing
- Sudden wheeziness.

You may occasionally feel sick, but this can usually be avoided by taking allopurinol after meals. Tell your doctor if this problem persists.

If you experience any of the following while you are taking Allopurinol, stop your tablets and tell your doctor as soon as possible:

The following rare side effects have been reported (affecting less than one person in 1,000 but more than one person in 10,000):

- Joint pain or painful swelling in the groin, armpits or neck
- Jaundice (yellowing of the skin and whites of the eyes)
- Nausea and vomiting (in some cases, blood may be present)
- May affect your liver or kidney function.

The following very rare side effects have been reported (affecting less than one person in 10,000):

- High temperature
- Blood in the urine
- High fat levels in the blood
- A general feeling of being unwell
- Weakness, numbness, unsteadiness on feet, inability to move muscles (paralysis) or loss of consciousness
- Headache, dizziness, drowsiness or disturbance of vision
- Chest pain, high blood pressure or a slow pulse
- Retention of fluid leading to swelling (oedema) particularly of the ankles
- Male infertility or erectile dysfunction
- Enlargement of the breasts, in men as well as women
- A change in your normal bowel habit
- A change in taste perception
- Cataracts
- Hair loss or discoloration
- Convulsions, fits or depression
- Feeling thirsty, tired and losing weight (these may be symptoms of diabetes). Your doctor may wish to measure the level of sugar in your blood to decide if this is happening.

Occasionally Allopurinol tablets may affect your blood or lymphatic system. These effects have usually occurred in people with liver or kidney problems. However, tell your doctor as soon as you can if you notice that you are bruising more easily than usual, or if you develop a sore throat or other signs of an infection.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Allopurinol

Keep out of the reach and sight of children. Do not store above 25°C. Store in the original package. Do not use Allopurinol after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further information

What Allopurinol contains:
- Each 100 mg tablet contains 100 mg of Allopurinol
- The other ingredients are lactose monohydrate, colloidal anhydrous silica, maize starch, powdered cellulose, sodium starch glycylolate, sodium lauryl sulphate, povidone and magnesium stearate.

What Allopurinol looks like and contents of the pack:
- Allopurinol 100 mg Tablets contain 100 mg of allopurinol and are white, round, biconvex tablets, debossed “4K1” on one side and plain on the other
- Allopurinol 300 mg Tablets contain 300 mg of allopurinol and are white, round, biconvex tablets, debossed “2K1” on one side and plain on the other
• The product is available in pack sizes of 7, 10, 14, 21, 28, 30, 56, 60, 84, 90, 100, 110, 112, 120, 150, 160 and 168, 250 and 500 tablets.

Marketing Authorisation Holder and Manufacturer

The Marketing Authorisation holder and company responsible for manufacture is TEVA UK Limited, Brampton Road, Hampden Park, Eastbourne, BN22 9AG

OR

The Marketing Authorisation holder is TEVA UK Limited, Brampton Road, Hampden Park, Eastbourne, BN22 9AG and the Company responsible for manufacture is TEVA Pharmaceutical Works Private Limited Company, H-4042 Debrecen, Hungary.

OR

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PACKAGE LEAFLET: INFORMATION FOR THE USER

Allopurinol 200 mg Tablets

Read all of this leaflet carefully before you start using this medicine.
• Keep this leaflet. You may need to read it again.
• If you have any further questions, ask your doctor or pharmacist.
• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
• If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

IN THIS LEAFLET:
1. What Allopurinol is and what it is used for
2. Before you take Allopurinol
3. How to take Allopurinol
4. Possible side effects
5. How to store Allopurinol
6. Further information

1. What Allopurinol is and what it is used for

• Allopurinol belongs to a group of medicines called enzyme inhibitors, which act to control the speed at which chemical changes occur in the body.
• 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.

2. Before you take Allopurinol

Do NOT take Allopurinol:
• If you are allergic (hypersensitive) to Allopurinol or any of the other ingredients of this medicine
• If you are currently having an attack of gout.

Take special care with Allopurinol:
• If you are suffering from, or have previously suffered from any form of liver or kidney disease
• If you are pregnant or trying to become pregnant
• If you are taking other medication to treat gout e.g. probenecid
• If you are taking large doses of aspirin-type drugs (salicylates)
• If you are taking medicines for high blood pressure or heart disease
• If you are taking any diuretics (water tablets)
• If you are taking any medicines used to thin your blood (anticoagulants) e.g. warfarin
If you are taking mercaptopurine (used to treat leukaemia)
- If you are taking ciclosporin or azathioprine (used to suppress the immune system)
- If you are taking Didanosine (used to treat HIV infections)
- If you are taking chlorpropamide (used to treat diabetes)
- If you are using vidarabine (adenine arabinoside), used in the treatment of herpes
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- If you are taking theophylline (used for respiratory problems)
- If you are taking the antibiotics amoxicillin or ampicillin
- If you are taking cyclophosphamide or any other anti-cancer medication.

**Taking other medicines**

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

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Ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines**

Allopurinol Tablets can cause drowsiness, giddiness and can affect your coordination. If you are affected do not drive, operate machinery or participate in dangerous activities.

**Important information about some of the ingredients of Allopurinol**

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

### 3. How to take Allopurinol

Always use Allopurinol exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

You should take your tablets after a meal.

The usual dose is:

**Adults (including the elderly):**

Starting dose: 100 - 300 mg/day, this may be increased depending on the severity of the condition.

Your dosage may be altered by your doctor if you have reduced kidney and liver function particularly if you are elderly.

**Children (under 15 years):**

100 - 400 mg/day.
If the daily dose exceeds 300 mg/day, your doctor may prescribe allopurinol in divided doses.

If you take more Allopurinol than you should

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- Difficulty swallowing or breathing
- Sudden wheeziness.

You may occasionally feel sick, but this can usually be avoided by taking allopurinol after meals. Tell your doctor if this problem persists.

If you experience any of the following while you are taking Allopurinol, stop your tablets and tell your doctor as soon as possible:

The following rare side effects have been reported (affecting less than one person in 1,000 but more than one person in 10,000):

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• Blood in the urine
• High fat levels in the blood
• A general feeling of being unwell
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• Chest pain, high blood pressure or a slow pulse
• Retention of fluid leading to swelling (oedema) particularly of the ankles
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• Enlargement of the breasts, in men as well as women
• A change in your normal bowel habit
• A change in taste perception
• Cataracts
• Hair loss or discolouration
• Convulsions, fits or depression
• Feeling thirsty, tired and losing weight (these may be symptoms of diabetes). Your doctor may wish to measure the level of sugar in your blood to decide if this is happening.

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Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further information

What Allopurinol contains:
• Each 200 mg tablet contains 200 mg of Allopurinol.
• The other ingredients are lactose monohydrate, colloidal anhydrous silica, maize starch, powdered cellulose, sodium starch glycolate, sodium lauryl sulphate, povidone and magnesium stearate.

What Allopurinol looks like and contents of the pack:
• Allopurinol 200 mg Tablets contain 200 mg of allopurinol and are white, round, biconvex tablets, debossed “3K1” on one side and plain on the other
• The product is available in pack sizes* of 7, 10, 14, 21, 28, 30, 50, 56, 60, 84, 90, 100, 110, 112, 120, 150, 160 and 168 tablets.

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