ALLOPURINOL 100MG TABLETS
PL 17907/0139

&

ALLOPURINOL 300MG TABLETS
PL 17907/0140

(ALLOPURINOL)

UKPAR

TABLE OF CONTENTS

Lay Summary Page 2

Scientific discussion Page 3

Steps taken for assessment Page 11

Summary of Product Characteristics Page 12

Product Information Leaflets Page 22

Labelling Page 24
ALLOPURINOL 100MG & 300MG TABLETS
PL 17907/0139-0140
(ALLOPURINOL)

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Bristol Laboratories Limited Marketing Authorisations (licences) for the medicinal products Allopurinol 100mg Tablets (PL 17907/0139) and Allopurinol 300mg Tablets (PL 17907/0140) on 12th March 2009. These are prescription-only medicines (POM).

The active ingredient, allopurinol, is one of a group of medicines known as ‘enzyme inhibitors’ which act to control the speed at which certain chemical changes occur in the body. Allopurinol Tablets are used to prevent gout and other conditions associated with excess uric acid in the body, including kidney stones and certain types of kidney disease.

These applications are duplicates of previously granted applications for Allopurinol Tablets 100mg and 300mg (PL 04416/0132-3), held by Sandoz Limited, and authorised on 3rd December 1987. The test and reference products are identical.

No new or unexpected safety concerns arose from these simple applications and it was therefore judged that the benefits of taking Allopurinol 100mg & 300mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.
ALLOPURINOL 100MG & 300MG TABLETS
PL 17907/0139-0140
(ALLOPURINOL)

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>4</td>
</tr>
<tr>
<td>Pharmaceutical assessment</td>
<td>5</td>
</tr>
<tr>
<td>Preclinical assessment</td>
<td>8</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>9</td>
</tr>
<tr>
<td>Overall conclusion and risk benefit assessment</td>
<td>10</td>
</tr>
</tbody>
</table>
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Bristol Laboratories Limited Marketing Authorisations for the medicinal products Allopurinol 100mg Tablets (PL 17907/0139) and Allopurinol 300mg Tablets (PL 17907/0140) on 12th March 2009. The products are prescription-only medicines.

These applications were submitted as simple abridged ‘informed consent’ applications according to article 10c of Directive 2001/83/EC (as amended), cross-referring to the Marketing Authorisations Allopurinol Tablets 100mg & 300mg (PL 04416/0132-3), granted to Sandoz Limited on 3rd December 1987.

The active ingredient, allopurinol, is a xanthine-oxidase inhibitor. Allopurinol Tablets are indicated for the treatment of gout, primary hyperuricaemia, secondary hyperuricaemia, and for the prophylaxis of uric acid and calcium oxalate stones. In adults, the initial dose is 100mg to 200mg, the maintenance dose is 200mg to 600mg daily, and the maximum single dose is 300mg. The dose should be adjusted by monitoring serum uric acid and/or urinary uric acid levels at appropriate intervals until the desired effect is attained, which may take 1 to 3 weeks.

No new data were submitted nor was it necessary for these simple applications, as the data are identical to that of the previously granted cross-reference products. As the cross-reference products were granted prior to the introduction of current legislation, no PAR was generated for them.

These applications for Allopurinol 100mg & 300mg Tablets were submitted at the same time and were assessed concurrently. Consequently, all sections of this Scientific Discussion refer to both products.
PHARMACEUTICAL ASSESSMENT

LICENCE NUMBERS: PL 17907/0139 & 0140
PROPRIETARY NAME: Allopurinol 100mg & 300mg Tablets
ACTIVE INGREDIENTS: Allopurinol
COMPANY NAME: Bristol Laboratories Limited
E.C. ARTICLE: Article 10c of Directive 2001/83/EC (as amended)
LEGAL STATUS: POM

1. INTRODUCTION

These are simple abridged applications, submitted under Article 10c of Directive 2001/83/EC (as amended) for Allopurinol 100mg & 300mg Tablets. The proposed MA holder is ‘Bristol Laboratories Ltd, Unit 3, Canalside, Northbridge Road, Berkhamsted, Herts, HP4 1EG’.

The reference products are Allopurinol Tablets 100mg and 300mg (PL 04416/0132-0133), granted to Sandoz Limited on 3rd December 1987. The test and reference products are identical.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The proposed names of the products are Allopurinol 100mg Tablets and Allopurinol 300mg Tablets. The products have been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

Each tablet contains 100mg or 300mg of the active ingredient allopurinol. The tablets are marketed in Securitainers with polyethylene closures in pack sizes of 28, 30, 56, 60, 84, 90 and 250 for the 100mg strength (PL 17907/0139), and in pack sizes of 28, 30, 56, 60 and 100 for the 300mg strength (PL 17907/0140). The tablets are additionally marketed in PVC (polyvinylchloride) - aluminium foil blisters. The blisters are packed with the Patient Information Leaflet (PIL) into cardboard outer cartons and presented in pack sizes as described above for the two tablet strengths.

The proposed shelf-life (5 years) and storage conditions (Securitainers: Store in a cool, dry place and protect from light. Blister packs: Do not store above 25°C. Keep the blister in the outer carton to protect from light and moisture.) are consistent with the details registered for the cross-reference products.

2.3 Legal status

The products are available by supply through pharmacies, subject to a medical prescription.

2.4 Marketing authorisation holder / Contact Persons/Company

The proposed Marketing Authorisation holder is ‘Bristol Laboratories Ltd, Unit 3, Canalside, Northbridge Road, Berkhamsted, Herts, HP4 1EG’. The QP responsible for pharmacovigilance is stated and their CV is included.
2.5 Manufacturers
The proposed manufacturing site is consistent with that registered for the cross-reference products and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition
The proposed compositions are consistent with the details registered for the cross-reference products.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference products and the maximum batch sizes are stated.

2.8 Finished product / shelf-life specification
The proposed finished product specifications are in line with the details registered for the cross-reference products.

2.9 Drug substance specification
The proposed drug substance specifications are consistent with the details registered for the cross-reference products.

2.10 TSE Compliance
The magnesium stearate is of vegetable origin. The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

3. EXPERT REPORTS
Satisfactory expert reports and curriculum vitae of experts were provided.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product names. The appearance of the products is consistent with that of the cross-reference products.

5. SUMMARY OF PRODUCT CHARACTERISTICS
The approved SmPCs are consistent with the details registered for the cross-reference products.

6. PATIENT INFORMATION LEAFLET (PIL) / CARTON

PIL
The patient information leaflet has been prepared in the user tested format and in line with the details registered for the cross-reference products. The approved PIL is satisfactory.
Cartons

Colour mock-ups of the labelling have been provided and are satisfactory. The approved artwork is comparable to the artwork registered for the cross-reference products and complies with statutory requirements. In line with current legislation the applicant has included the name of the products in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSIONS

The grounds for these applications are considered adequate. Marketing Authorisations were therefore granted.
PRECLINICAL ASSESSMENT

These applications were submitted as simple abridged applications according to article 10c of Directive 2001/83/EC (as amended).

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

These applications were submitted as simple abridged applications according to article 10c of Directive 2001/83/EC (as amended).

As these are duplicate applications for PLs 04416/0132 and 0133, no new clinical data have been supplied with the applications, and none are required for applications of this type.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data for these applications are consistent with that previously assessed for the cross-reference products and as such has been judged to be satisfactory.

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

EFFICACY
Medicinal products containing allopurinol have been available in the UK for much more than ten years. Their use is well established with recognised efficacy and acceptable safety.

These applications are identical to the cross-reference products Allopurinol Tablets 100mg and 300mg (PL 04416/0132-3, Sandoz Limited).

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The approved SmPCs, PIL and labelling are satisfactory and consistent with that for the cross-reference products.

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

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant’s products are identical to the cross-reference products. Extensive clinical experience with allopurinol is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.
ALLOPURINOL 100MG & 300MG TABLETS
PL 17907/0139-0140
(ALLOPURINOL)

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the marketing authorisation applications on 24th March 2006

2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 5th May 2006

3 Following assessment of the application the MHRA requested further information relating to the quality dossier on 13th July 2006 and 29th August 2007

4 The applicant responded to the MHRA’s request, providing further information for the quality sections on 30th May 2007 and 31st October 2008 respectively

5 The applications were determined on 10th March 2009 and granted on 12th March 2009
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Allopurinol 100mg Tablets (PL 17907/0139) is as follows:

1 NAME OF THE MEDICINAL PRODUCT
Allopurinol 100mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains allopurinol 100mg
Also contains Lactose monohydrate 138.500mg
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablet.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Adults:
The initial dose is 100mg to 200mg. The maintenance dose is 200mg to 600mg daily. Maximum single dose 300mg. It has rarely been found necessary to exceed 900mg per day. The dose should be adjusted by monitoring serum uric acid and/or urinary uric acid levels at appropriate intervals until the desired effect is attained, which may take 1 to 3 weeks.

Elderly patients:
The dose should be maintained at the minimum necessary to maintain normal serum and urinary urate levels.

Children:
10mg to 20mg/kg bodyweight/day. Use in children is mainly indicated in malignant conditions, especially leukaemia and certain enzyme disorders, for example Lesch-Nyhan syndrome.

Patients with hepatic disease:
The dosage of allopurinol should be reduced in patients with hepatic disease.

Dose recommendations in impaired renal function:
Allopurinol and its metabolites are excreted via the kidney. Impairment of renal function may lead to retention of the drug and its metabolites with consequent prolongation of action.
The amount and frequency of the dosage may require reduction as indicated by monitoring serum uric acid levels. The following schedule is provided for guidance in adults.

<table>
<thead>
<tr>
<th>CREATININE CLEARANCE</th>
<th>DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than 20ml/minute</td>
<td>Standard dose</td>
</tr>
<tr>
<td>10ml to 20ml/minute</td>
<td>100mg to 200mg/day</td>
</tr>
<tr>
<td>2ml to 10ml/minute</td>
<td>100mg/day or at longer intervals</td>
</tr>
</tbody>
</table>
Dose recommendations in renal dialysis:
Allopurinal and its metabolites are removed by renal dialysis. If frequent dialysis is required an alternative schedule of 300mg to 400mg allopurinal after each dialysis with none in the interim should be considered.

Initiation of therapy:
In the early stages of treatment with allopurinol, as with uricosuric agents, an acute attack of gouty arthritis may be precipitated. Therefore, it is advisable to give a prophylactic dose of a suitable anti-inflammatory agent or colchicine (0.5mg, 3 times a day) for at least 1 month.

Use with uricosurics:
Allopurinol does not interfere with the action of uricosuric agents. When changing from uricosuric therapy to allopurinol, 1 to 3 weeks overlap of treatment is recommended to ensure a continuous hypouricaemic effect.

Use in neoplasia:
When giving allopurinol to prevent uric acid nephropathy in neoplastic conditions, it is advisable to start treatment with Allopurinol before cytotoxic therapy.

Method of administration: Oral.

4.3 CONTRAINDICATIONS
Acute gout. Known intolerance to allopurinol.
These tablets contain lactose and patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
The dosage of allopurinol should be reduced in patients with renal or hepatic diseases.
Use in the elderly: the dose should be maintained at the minimum necessary to maintain serum and urinary urate levels.
Allopurinol should be withdrawn immediately when a skin rash or other evidence of sensitivity occurs. Reduced doses should be used in patients with hepatic or renal impairment. Patients under treatment for hypertension or cardiac insufficiency, for example with diuretics or ACE inhibitors, may have some concomitant impairment of renal function and allopurinol should be used with care in this group.
Asymptomatic hyperuricaemia per se is generally not considered an indication for use of allopurinol. Fluid and dietary modification with management of the underlying cause may correct the condition.
Acute gouty attacks: Allopurinol treatment should not be started until an acute attack of gout has been completely subsided, as further attacks may be precipitated.
In the early stages of treatment with allopurinol, as with uricosuric agents, an acute attack of gouty arthritis may be precipitated. Therefore it is advisable to give prophylaxis with a suitable anti-inflammatory agent or colchicines for at least one month. The literature should be consulted for details of appropriate dosage and precautions and warnings.
If acute attacks develop in patients receiving allopurinol, treatment should continue at the same dosage while the attack is treated with a suitable anti-inflammatory agent.
Xanthine deposition: In conditions where the rate of urate formation is greatly increased (e.g. malignant disease and its treatment, Lesch-Nyhan syndrome) the absolute concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract. This risk may be minimised by adequate hydration to achieve optimal urine dilution.
Impaction of uric acid renal stones: Adequate therapy with allopurinol will lead to dissolution of large uric acid renal pelvic stones, with the remote possibility of impaction in the ureter.
4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

If allopurinol is given concomitantly with chlorpropamide when renal function is poor, there may be an increased risk of prolonged hypoglycaemia activity.

ACE Inhibitors: increased risk of toxicity when allopurinol given with captopril especially in renal impairment.

Antibacterials: increased risk of rash when allopurinol given with amoxicillin or ampicillin.

Anticoagulants: allopurinol possibly enhances anticoagulant effect of coumarins.

Antivirals: allopurinol possibly increases plasma concentration of didanosine.

Ciclosporin: allopurinol possibly increases plasma concentration of ciclosporin (risk of nephrotoxicity)

Cytotoxics: allopurinol enhances effects and increase toxicity of azathioprine and mercaptopurine (reduce dose of azathioprine and mercaptopurine) avoided by the manufacturer of capecitabine.

Diuretics: Increased risk of hypersensitivity when allopurinol given with thiazides and related diuretics especially in renal impairment.

Theophylline: allopurinol possibly increases plasma concentrations of theophylline,

4.6 PREGNANCY AND LACTATION

High dose intraperitoneal Allopurinol in mice has been associated with foetal abnormalities, but extensive animal studies with oral Allopurinol have shown none. In human pregnancy, there is no evidence that Allopurinol taken orally causes foetal abnormalities, however, as with all drugs, due caution should be exercised in the use of Allopurinol in pregnancy.

Allopurinol is present in breast milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Nausea and drowsiness has been reported, therefore caution should be exercised.

4.8 UNDESIRABLE EFFECTS

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

Skin reactions are the most common reactions and may occur at any time during treatment. They may be pruritic, maculopapular, sometimes scaly or 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 low dose (eg 50mg/day) which may be gradually increased. If the rash recurs, allopurinol should be permanently withdrawn.

Generalised hypersensitivity: skin reactions associated with exfoliation, fever, lymphadenopathy, arthralgia and/or eosinophilia resembling Stevens-Johnson and/or Lyell’s syndrome occur rarely. Associated vasculitis and tissue response may be manifested in various ways including hepatitis, interstitial nephritis and, very rarely, epilepsy. If such reactions do occur, it may be at any time during treatment. Allopurinol should then be withdrawn immediately and permanently. Corticosteroids may be beneficial in overcoming them. When generalised hypersensitivity reactions have occurred, renal and/or hepatic disorder has usually been present particularly when the outcome has been fatal.

Granulomatous hepatitis: very rarely granulomatous hepatitis, without overt evidence of more generalised hypersensitivity has been described. It appears to be reversible on withdrawal of allopurinol.
Gastrointestinal disorder: 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. Recurrent haematemesis has been reported as an extremely rare event, as has steatorrhoea.

Blood and lymphatic system: there have been occasional reports of transient reduction in the numbers of circulating formed elements of the blood, usually in association with renal and/or hepatic disorder. The clinical significance has yet to be demonstrated.

Miscellaneous: exacerbation of acute gouty attacks may occur in the early stages of hypouricaemic therapy, see sub-section 4.2 Posology and Method of Administration. In those conditions where the body’s miscible urate pool is greatly increased (e.g., malignant disease and its treatment, Lesch-Nyhan syndrome), the rise in the xanthine concentration resulting from the action of allopurinol may lead to tissue deposits of xanthine. Fluid intake should ensure adequate urinary output. Xanthine crystals have been seen in the muscle tissue of patients receiving allopurinol, but this appears to have no clinical significance.

The following complaints have been reported occasionally, but do not appear to have clear cause and effect relationship with allopurinol: fever, general malaise, asthenia, headache, vertigo, ataxia, somnolence, coma, depression, paralysis, paraesthesias, neuropathy, visual disorder, cataract, macular changes, taste perversion, stomatitis, changed bowel habit, infertility, impotence, nocturnal emission, diabetes mellitus, hyperlipaemia, furunculosis, alopecia, discoloured hair, angina, hypertension, bradycardia, oedema, uraemia and haematuria.

4.9 OVERDOSE

No reports of overdosage or acute intoxication are available. The most likely reaction would be gastro-intestinal tolerance. Massive absorption of allopurinol may lead to considerable inhibition of xanthine oxidase activity, which should have no untoward effects unless 6-mercaptopurine, adenine, arabinoside, and/or azathioprine is being taken concurrently. In this case, the risk of increased activity of these drugs must be recognised. Adequate hydration to maintain optimum diuresis facilitates excretion of allopurinol and its metabolites. Dialysis may be resorted to if considered necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Allopurinol is a xanthine-oxidase inhibitor.

ATC CODE: M04AA01

5.2 PHARMACOKINETIC PROPERTIES

The following results (mean ± SE) were obtained in a bioavailability study with Allopurinol Tablets 300mg.

- $T_{\text{max}} = 2.2 \pm 0.2 \text{ hours}$
- Peak = $924 \pm 120.94 \text{ µg/dl}$
- $T_{1/2} = 3.291 \pm 0.224 \text{ hours}$
- $\text{AUC}_{24} = 6810.89 \pm 659.41 \text{ µg/dl/hours}$
- Mean concentration = $283.79 \pm 27.476 \text{ µg/dl}$

5.3 PRECLINICAL SAFETY DATA

There are no preclinical safety data of relevance to the prescriber.
6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
Lactose
Maize starch
Povidone
Magnesium stearate

6.2 INCOMPATIBILITIES
Not known.

6.3 SHELF LIFE
60 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Securitainers: Store in a cool, dry place and protect from light.
Blisters packs: Do not store above 25°C. Keep the blister in the outer carton to protect from light and moisture.

6.5 NATURE AND CONTENTS OF CONTAINER
Securitainer with polyethylene closures.
Blisters strips comprising 250μm PVC film and 20μm Aluminium foil packed into an outer carton.
Pack sizes: 28, 30, 56, 60, 84, 90 and 250.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Not applicable.

7 MARKETING AUTHORISATION HOLDER
Bristol Laboratories Ltd
Unit 3, Canalside
Northbridge Road
Berkhamsted
Herts
HP4 1EG

8 MARKETING AUTHORISATION NUMBER(S)
PL 17907/0139

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
12/03/2009

10 DATE OF REVISION OF THE TEXT
12/03/2009
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Allopurinol 300mg Tablets (PL 17907/0140) is as follows:

1 NAME OF THE MEDICINAL PRODUCT
Allopurinol 300mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains allopurinol 300mg
Also contains Lactose monohydrate 70.080mg
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablet.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Adults:
The initial dose is 100mg to 200mg. The maintenance dose is 200mg to 600mg daily. Maximum single dose 300mg. It has rarely been found necessary to exceed 900mg per day. The dose should be adjusted by monitoring serum uric acid and/or urinary uric acid levels at appropriate intervals until the desired effect is attained, which may take 1 to 3 weeks.

Elderly patients:
The dose should be maintained at the minimum necessary to maintain normal serum and urinary urate levels.

Children:
10mg to 20mg/kg bodyweight/day. Use in children is mainly indicated in malignant conditions, especially leukaemia and certain enzyme disorders, for example Lesch-Nyhan syndrome.

Patients with hepatic disease:
The dosage of allopurinol should be reduced in patients with hepatic disease.

Dose recommendations in impaired renal function:
Allopurinol and its metabolites are excreted via the kidney. Impairment of renal function may lead to retention of the drug and its metabolites with consequent prolongation of action.
The amount and frequency of the dosage may require reduction as indicated by monitoring serum uric acid levels. The following schedule is provided for guidance in adults.

<table>
<thead>
<tr>
<th>CREATININE CLEARANCE</th>
<th>DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than 20ml/minute</td>
<td>Standard dose</td>
</tr>
<tr>
<td>10ml to 20ml/minute</td>
<td>100mg to 200mg/day</td>
</tr>
<tr>
<td>2ml to 10ml/minute</td>
<td>100mg/day or at longer intervals</td>
</tr>
</tbody>
</table>
Dose recommendations in renal dialysis:
Allopurinol and its metabolites are removed by renal dialysis. If frequent dialysis is required an alternative schedule of 300mg to 400mg allopurinal after each dialysis with none in the interim should be considered.

Initiation of therapy:
In the early stages of treatment with allopurinol, as with uricosuric agents, an acute attack of gouty arthritis may be precipitated. Therefore, it is advisable to give a prophylactic dose of a suitable anti-inflammatory agent or colchicine (0.5mg, 3 times a day) for at least 1 month.

Use with uricosurics:
Allopurinol does not interfere with the action of uricosuric agents. When changing from uricosuric therapy to allopurinol, 1 to 3 weeks overlap of treatment is recommended to ensure a continuous hypouricaemic effect.

Use in neoplasia:
When giving allopurinol to prevent uric acid nephropathy in neoplastic conditions, it is advisable to start treatment with Allopurinol before cytotoxic therapy.

Method of administration: Oral.

4.3 CONTRAINDICATIONS
Acute gout. Known intolerance to allopurinol.
These tablets contain lactose and patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
The dosage of allopurinol should be reduced in patients with renal or hepatic diseases.

Use in the elderly: the dose should be maintained at the minimum necessary to maintain serum and urinary urate levels.

Allopurinol should be withdrawn immediately when a skin rash or other evidence of sensitivity occurs. Reduced doses should be used in patients with hepatic or renal impairment. Patients under treatment for hypertension or cardiac insufficiency, for example with diuretics or ACE inhibitors, may have some concomitant impairment of renal function and allopurinol should be used with care in this group.

Asymptomatic hyperuricaemia per se is generally not considered an indication for use of allopurinol. Fluid and dietary modification with management of the underlying cause may correct the condition.

Acute gouty attacks: Allopurinol treatment should not be started until an acute attack of gout has been completely subsided, as further attacks may be precipitated.

In the early stages of treatment with allopurinol, as with uricosuric agents, an acute attack of gouty arthritis may be precipitated. Therefore it is advisable to give prophylaxis with a suitable anti-inflammatory agent or colchicines for at least one month. The literature should be consulted for details of appropriate dosage and precautions and warnings.

If acute attacks develop in patients receiving allopurinol, treatment should continue at the same dosage while the attack is treated with a suitable anti-inflammatory agent.

Xanthine deposition: In conditions where the rate of urate formation is greatly increased (e.g. malignant disease and its treatment, Lesch-Nyhan syndrome) the absolute concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract. This risk may be minimised by adequate hydration to achieve optimal urine dilution.

Impaction of uric acid renal stones: Adequate therapy with allopurinol will lead to dissolution of large uric acid renal pelvic stones, with the remote possibility of impaction in the ureter.
4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

If allopurinol is given concomitantly with chlorpropamide when renal function is poor, there may be an increased risk of prolonged hypoglycaemia activity.

ACE Inhibitors: increased risk of toxicity when allopurinol given with captopril especially in renal impairment.

Antibacterials: increased risk of rash when allopurinol give with amoxicillin or ampicillin.

Anticoagulants: allopurinol possibly enhances anticoagulant effect of coumarins.

Antivirals: allopurinol possibly increases plasma concentration of didanosine.

Ciclosporin: allopurinol possibly increases plasma concentration of ciclosporin (risk of nephrotoxicity).

Cytotoxics: allopurinol enhances effects and increase toxicity of azathioprine and mercaptopurine (reduce dose of azathioprine and mercaptopurine) avoidance of allopurinol advised by the manufacturer of capecitabine.

Diuretics: Increased risk of hypersensitivity when allopurinol given with thiazides and related diuretics especially in renal impairment.

Theophylline: allopurinol possibly increases plasma concentrations of theophylline.

4.6 PREGNANCY AND LACTATION

High dose intraperitoneal Allopurinol in mice has been associated with foetal abnormalities, but extensive animal studies with oral Allopurinol have shown none. In human pregnancy, there is no evidence that Allopurinol taken orally causes foetal abnormalities, however, as with all drugs, due caution should be exercised in the use of Allopurinol in pregnancy.

Allopurinol is present in breast milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Nausea and drowsiness has been reported, therefore caution should be exercised.

4.8 UNDESIRABLE EFFECTS

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

Skin reactions are the most common reactions and may occur at any time during treatment. They may be pruritic, maculopapular, sometimes scaly or 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 low dose (eg 50mg/day) which may be gradually increased. If the rash recurs, allopurinol should be permanently withdrawn.

Generalised hypersensitivity: skin reactions associated with exfoliation, fever, lymphadenopathy, arthralgia and/or eosinophilia resembling Stevens-Johnson and/or Lyell’s syndrome occur rarely. Associated vasculitis and tissue response may be manifested in various ways including hepatitis, interstitial nephritis and, very rarely, epilepsy. If such reactions do occur, it may be at any time during treatment. Allopurinol should then be withdrawn immediately and permanently. Corticosteroids may be beneficial in overcoming them. When generalised hypersensitivity reactions have occurred, renal and/or hepatic disorder has usually been present particularly when the outcome has been fatal.

Granulomatous hepatitis: very rarely granulomatous hepatitis, without overt evidence of more generalised hypersensitivity has been described. It appears to be reversible on withdrawal of allopurinol.
Gastrointestinal disorder: 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. Recurrent haematemesis has been reported as an extremely rare event, as has steatorrhoea.

Blood and lymphatic system: there have been occasional reports of transient reduction in the numbers of circulating formed elements of the blood, usually in association with renal and/or hepatic disorder. The clinical significance has yet to be demonstrated.

Miscellaneous: exacerbation of acute gouty attacks may occur in the early stages of hypouricaemic therapy, see sub-section 4.2 Posology and Method of Administration. In those conditions where the body’s miscible urate pool is greatly increased (eg malignant disease and its treatment; Lesch-Nyhan syndrome), the rise in the xanthine concentration resulting from the action of allopurinol may lead to tissue deposits of xanthine. Fluid intake should ensure adequate urinary output. Xanthine crystals have been seen in the muscle tissue of patients receiving allopurinol, but this appears to have no clinical significance.

The following complaints have been reported occasionally, but do not appear to have clear cause and effect relationship with allopurinol: fever, general malaise, asthenia, headache, vertigo, ataxia, somnolence, coma, depression, paralysis, paraesthesiae, neuropathy, visual disorder, cataract, macular changes, taste perversion, stomatitis, changed bowel habit, infertility, impotence, nocturnal emission, diabetes mellitus, hyperlipaemia, furunculosis, alopecia, discoloured hair, angina, hypertension, bradycardia, oedema, uraemia and haematuria.

4.9 OVERDOSE

No reports of overdosage or acute intoxication are available. The most likely reaction would be gastro-intestinal tolerance. Massive absorption of allopurinol may lead to considerable inhibition of xanthine oxidase activity, which should have no untoward effects unless 6-mercaptopurine, adenosine, arabinoside, and/or azathioprine is being taken concurrently. In this case, the risk of increased activity of these drugs must be recognised. Adequate hydration to maintain optimum diuresis facilitates excretion of allopurinol and its metabolites. Dialysis may be resorted to if considered necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Allopurinol is a xanthine-oxidase inhibitor.

ATC CODE: M04AA01

5.2 PHARMACOKINETIC PROPERTIES

The following results (mean \( \pm \) SE) were obtained in a bioavailability study with Allopurinol Tablets 300mg.

- \( T_{\text{max}} \) = 2.2 \( \pm \) 0.2 hours
- Peak = 924 \± 120.94 \( \mu \)g/dl
- \( T_{1/2} \) = 3.291 \( \pm \) 0.224 hours
- \( \text{AUC}_{24} \) = 6810.89 \( \pm \) 659.41 \( \mu \)g/dl/hours
- Mean concentration = 283.79 \( \pm \) 27.476 \( \mu \)g/dl

5.3 PRECLINICAL SAFETY DATA

There are no preclinical safety data of relevance to the prescriber.
6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Lactose
Maize starch
Povidone
Magnesium stearate
Sodium starch glycolate

6.2 INCOMPATIBILITIES
Not known.

6.3 SHELF LIFE
60 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Securitainers: Store in a cool, dry place and protect from light.
Blisters packs: Do not store above 25°C. Keep the blister in the outer carton to protect from light and moisture.

6.5 NATURE AND CONTENTS OF CONTAINER
Blisters strips comprising 250μm PVC film and 20μm Aluminium foil packed into an outer carton.
Pack sizes: 28, 30, 56, 60, 100
Securitainer with polyethylene closures.
Pack sizes: 28, 30, 56, 60 and 100.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Not applicable.

7 MARKETING AUTHORISATION HOLDER
Bristol Laboratories Ltd
Unit 3, Canalside
Northbridge Road
Berkhamsted
Herts
HP4 1EG

8 MARKETING AUTHORISATION NUMBER(S)
PL 17907/0140

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
12/03/2009

10 DATE OF REVISION OF THE TEXT
12/03/2009
PATIENT INFORMATION LEAFLET

UKPAR Allopurinol 100mg & 300mg Tablets
PL 17907/0139-140

Take special care with this medicine:
Check with your doctor or pharmacist before taking your medicine if:
- you have problems with your liver or kidneys. Your doctor may give you a lower dose or ask you to take it less often than each day. They will also monitor you more closely.
- you have heart problems or high blood pressure
- you are currently having an attack of gout.
- if you are not sure if any of the above applies to you, talk to your doctor or pharmacist before taking this medicine.

Taking other medicines
Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed, for example, herbal remedies and health supplements from a pharmacy, supermarket or health food shop, as they may interact with this medicine.

It is important to let your doctor know if you are taking any of the following medicines:
- aspirin
- theophylline, used for breathing problems
- antibiotics
- cidanosine, used to treat HIV infection
- medicines used to reduce your immune response (immunosuppressants) such as azathioprine and ciclosporin
- medicines used to treat diabetes such as glibenclamide
- medicines for heart problems or high blood pressure such as 'ACE inhibitors' or water tablets (diuretics)
- medicines used to thin your blood (anticoagulants), such as warfarin
- any other medicine to treat gout

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

Driving and Using Machines
- If you experience dizziness, weakness, drowsiness or problems with your eyesight while taking allopurinol, DO NOT drive or operate machines.

Important information about some of the ingredients of these Tablets
- This medicine contains LACTOSE.
- Allopurinol 100mg Tablets: Each 100mg tablet contains 138.5mg of lactose.
- Allopurinol 300mg Tablets: Each 300mg tablet contains 70.08mg of lactose.
- If you have been previously told by your doctor that you have intolerance to some sugars (such as lactose), contact your doctor or pharmacist before taking this medicine.
- Allopurinol tablets 300mg also contains SODIUM STARCH GYCOLATE. Sodium may be harmful to people on a low sodium diet.

3. How to take this medicine
- Always take this medicine exactly as prescribed by your doctor. You should check with your doctor or pharmacist if you are unsure.
- The whole tablets should be swallowed with plenty of water. If Allopurinol Tablets make you feel sick or vomit, this may be avoided by taking the tablets after meals.
- Check the label to see how often you should take your tablets.
- If you are changing from an alternative uricosuric medicine to allopurinol, 1 to 3 weeks overlap of treatment is recommended.
- You may also be prescribed an anti-inflammatory pain killer or colchicine over the first few weeks in case you get an acute attack of gouty arthritis.

Dosage
Adults and the elderly:
- The initial starting dose is 100mg to 200mg. Your doctor will monitor the uric acid levels in your blood or urine at regular intervals, and will adjust the dose to suit you, as necessary.
- The maintenance dose is usually 200mg to 600mg daily.
- The maximum single dose is 300mg.
- It is unlikely that you will be prescribed more than
UKPAR Allopurinol 100mg & 300mg Tablets

PL 17907/0139-140

900mg per day.
- Elderly patients will be given the minimum necessary dose to maintain uric acid levels in the blood and urine.

Children:
- The dose is 10mg to 20mg per kilogram of the child's weight, per day.

If you have liver or kidney problems:
- Patients with liver disease or kidney problems will be given a reduced dosage.
- If you are having frequent kidney dialysis, you may be given 300mg to 400mg of Allopurinol after each dialysis instead of the usual dosage schedules.

If you take more Allopurinol Tablets than you should:
- If you have accidentally taken one extra dose, this is unlikely to be a cause for concern. However if you or someone else has taken a large overdose, contact your nearest hospital A&E (casually department) or your doctor immediately. Take your medicine in its original packaging with you in order to enable the doctor to identify your medication easily.

If you forget to take Allopurinol Tablets:
- If you have forgotten to take your medicine and your next dose is not due for another 12 hours or more, take a dose now and take the next one on time. Otherwise, skip the missed dose, and take your next dose at the correct time. If you are concerned, consult your doctor or pharmacist.

DO NOT TAKE A DOUBLE DOSE TO MAKE UP FOR A FORGOTTEN DOSE.

If you stop taking Allopurinol Tablets:
- Do not suddenly stop taking these tablets without talking to your doctor. Your symptoms may recur if you stop them suddenly. Treatment should continue for as long as your doctor feels it is needed. If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible Side Effects

Like all other medicines, Allopurinol Tablets may cause side effects, although not everybody gets them.

STOP TAKING this medicine and tell your doctor immediately if you suffer from any of the following:
- Sudden wheeziness and chest pain or dizziness
- Swelling of eyelids, face or lips
- Skin rash, flaking skin, boils, red spots or hives (skin bumps)
- Collapse

The above symptoms may mean that you are allergic to Allopurinol. Do not take more tablets unless your doctor tells you to do so.

If you experience any of the following rare side effects, tell your doctor as soon as possible:
- Gastrointestinal: feeling or being sick, vomiting blood, diarrhoea, changes in bowel habits, swollen mouth and changes in taste
- Nervous system: headache, general tiredness, dizziness, depression, coma, nerve disorders including lack of muscle control, paralysis, weakness and numbness, "pins and needles", sleepiness
- Heart: chest pain (angina), slow heart beat, oedema (water retention) particularly of the ankles, high blood pressure
- Other effects: fever, worsening of acute gout attacks, cataract, diabetes, hair loss, changes in hair colour, boils, changes in blood chemistry and blood cells, disturbances of vision, difficulty maintaining an erection, "wet dreams", infertility, blood in the urine, high levels of fat or urea in the blood.

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 these side effects gets serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

5. How to store this medicine

- Keep the medicines in a safe place where children can not see or reach it.
- Do not use Allopurinol Tablets after the expiry date shown on the label or carton after EXP.
- The expiry date refers to the last day of that month.
- Secure containers: Store in a cool, dry place and protect from light.
- Blister packs: Do not store above 25°C. Keep the blister in the outer carton to protect from light and moisture.
- If you have any leftover tablets take them back to your pharmacist for safe disposal.

6. Further Information

What Allopurinol Tablets contain
- Each tablet contains Allopurinol as the active ingredient
- Each Allopurinol 100mg Tablet contains 100mg of Allopurinol
- Each Allopurinol 300mg Tablet contains 300mg of Allopurinol
- The other ingredients are: lactose, maize starch, povidone and magnesium stearate. The 300mg tablets also contain sodium starch glycolate.

What Allopurinol Tablets look like and contents of the pack:
- Allopurinol 100mg Tablets come in packs of 28, 30, 56, 60, 84, 90 and 250
- Allopurinol 300mg Tablets come in packs of 28, 30, 56, 60, and 100

Marketing Authorisation Holder and Batch Release Manufacturer:
Name and address: Bristol Laboratories Ltd, Unit 3, Canalside, Northbridge Road, Berkhamsted, Hertfordshire, United Kingdom, HP4 1EG.
Telephone: 01442 200922
Fax: 01442 873717
Email: info@bristol-labs.co.uk

This leaflet was last approved in February 2009
To request a copy of this leaflet in Braille, large print or audio format, contact the licence holder at the address (or telephone, fax, email) above.
UKPAR Allopurinol 100mg & 300mg Tablets

LABELLING

Allopurinol 100mg Tablets

Carton for blisters

Braille

Securitainer label
Allopurinol 300mg Tablets
Carton for blisters

Each tablet contains 300 mg of allopurinol BP, as the active ingredient. Other ingredients include lactose, PEG 400, and silicon dioxide. For oral administration. Use as directed by the physician. Please read the enclosed leaflet. Store in a cool dry place and protect from light. Keep the container tightly closed.

KEEP ALL MEDICINES OUT OF THE REACH AND SIGHT OF CHILDREN.