TABLE OF CONTENTS

Lay Summary .................................................. Page 2
Scientific discussion .......................................... Page 3
Steps taken for assessment .................................. Page 14
Steps taken after authorisation – summary ............... Page 15
Summary of Product Characteristics ....................... 
Product Information Leaflet ............................... 
Labelling .........................................................
BENDROFLUMETHIAZIDE 2.5MG TABLETS  
PL 17907/0082  

BENDROFLUMETHIAZIDE 5MG TABLETS  
PL 17907/0083  

LAY SUMMARY  
The MHRA today granted Bristol Laboratories Limited Marketing Authorisations (licences) for the medicinal products Bendroflumethiazide 2.5mg Tablets (PL 17907/0082) and Bendroflumethiazide 5mg Tablets (PL 17907/0083). These are prescription-only medicines (POM) for the treatment of oedema and hypertension. Bendroflumethiazide tablets may also be used to suppress lactation.  

Bendroflumethiazide tablets contain the active ingredient bendroflumethiazide. These tablets belong to a group of medicines called thiazide diuretics.  

The test product was considered the same as the original products Aprinox 2.5mg and 5mg Tablets Waymade Plc (previously Boots Plc) based on the bioequivalence study submitted and no new safety issues arose as a result of this study. No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Bendroflumethiazide 2.5mg and 5mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.
BENDROFLUMETHIAZIDE 2.5MG TABLETS
PL 17907/0082

BENDROFLUMETHIAZIDE 5MG TABLETS
PL 17907/0083

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 13
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Bendroflumethiazide 2.5mg Tablets (PL 17907/0082) and Bendroflumethiazide 5mg Tablets (PL 17907/0083) on 1st February 2007. The products are prescription-only medicines.

These are two strengths of bendroflumethiazide tablets, submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming essential similarity to the original products Aprinox 2.5mg and 5mg Tablets (Waymade Plc). The reference products have been authorised in the UK since September 1986 and so the 10-year period of data exclusivity has expired.

Bendroflumethiazide is a thiazide diuretic which reduces the absorption of electrolytes from the renal tubules, thereby increasing the excretion of sodium and chloride ions, and consequently of water. The excretion of other electrolytes, notably potassium and magnesium, is also increased.

Bendroflumethiazide 2.5mg and 5mg Tablets are indicated for the treatment of oedema and hypertension. Bendroflumethiazide tablets may also be used to suppress lactation.

These applications were submitted at the same time and both depend on the bioequivalence study comparing the applicant’s 2.5mg and 5mg products with the reference product Aprinox 2.5mg and 5mg tablets (Waymade Plc). Consequently, all sections of this scientific discussion refer to both products.
### PHARMACEUTICAL ASSESSMENT

#### DRUG SUBSTANCE

**Bendroflumethiazide**

INN: Bendroflumethiazide  
Chemical Name: 3-benzyl-3,4-dihydro-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7 sulphonamide 1,1-dioxide

CAS No: 73-4803  

![Chemical Structure](image)

Molecular formula: C_{15}H_{14}F_{3}N_{3}O_{4}S_{2}  
Molecular weight: 421.4

Physical form: A white or almost white, crystalline powder

Solubility: Practically insoluble in water, freely soluble in acetone, soluble in alcohol.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active bendroflumethiazide is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Acceptable justification of the proposed specifications are provided.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been provided for both manufacturers of active.

#### DRUG PRODUCT

Other ingredients
Other ingredients consist of pharmaceutical excipients, namely lactose anhydrous, pregelatinised starch, talc and stearic acid. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeial monograph. Satisfactory certificates of analysis have been provided for all excipients.

The only excipient used that contains material of animal or human origin is lactose anhydrous. The applicant has provided a declaration that milk used in the production of lactose anhydrous is sourced from healthy animals under the same conditions as that for human consumption. There were no novel excipients used and no overages.

**Dissolution and impurity profiles**
Dissolution and impurity profiles for both strengths of drug product were found to be similar to those for the reference products.

**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 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**
Product is packaged in either high density polyethylene (HDPE) containers or blisters composed of aluminium and polyvinyl chloride (PVC). Specifications and certificates of analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food. The product is packaged in sizes of 50, 100, 250 and 500 or 1000 tablets for the HDPE containers and sizes of 14, 28, 56 and 84 tablets for the aluminium/PVC blister packs.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. The shelf-life was supported by evidence of stability under appropriate storage conditions compliant with European standards.

All results obtained were within specification

**Conclusion**
It is recommended that Marketing Authorisations are granted for these applications.
The requirements for essential similarity of the proposed and reference products have been met with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.
**PRECLINICAL ASSESSMENT**

These applications for generic products claim essential similarity to Aprinox 2.5mg and 5mg Tablets (Waymade Plc), which have been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications and none are required for applications of this type.
INTRODUCTION
These are two national, abridged, non-committee applications for two doses of a thiazide diuretic, bendroflumethiazide claiming essential similarity to innovator product Aprinox from M/s Waymade Plc (Previously Boots Plc). Aprinox was first authorised in the UK in two strengths, 2.5 mg and 5 mg in 1986. Apparently, for several years, the innovator has not marketed the 5mg strength for commercial reasons. There are several other authorised generic preparations of Bendroflumethiazide at 2.5 and 5mg doses in the UK however. The applicant supports the claim for essential similarity with one bioequivalence study in this dossier.

The dossier is presented in the CTD with module 5 containing the bioequivalence study and other literature references as deemed relevant by the applicant.

GCP aspects
There are no obvious GCP concerns with the MAA or the biostudy.

Therapeutic Class
A thiazide diuretic. ATC Code: CO3A A01.

BACKGROUND & REGULATORY STATUS
Bendroflumethiazide is a thiazide diuretic first authorised in the UK formulated by Waymade Laboratories in 1986. Two strengths were authorised (2.5 and 5mg) for use in hypertension, heart failure, oedema of other causes and to suppress lactation (5mg strength). For commercial reasons, the MAH (Boots Plc / Ms Waymade Plc) has opted not to market the 5mg strength, while the lower strength has been fairly commonly used for the above indications although more recently, better diuretics have replaced this agent.

The current formulation has not been marketed in any other member state in the EU or outside of the EU. There have been no refusals/ suspensions or revoked licences.

INDICATIONS
The applicant seeks the following indications:

THERAPEUTIC INDICATIONS
For the treatment of oedema and hypertension. Bendroflumethiazide tablets may also be used to suppress lactation.

DOSE AND DOSE REGIMEN
The applicant proposes the following;

POSOLOGY AND METHOD OF ADMINISTRATION
For oral administration.
Adults:
Oedema
Initially, 5-10 mg in the morning, daily or on alternate days; maintenance dose 5-10 mg one to three times weekly.

Hypertension
The usual dose is 2.5 mg taken in the morning. Higher doses are rarely necessary.

Suppression of lactation
5 mg in the morning and 5 mg at midday for about five days.

Children: Dosage in children may be up to 400 mcg/kg bodyweight initially, reducing to 50-100 mcg/kg bodyweight daily for maintenance.

Elderly: The dosage of thiazide diuretics may need to be reduced in the elderly, particularly when renal function is impaired, because of the possibility of electrolyte imbalance.

Assessor Comment on indications and posology:
These are identical to the innovator product and are therefore acceptable. As discussed bendroflumethiazide is authorised for use in children with the dosage based on body weight and as there have been no major safety concerns, this seems acceptable.

CONSIDERATION FOR PAEDIATRIC USE
The current applicant does not have a paediatric development programme and as a generic applicant, this is not expected. It should be noted that bendroflumethiazide is authorised for use in children with specific dose recommendation based on body weight.

ASSESSOR'S COMMENT
Overall the basis of the application, the indication and posology proposed and the GCP compliance appear acceptable.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Summary
Bendroflumethiazide is nearly completely absorbed after oral administration and 30% is excreted unchanged in the urine. Whilst the rest of the administered dose is metabolised or excreted unabsorbed in the faeces, the metabolites have not been appropriately characterised. Over the years it is believed that bendroflumethiazide is likely to exhibit linear pharmacokinetics but this gain has not been sufficiently explored. These facts have a bearing on the bioequivalence studies in applications claiming essential similarity. The generic applicants will have to either demonstrate bioequivalence with all strengths proposed in appropriate studies or provide evidence and data to support the linear pharmacokinetics.

PHARMACODYNAMICS
The applicant has not submitted any new pharmacodynamic data. As this is a generic application claiming essential similarity to an established product and no new indications or posology are proposed, this is considered appropriate and acceptable.
BIOAVAILABILITY & BIOEQUIVALENCE

Bioequivalence study

The applicant has submitted a single bioequivalence study for 2.5 mg strength comparing the test and the reference product (Aprinox, Waymade Plc). The appropriateness of study, the results, and conclusions are discussed below.

This was an open label, randomised, two treatment, two-sequence two-period, crossover single dose study comparing test product, Bendroflumethiazide from manufacturer of product and test product, Aprinox 2.5mg (Waymade Plc) in 26 healthy adult male volunteers under fasting conditions. The study was conducted between the following dates; 19th May 2003 to 3rd Jun 2003 clinical part of the study and the analysis between 20th Jun 2003 and 3rd Jul 2003.

Blood samples were collected pre-dose and up to 12 hours post dose (15 samples) and the bendroflumethiazide was assayed using a validated HPCL method. The LLOQ was 0.04ng/ml and this seems acceptable.

Results:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Reference</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>40.05 ± 9.48</td>
<td>37.41 ± 8.90</td>
<td>107.9 (97.9 to 118.9)</td>
</tr>
<tr>
<td>AUC_{0-t} (ng*h/ml)</td>
<td>210.51 ± 51.87</td>
<td>192.83 ±42.37</td>
<td>109.0 (99.5 to 119.5)</td>
</tr>
<tr>
<td>AUC_{inf} (ng*h/ml)</td>
<td>235.93 ± 57.95</td>
<td>218.01 ± 51.04</td>
<td>108.3 (99.0 to 118.4)</td>
</tr>
</tbody>
</table>

The results suggest that the test product may have marginal supra-bioavailability but this is within the limits suggested by the CPMP guideline (CPMP/EWP/1401/98). The applicant has offered no explanation for this finding. The AUC_t appears to cover 80% of AUC_{inf} overall and this again is as per the guideline.

The applicant concludes from the above study that the test and reference products are bioequivalent. The applicant further concludes that as the kinetics of bendroflumethiazide are expected to be linear, the results can be extrapolated to 5mg strength. The applicant is unable to carry out a specific study for the 5mg strength as this is not currently marketed by the innovator.

CLINICAL EFFICACY

The applicant has not provided any new efficacy studies in this application based on essential similarity. The efficacy of bendroflumethiazide in the indications sought, have been well established and therefore new efficacy data are not required. This is acceptable.

CLINICAL SAFETY

Bendroflumethiazide has been in clinical use in man since at least 1986 in the UK. There are adverse events associated with its continued use and these have been well established. The product has not had any regulatory actions since authorisation. Therefore there do not appear to be any major safety concerns.

The biostudy (with 2.5mg strength) submitted by the applicant did not raise any new issues and adverse events were similar to those observed before. The applicant has not included any new safety data in the dossier. This is considered acceptable.
EXPERT REPORT
The expert report is written by a medically qualified pharmaceutical consultant and is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS
These are satisfactory.

PATIENT INFORMATION LEAFLET
This is satisfactory.

CONCLUSIONS
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 Bendroflumethiazide 2.5mg and 5mg 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 the applicant’s Bendroflumethiazide 2.5mg Tablets and Aprinox 2.5mg tablets (Waymade Plc). Given that linear kinetics apply between the 2.5mg and 5mg tablets, that proportional formulae for the tablets have been used and that similar dissolution results have been shown for the two strengths, a separate bioequivalence study using the 5mg tablets is not considered necessary.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those for Aprinox tablets.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with Bendroflumethiazide is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
BENDROFLUMETHIAZIDE 2.5MG TABLETS
PL 17907/0082

BENDROFLUMETHIAZIDE 5 MG TABLETS
PL 17907/0083

**STEPS TAKEN FOR ASSESSMENT**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong></td>
<td>The MHRA received the marketing authorisation applications on 12th March 2004</td>
</tr>
<tr>
<td><strong>2</strong></td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 17th November 2006</td>
</tr>
<tr>
<td><strong>3</strong></td>
<td>Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 25th October 2004, and further information relating to the quality dossiers on 9th December 2004, 20th January 2006, and 12th September 2006.</td>
</tr>
<tr>
<td><strong>4</strong></td>
<td>The applicant responded to the MHRA’s requests, providing further information on 20th January 2006 for the clinical sections, and 11th September 2006 and 17th November 2006 for the quality sections.</td>
</tr>
<tr>
<td><strong>5</strong></td>
<td>The applications were determined on 1st February 2007</td>
</tr>
</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Bendroflumethiazide 2.5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains Bendroflumethiazide 2.5mg

For excipients, see 6.1

3 PHARMACEUTICAL FORM
Tablets.

White to off white circular, biconvex, uncoated tablets.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
For the treatment of oedema and hypertension. Bendroflumethiazide tablets may also be used to suppress lactation.

4.2 Posology and method of administration
For oral administration.

Adults:

Oedema
Initially, 5-10 mg in the morning, daily or on alternate days; maintenance dose 5-10 mg one to three times weekly.

Hypertension
The usual dose is 2.5 mg taken in the morning. Higher doses are rarely necessary.

Suppression of lactation
5 mg in the morning and 5 mg at midday for about five days.

Children: Dosage in children may be up to 400 mcg/kg bodyweight initially, reducing to 50-100 mcg/kg bodyweight daily for maintenance.

Elderly: The dosage of thiazide diuretics may need to be reduced in the elderly, particularly when renal function is impaired, because of the possibility of electrolyte imbalance.

4.3 Contraindications
Bendroflumethiazide is contra-indicated in patients with known hypersensitivity to Bendroflumethiazide, other thiazide, other sulphonylurea derivatives and the excipients in the tablet.
Bendroflumethiazide is also contraindicated in patients with the following conditions;
- Refractory hypokalaemia, hyponatraemia, or hypercalcaemia
- Severe renal and hepatic impairment
- Symptomatic hyperuricaemia
- Addison’s disease.

4.4 Special warnings and precautions for use

Bendroflumethiazide should be used with caution in patients with mild to moderate hepatic or renal impairment (avoid if severe). Renal function should be continuously monitored during thiazide therapy. Thiazide diuretics may exacerbate or activate systemic lupus erythematosus in susceptible patients.

All thiazide diuretics can produce a degree of electrolyte imbalance, especially in patients with renal or hepatic impairment or when dosage is high or prolonged. Serum electrolytes should be checked for abnormalities, particularly hypokalaemia, and the latter corrected by the addition of a potassium supplement to the regimen. Aggravates diabetes and gout; increased risk of hypomagnesaemia in alcoholic cirrhosis.

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

4.5 Interaction with other medicinal products and other forms of interaction

Sensitivity to digitalis glycosides may be increased by the hypokalaemic effect of concurrent bendroflumethiazide. Patients should be observed for signs of digitalis intoxication, in particular arrhythmias, and if these appear, the dosage of the digitalis glycoside should be temporarily reduced and a potassium supplement given to restore stability.

ACTH, corticosteroids, acetazolamide and carbenoxolone may exacerbate the hypokalaemia associated with thiazide use. The cardiac toxicity of disopyramide, amiodarone, flecainide and quinidine is increased if hypokalaemia occurs. The action of lidocaine and mexiletine is antagonised by hypokalaemia. There may be an increased risk of hypokalaemia if thiazides are given with reboxetine.

Hypokalaemia also increases the risk of ventricular arrhythmias with pimozide or thioridazine, therefore, concomitant use should be avoided. Hypokalaemia or other electrolyte imbalance also increases the risk of ventricular arrhythmias with terfenadine.

Thiazides may enhance the effects of antihypertensive agents, while postural hypotension associated with therapy may be enhanced by concomitant ingestion of alcohol, barbiturates or opioids. Calcium-channel blockers and moxisylyte can cause an enhanced hypotensive effect and concomitant use with monoamine oxidase inhibitors (MAOIs), baclofen or tizanidine may also give an increased hypotensive effect. There is an increased risk of postural hypotension with tricyclic antidepressants and an increased risk of first-dose hypotensive effect of post-synaptic alpha-blockers such as prazosin.

Serum lithium concentrations may be increased by concurrent use of thiazide diuretics.

Non-steroidal anti-inflammatory agents may blunt the diuretic and antihypertensive effects of thiazide diuretics. Diuretics may increase the risk of nephrotoxicity of NSAIDs.

Thiazide diuretics may enhance the neuromuscular blocking effects of the non-depolarising muscle relaxants, e.g. tubocurarine.
Concomitant use of carbamazepine may increase the risk of hyponatraemia.

There is an increased risk of hyponatraemia if thiazides are given with amphotericin or if used concomitantly with aminoglutethimide.

Thiazides can cause an increased risk of hypercalcaemia with toremifene. The risk of hypercalcaemia is increased by the concomitant intake of calcium salts or vitamin D preparations.

Concomitant use with cisplatin can lead to an increased risk of nephrotoxicity and ototoxicity.

Colestipol and colestyramine may reduce the absorption of thiazide diuretics and should therefore be given 2 hours prior to, or after the ingestion of Bendroflumethiazide.

Oestrogens and combined oral contraceptives may antagonise the diuretic effect of thiazides.

Bendroflumethiazide may interfere with a number of laboratory tests, including estimation of serum protein-bound iodine and tests of parathyroid function.

4.6 Pregnancy and lactation

Diuretics are best avoided for the management of oedema of pregnancy or hypertension in pregnancy as their use may be associated with hypokalaemia, increased blood viscosity and reduced placental perfusion.

There is inadequate evidence of safety in human pregnancy and foetal bone marrow depression and thrombocytopenia have been described. Foetal and neonatal jaundice have also been described.

As diuretics pass into breast milk and Bendroflumethiazide can suppress lactation, its use should be avoided in mothers who wish to breast feed.

4.7 Effects on ability to drive and use machines

Although Bendroflumethiazide may not affect driving ability directly, adverse events such as hypotension, dizziness etc may impact this ability. Therefore, patients experiencing such adverse events should take care not to drive.

4.8 Undesirable effects

All thiazide diuretics can produce a degree of electrolyte imbalance, e.g. hypokalaemia.

Thiazide diuretics may raise the serum uric acid levels with subsequent exacerbation of gout in susceptible subjects.

Thiazide diuretics sometimes lower carbohydrate tolerance and the insulin dosage of the diabetic patient may require adjustment. Care is necessary when Bendroflumethiazide is administered to those with a known predisposition to diabetes.

Impotence has been reported which is reversible on withdrawal of treatment.

The following undesirable effects, which are listed in system order class, have previously been associated with Bendroflumethiazide. Specific frequencies for the occurrence of these effects are not available.

**Adverse events listed in system class order:**

Blood and lymphatic system disorders:
Agranulocytosis, aplastic anaemia, neutropenia, thrombocytopenia (neonatal thrombocytosis reported when given in late pregnancy.

Immune system disorders:
hypersensitivity reactions

Metabolism and nutrition disorders:
gout, hypoglycaemia

Cardiac and vascular disorders:
postural hypotension

Respiratory, thoracic and mediastinal disorders:
pneumonitis, pulmonary oedema

Gastrointestinal effects:
Mild gastro-intestinal effects have been reported, pancreatitis

Hepato-biliary disorders:
 intrahepatic cholestasis

Skin and subcutaneous tissue disorders:
Rash, photosensitivity, severe skin reactions also reported

Reproductive system and breast disorders:
Impotence

Investigations:
Hypocalcaemia, hypomagnesaemia, hyponatraemia, hypercalcaemia, hypochlorhaemic alkalosis, hyperuricaemia, altered plasma lipid concentrations.

4.9 Overdose
Symptoms of overdosage include anorexia, nausea, vomiting, diarrhoea, diuresis, dehydration, hypotension, dizziness, weakness, muscle cramps, paraesthesia, tetany, gastrointestinal bleeding, hyponatraemia, hypo- or hyperglycaemia, hypokalaemia and metabolic alkalosis. Initial treatment consists of either emesis or gastric lavage, if appropriate. Otherwise treatment should be symptomatic and supportive including the correction of fluid and electrolyte imbalance.

Blood pressure should also be monitored.

There is no specific antidote.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: diuretic, ATC code: C03AA01

Bendroflumethiazide is a thiazide diuretic which reduces the absorption of electrolytes from the renal tubules, thereby increasing the excretion of sodium and chloride ions, and consequently of water. The excretion of other electrolytes, notably potassium and magnesium, is also increased.

The excretion of calcium is reduced. Thiazides also reduce carbonic anhydrase activity so that bicarbonate excretion is increased, but this effect is generally small.
and does not appreciably alter the acid base balance or the pH of the urine. Thiazides also have a hypotensive effect, due to a reduction in peripheral resistance and enhance the effects of other antihypertensive agents.

5.2 Pharmacokinetic properties
Bendroflumethiazide is completely absorbed from the gastrointestinal tract and it is fairly extensively metabolised. About 30% is excreted unchanged in the urine. The onset of diuretic action of the thiazides following oral administration occurs within two hours and the peak effect between three and six hours after administration. The duration of the diuretic action of Bendroflumethiazide is between 18 and 24 hours. The onset of the hypotensive action is generally three or four days.

5.3 Preclinical safety data
Not applicable

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Anhydrous Lactose
Talc
Pregelatinised starch
Stearic acid

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
PVC/PVDC Aluminium foil blisters: 2 years
HDPE containers: 18 months

6.4 Special precautions for storage
PVC/PVDC Aluminium foil blisters: Do not store above 25°C. Store in the original package
HDPE containers: Do not store above 25°C. Keep the container tightly closed.

6.5 Nature and contents of container
PVC/PVDC Aluminium foil blister, pack sizes of 14, 28, 56, 84 tablets.
HDPE tablet containers, pack sizes of 50, 100, 250, 500, 1000 tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Bristol Laboratories Limited
Unit 3, Canalside
Northbridge Road
Berkhamsted
HP4 1EG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 17907/0082

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
01/02/2007

10 DATE OF REVISION OF THE TEXT
01/02/2007
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Bendroflumethiazide 5mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains Bendroflumethiazide 5mg
For excipients, see 6.1

3. PHARMACEUTICAL FORM
Tablets.
White to off white, circular, flat, beveled edged, uncoated tablets with ‘5’ embossed on one side and plain on the other side

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
For the treatment of oedema and hypertension. Bendroflumethiazide tablets may also be used to suppress lactation.

4.2 Posology and method of administration
For oral administration.
Adults:
Oedema
Initially, 5-10 mg in the morning, daily or on alternate days; maintenance dose 5-10 mg one to three times weekly.
Hypertension
The usual dose is 2.5 mg taken in the morning. Higher doses are rarely necessary.

Suppression of lactation
5 mg in the morning and 5 mg at midday for about five days.

Children: Dosage in children may be up to 400 mcg/kg bodyweight initially, reducing to 50-100 mcg/kg bodyweight daily for maintenance.

Elderly: The dosage of thiazide diuretics may need to be reduced in the elderly, particularly when renal function is impaired, because of the possibility of electrolyte imbalance.
4.3 Contraindications
Bendroflumethiazide is contra-indicated in patients with known hypersensitivity to Bendroflumethiazide, other thiazide, other sulphonylurea derivatives and the excipients in the tablet.

Bendroflumethiazide is also contraindicated in patients with the following conditions;
- Refractory hypokalaemia, hyponatraemia, or hypercalcaemia
- Severe renal and hepatic impairment
- Symptomatic hyperuricaemia
- Addison’s disease.

4.4 Special warnings and precautions for use
Bendroflumethiazide should be used with caution in patients with mild to moderate hepatic or renal impairment (avoid if severe). Renal function should be continuously monitored during thiazide therapy. Thiazide diuretics may exacerbate or activate systemic lupus erythematosus in susceptible patients.

All thiazide diuretics can produce a degree of electrolyte imbalance, especially in patients with renal or hepatic impairment or when dosage is high or prolonged. Serum electrolytes should be checked for abnormalities, particularly hypokalaemia, and the latter corrected by the addition of a potassium supplement to the regimen. Aggravates diabetes and gout; increased risk of hypomagnesaemia in alcoholic cirrhosis.

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

4.5 Interaction with other medicinal products and other forms of interaction
Sensitivity to digitalis glycosides may be increased by the hypokalaemic effect of concurrent bendroflumethiazide. Patients should be observed for signs of digitalis intoxication, in particular arrhythmias, and if these appear, the dosage of the digitalis glycoside should be temporarily reduced and a potassium supplement given to restore stability.

ACTH, corticosteroids, acetazolamide and carbenoxolone may exacerbate the hypokalaemia associated with thiazide use. The cardiac toxicity of disopyramide, amiodarone, flecainide and quinidine is increased if hypokalaemia occurs. The action of lidocaine and mexiletine is antagonised by hypokalaemia. There may be an increased risk of hypokalaemia if thiazides are given with reboxetine.

Hypokalaemia also increases the risk of ventricular arrhythmias with pimozide or thioridazine, therefore, concomitant use should be avoided. Hypokalaemia or other electrolyte imbalance also increases the risk of ventricular arrhythmias with terfenadine.

Thiazides may enhance the effects of antihypertensive agents, while postural hypotension associated with therapy may be enhanced by concomitant ingestion of alcohol, barbiturates or opioids. Calcium-channel blockers and moxisylyte can cause an enhanced hypotensive effect and concomitant use with monoamine oxidase inhibitors (MAOIs), baclofen or tizanidine may also give an increased hypotensive effect. There is an increased risk of postural hypotension with tricyclic antidepressants and an increased risk of first-dose hypotensive effect of post-synaptic alpha-blockers such as prazosin.
Serum lithium concentrations may be increased by concurrent use of thiazide diuretics.

Non-steroidal anti-inflammatory agents may blunt the diuretic and antihypertensive effects of thiazide diuretics. Diuretics may increase the risk of nephrotoxicity of NSAIDs.

Thiazide diuretics may enhance the neuromuscular blocking effects of the non-depolarising muscle relaxants, e.g. tubocurarine.

Concomitant use of carbamazepine may increase the risk of hyponatraemia.

There is an increased risk of hyponatraemia if thiazides are given with amphotericin or if used concomitantly with aminoglutethimide.

Thiazides can cause an increased risk of hypercalcaemia with toremifene. The risk of hypercalcaemia is increased by the concomitant intake of calcium salts or vitamin D preparations.

Concomitant use with cisplatin can lead to an increased risk of nephrotoxicity and ototoxicity.

Colestipol and colestyramine may reduce the absorption of thiazide diuretics and should therefore be given 2 hours prior to, or after the ingestion of Bendroflumethiazide.

Oestrogens and combined oral contraceptives may antagonise the diuretic effect of thiazides.

Bendroflumethiazide may interfere with a number of laboratory tests, including estimation of serum protein-bound iodine and tests of parathyroid function.

4.6 Pregnancy and lactation

Diuretics are best avoided for the management of oedema of pregnancy or hypertension in pregnancy as their use may be associated with hypokalaemia, increased blood viscosity and reduced placental perfusion.

There is inadequate evidence of safety in human pregnancy and foetal bone marrow depression and thrombocytopenia have been described. Foetal and neonatal jaundice have also been described.

As diuretics pass into breast milk and Bendroflumethiazide can suppress lactation, its use should be avoided in mothers who wish to breast feed.

4.7 Effects on ability to drive and use machines

Although Bendroflumethiazide may not affect driving ability directly, adverse events such as hypotension, dizziness etc may impact this ability. Therefore, patients experiencing such adverse events should take care not to drive.

4.8 Undesirable effects

All thiazide diuretics can produce a degree of electrolyte imbalance, e.g. hypokalaemia.

Thiazide diuretics may raise the serum uric acid levels with subsequent exacerbation of gout in susceptible subjects.

Thiazide diuretics sometimes lower carbohydrate tolerance and the insulin dosage of the diabetic patient may require adjustment. Care is necessary when Bendroflumethiazide is administered to those with a known predisposition to diabetes.
Impotence has been reported which is reversible on withdrawal of treatment. The following undesirable effects, which are listed in system order class, have previously been associated with Bendroflumethiazide. Specific frequencies for the occurrence of these effects are not available.

**Adverse events listed in system class order:**

**Blood and lymphatic system disorders:**

Agranulocytosis, aplastic anaemia, neutropenia, thrombocytopenia (neonatal thrombocytosis reported when given in late pregnancy.

**Immune system disorders:**

hypersensitivity reactions

**Metabolism and nutrition disorders:**

gout, hypoglycaemia

**Cardiac and vascular disorders:**

postural hypotension

**Respiratory, thoracic and mediastinal disorders:**

pneumonitis, pulmonary oedema

**Gastrointestinal effects:**

Mild gastro-intestinal effects have been reported, pancreatitis

**Hepato-biliary disorders:**

intrahepatic cholestasis

**Skin and subcutaneous tissue disorders:**

Rash, photosensitivity, severe skin reactions also reported

**Reproductive system and breast disorders:**

Impotence

**Investigations:**

Hypokalaemia, hypomagnesaemia, hyponatraemia, hypercalcaemia, hypochloraemic alkalosis, hyperuricaemia, altered plasma lipid concentrations.

### 4.9 Overdose

Symptoms of overdosage include anorexia, nausea, vomiting, diarrhoea, diuresis, dehydration, hypotension, dizziness, weakness, muscle cramps, paraesthesia, tetany, gastrointestinal bleeding, hyponatraemia, hypo- or hyperglycaemia, hypokalaemia and metabolic alkalosis. Initial treatment consists of either emesis or gastric lavage, if appropriate. Otherwise treatment should be symptomatic and supportive including the correction of fluid and electrolyte imbalance.

Blood pressure should also be monitored.

There is no specific antidote.
5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: diuretic, ATC code: C03AA01

Bendroflumethiazide is a thiazide diuretic which reduces the absorption of electrolytes from the renal tubules, thereby increasing the excretion of sodium and chloride ions, and consequently of water. The excretion of other electrolytes, notably potassium and magnesium, is also increased.

The excretion of calcium is reduced. Thiazides also reduce carbonic anhydrase activity so that bicarbonate excretion is increased, but this effect is generally small and does not appreciably alter the acid base balance or the pH of the urine. Thiazides also have a hypotensive effect, due to a reduction in peripheral resistance and enhance the effects of other antihypertensive agents.

5.2 Pharmacokinetic properties
Bendroflumethiazide is completely absorbed from the gastrointestinal tract and it is fairly extensively metabolised. About 30% is excreted unchanged in the urine. The onset of diuretic action of the thiazides following oral administration occurs within two hours and the peak effect between three and six hours after administration. The duration of the diuretic action of Bendroflumethiazide is between 18 and 24 hours. The onset of the hypotensive action is generally three or four days.

5.3 Preclinical safety data
Not applicable

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Anhydrous Lactose
Talc
Pregelatinised starch
Stearic acid

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
PVC/PVDC Aluminium foil blisters: 2 years
HDPE containers: 18 months

6.4 Special precautions for storage
PVC/PVDC Aluminium foil blisters: Do not store above 25°C. Store in the original package
HDPE containers: Do not store above 25°C. Keep the container tightly closed.

6.5 Nature and contents of container
PVC/PVDC Aluminium foil blister, pack sizes of 14, 28, 56, 84 tablets.
HDPE tablet containers, pack sizes of 50, 100, 250, 500, 1000 tablets
Not all pack sizes may be marketed.
6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Bristol Laboratories Limited
Unit 3, Canalside
Northbridge Road
Berkhamsted
HP4 1EG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 17907/0083

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORITYZATION
01/02/2007

10 DATE OF REVISION OF THE TEXT
01/02/2007
UKPAR Bendroflumethiazide 2.5 and 5 mg Tablets  

PL 17907/0082-3

What you should know about Bendroflumethiazide Tablets: 

- Bendroflumethiazide Tablets are white, circular tablets containing 2.5 or 5 mg of active ingredient bendroflumethiazide. 
- Bendroflumethiazide is a diuretic that works by increasing the amount of urine produced, which helps reduce water and salt levels in the body. 
- Bendroflumethiazide is used to treat high blood pressure and to reduce the amount of sodium in the body. 
- Bendroflumethiazide is also used to treat edema (water retention) and to prevent gout attacks. 
- Bendroflumethiazide may also be used for other conditions as determined by your doctor. 

What are Bendroflumethiazide Tablets used for? 

- Bendroflumethiazide Tablets are used to treat high blood pressure. 
- Bendroflumethiazide Tablets are also used to treat edema caused by heart failure, liver disease, kidney disease, and other conditions. 
- Bendroflumethiazide Tablets are also used to treat gout and to prevent gout attacks. 

How should you take Bendroflumethiazide Tablets? 

- Bendroflumethiazide Tablets should be taken exactly as prescribed by your doctor. 
- Take Bendroflumethiazide Tablets with or without food. 
- Do not crush or chew Bendroflumethiazide Tablets. 
- Do not stop taking Bendroflumethiazide Tablets without first talking to your doctor. 

What are the possible side effects of Bendroflumethiazide Tablets? 

- Some common side effects of Bendroflumethiazide Tablets include:
  - Diarrhea
  - Nausea
  - Headache
  - Dizziness
  - Fatigue
  - Rash
  - Blurred vision
  - Insomnia
  - Hair loss

- Less common side effects of Bendroflumethiazide Tablets include:
  - Low blood pressure
  - Low potassium levels in the blood
  - Low sodium levels in the blood
  - Low levels of certain enzymes in the blood
  - Low levels of certain cholesterol in the blood

- Severe side effects of Bendroflumethiazide Tablets include:
  - Severe allergic reactions (hives, rash, difficulty breathing, swelling of the tongue or throat)
  - Uncontrolled swelling of the feet or ankles
  - Severe or persistent diarrhea
  - Unusual bleeding or bruising
  - Unusual weight gain
  - New or worsening chest pain

- If you experience any of these severe side effects, stop taking Bendroflumethiazide Tablets and call your doctor or pharmacist right away.

Interactions with Bendroflumethiazide Tablets: 

- Bendroflumethiazide Tablets can interact with other medications and may cause interactions that could affect the effectiveness of Bendroflumethiazide Tablets. 
- Tell your doctor and pharmacist if you are taking any other medications, including prescription, over-the-counter, nonprescription, vitamins, herbs, or nutritional supplements. 

- Avoid getting too much sun while taking Bendroflumethiazide Tablets. 
- If you have a mold allergy, use caution when taking Bendroflumethiazide Tablets. 

- Bendroflumethiazide Tablets may make you drowsy or dizzy. Do not drive, operate heavy machinery, or engage in activities that require alertness until you know how Bendroflumethiazide Tablets affect you. 

- Bendroflumethiazide Tablets can cause electrolyte abnormalities, which can impair normal blood pressure control. 

- Bendroflumethiazide Tablets may cause changes in blood pressure, which can lead to dizziness or orthostatic hypotension. 

- If you have liver disease, kidney disease, or diabetes, tell your doctor before starting Bendroflumethiazide Tablets.

- Bendroflumethiazide Tablets can interact with other medications, which may affect the effectiveness of Bendroflumethiazide Tablets. 

- Bendroflumethiazide Tablets can increase the levels of certain medications in the blood, which may cause side effects. 

- Bendroflumethiazide Tablets can decrease the levels of certain medications in the blood, which may cause side effects.

- Bendroflumethiazide Tablets can interact with other medications, which may affect the effectiveness of Bendroflumethiazide Tablets. 

- If you have any questions about the use of Bendroflumethiazide Tablets, please consult your doctor or pharmacist.

SAFETY INSTRUCTIONS: 

- Do not exceed the recommended dosage of Bendroflumethiazide Tablets. 
- Do not use Bendroflumethiazide Tablets if you are allergic to any medication. 
- Do not use Bendroflumethiazide Tablets if you have certain medical conditions, such as kidney disease, liver disease, or gout. 
- Do not use Bendroflumethiazide Tablets if you are pregnant or breastfeeding. 
- Do not use Bendroflumethiazide Tablets if you are allergic to any medication. 
- Do not use Bendroflumethiazide Tablets if you have certain medical conditions, such as kidney disease, liver disease, or gout. 

SAFETY TIPS: 

- Keep your Bendroflumethiazide Tablets in a cool, dry place. 
- Do not share your Bendroflumethiazide Tablets with others. 
- Do not use Bendroflumethiazide Tablets if the bottle is damaged or the cap is loose. 
- Do not use expired Bendroflumethiazide Tablets. 
- Do not use Bendroflumethiazide Tablets if you have any concerns about their safety or effectiveness. 

SAFETY REMINDERS: 

- If you have any questions about the use of Bendroflumethiazide Tablets, please consult your doctor or pharmacist.

SAFETY INFORMATION Sheet: 

- Bendroflumethiazide Tablets are a diuretic that works by increasing the amount of urine produced, which helps reduce water and salt levels in the body. 
- Bendroflumethiazide Tablets are also used to treat edema caused by heart failure, liver disease, kidney disease, and other conditions. 
- Bendroflumethiazide Tablets are also used to treat gout and to prevent gout attacks. 
- Bendroflumethiazide Tablets may also be used for other conditions as determined by your doctor. 
- Bendroflumethiazide Tablets should be taken exactly as prescribed by your doctor. 
- Take Bendroflumethiazide Tablets with or without food. 
- Do not crush or chew Bendroflumethiazide Tablets. 
- Do not stop taking Bendroflumethiazide Tablets without first talking to your doctor. 
- Bendroflumethiazide Tablets can interact with other medications and may cause interactions that could affect the effectiveness of Bendroflumethiazide Tablets. 
- Tell your doctor and pharmacist if you are taking any other medications, including prescription, over-the-counter, nonprescription, vitamins, herbs, or nutritional supplements. 
- Avoid getting too much sun while taking Bendroflumethiazide Tablets. 
- If you have a mold allergy, use caution when taking Bendroflumethiazide Tablets. 
- If you have liver disease, kidney disease, or diabetes, tell your doctor before starting Bendroflumethiazide Tablets. 
- Bendroflumethiazide Tablets can cause electrolyte abnormalities, which can impair normal blood pressure control. 
- If you have any questions about the use of Bendroflumethiazide Tablets, please consult your doctor or pharmacist.
• Oedema, some found in menopausal therapy or the 
  combination

• The local area, discomfort.

• Dryness, unusual menstruation.

• The absence of menstruation, weight, and constipation. As both these reactions can interfere with the absorption of Bendrofluoridazide Tablets, have occasionally been reported.

Any potential of disodium, light headaches, edema and Bendrofluoridazide Tablets may be monitored by your doctor or pharmacist.

You may also experience if you are also taking similar drugs for treatment of similar conditions.

If the above reaction is unusual, that your doctor or pharmacist may need to alter your tablets medication.

• Vertigo, vomiting, headache, anorexia, dizziness, weakness, abdominal pain, diarrhoea, malaise, nausea.

• Drowsiness, malaise, nausea, back pain, headache, dizziness.

• Mental depression, tiredness, anxiety, depression, dizziness, headache, malaise, nausea.

• Back pain, malaise, nausea, anorexia, dizziness.

• Try taking these tablets on an empty stomach, the usual maintenance dose is 1 to 2 mg once or twice daily. The dose should be taken early in the morning.

For hypertension of bendrofluoridazide.

The usual dose is 1 to 2 mg once or twice daily. The maintenance dose for Hypertension depends on how much the drugs have to work and how long they have been working. Your doctor will tell you how many tablets to take. bendrofluoridazide Tablets may be used in elderly patients.

To take bendrofluoridazide Tablets, you are taking bendrofluoridazide Tablets or other medicines you are taking bendrofluoridazide Tablets, you are taking bendrofluoridazide Tablets, you are taking bendrofluoridazide Tablets, you are taking bendrofluoridazide Tablets.

Please take this medicine at a time that suits you. If you have any symptoms as pain of mouth and increase in pain, pain in the mouth, pain in the mouth.

Any tablet of bendrofluoridazide Tablets may be used in elderly patients.

For full information on bendrofluoridazide Tablets, contact your doctor or pharmacist.

4. Possible side effects

• If all symptoms of bendrofluoridazide Tablets may be used in elderly patients.

• Headache, feeling tired, feeling dizzy, dry mouth, loss of appetite, weakness, muscle pain or cramps, general pain, nausea, vomiting, headache, dizziness, weakness, malaise, nausea.

• The frequency of tablets as far as possible:

5. Storing Bendrofluoridazide Tablets

As an airmail, keep your tablets on or in the mouth of the patient. Store in the original package to protect your tablets from light.

How to take bendrofluoridazide Tablets after the expiry date as shown on the container or blister. Take any tablets remaining past the expiry date at your pharmacy.

The tablets are best approved in November 2006.