BENDROFLUMETHIAZIDE 2.5MG TABLETS
PL 17907/0082

BENDROFLUMETHIAZIDE 5MG TABLETS
PL 17907/0083

UKPAR

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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

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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.

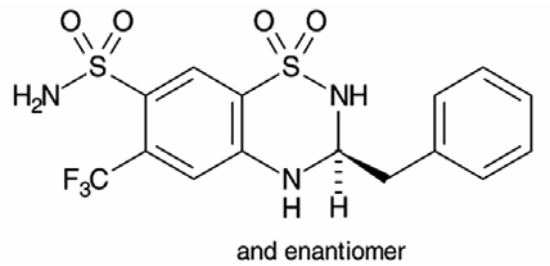
These applications were submitted at the same time and both depend on the bioequivalence study comparing the applicant's 2.5mg and 5mg products with the reference product Aprinox 2.5mg and 5mg tablets (Waymade Plc). Consequently, all sections of this scientific discussion refer to both products.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
Bendroflumethiazide

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

CAS No: 73-4803



and enantiomer

Molecular formula: $C_{15}H_{14}F_3N_3O_4S_2$
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.

CLINICAL ASSESSMENT

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, cross-over 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:

Parameter	Test	Reference	90% CI
C_{max} (ng/ml)	40.05 ± 9.48	37.41 ± 8.90	107.9 (97.9 to 118.9)
AUC_{0-t} (ng*h/ml)	210.51 ± 51.87	192.83 ±42.37	109.0 (99.5 to 119.5)
AUC_{inf} (ng*h/ml)	235.93 ± 57.95	218.01 ± 51.04	108.3 (99.0 to 118.4)

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 AUCt appears to cover 80% of AUCinf 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

1	The MHRA received the marketing authorisation applications on 12th March 2004
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 17th November 2006
3	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.
4	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.
5	The applications were determined on 1st February 2007

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 Bendroflumethaizide. 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, 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: 2years

HDPE containers: 18 months

6.4 Special precautions for storage

PVC/PVDC Aluminium foil blisters: Do not store above 25ºC. Store in the original package

HDPE containers: Do not store above 25ºC. 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 AUTHORISATION/RENEWAL OF THE AUTHORISATION

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.

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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 Bendroflumethaizide. 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:

Hypokalaemai, 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: 2years

HDPE containers: 18 months

6.4 Special precautions for storage

PVC/PVDC Aluminium foil blisters: Do not store above 25ºC. Store in the original package

HDPE containers: Do not store above 25ºC. 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)

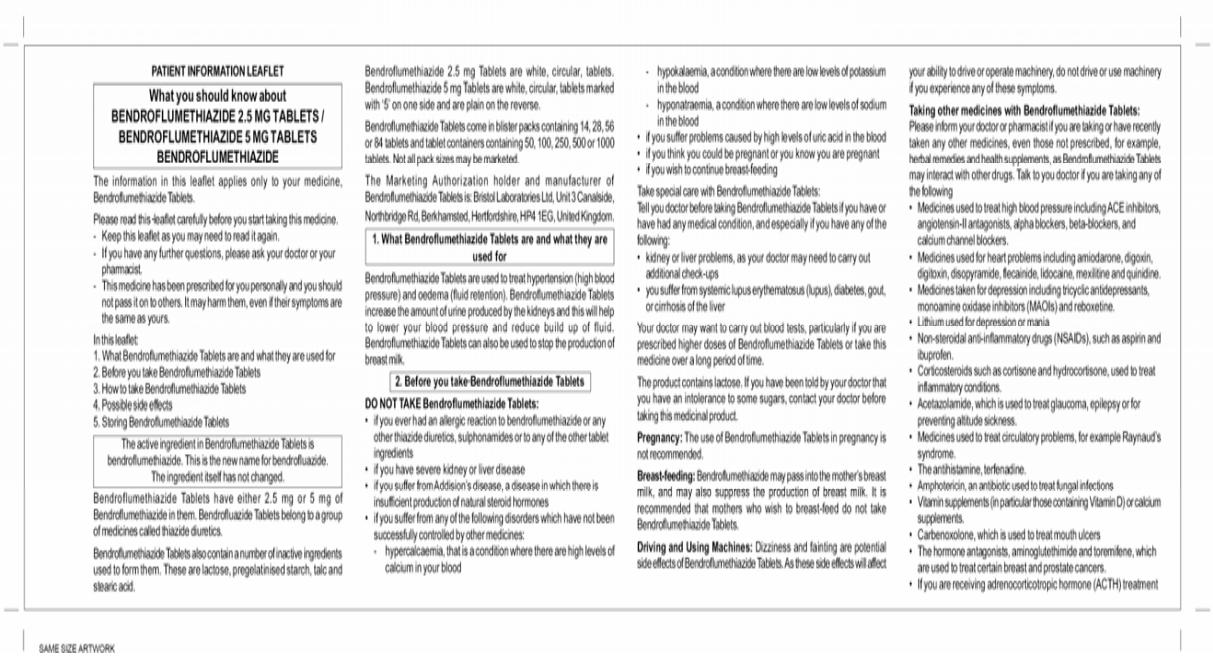
PL 17907/0083

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/02/2007

10 DATE OF REVISION OF THE TEXT

01/02/2007



PATIENT INFORMATION LEAFLET

What you should know about BENDROFLUMETHIAZIDE 2.5 MG TABLETS / BENDROFLUMETHIAZIDE 5 MG TABLETS BENDROFLUMETHIAZIDE

The information in this leaflet applies only to your medicine, Bendroflumethiazide Tablets.

Please read this leaflet carefully before you start taking this medicine.
- Keep this leaflet as you may need to read it again.
- If you have any further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

The active ingredient in Bendroflumethiazide Tablets is bendroflumethiazide. This is the new name for bendrofluazide. The ingredient itself has not changed.

Bendroflumethiazide Tablets have either 2.5 mg or 5 mg of Bendroflumethiazide in them. Bendrofluazide Tablets belong to a group of medicines called thiazide diuretics.

Bendroflumethiazide Tablets also contain a number of inactive ingredients used to form them. These are lactose, pregelatinised starch, talc and stearic acid.

Bendroflumethiazide 2.5 mg Tablets are white, circular, tablets. Bendroflumethiazide 5 mg Tablets are white, circular, tablets marked with '5' on one side and are plain on the reverse.

Bendroflumethiazide Tablets come in blister packs containing 14, 28, 56 or 84 tablets and tablet containers containing 50, 100, 250, 500 or 1000 tablets. Not all pack sizes may be marketed.

The Marketing Authorization holder and manufacturer of Bendroflumethiazide Tablets is: Bristol Laboratories Ltd, Unit 3 Canalside, Northbridge Rd, Berkhamsted, Hertfordshire, HP4 1EG, United Kingdom.

1. What Bendroflumethiazide Tablets are and what they are used for

Bendroflumethiazide Tablets are used to treat hypertension (high blood pressure) and oedema (fluid retention). Bendroflumethiazide Tablets increase the amount of urine produced by the kidneys and this will help to lower your blood pressure and reduce build up of fluid. Bendroflumethiazide Tablets can also be used to stop the production of breast milk.

2. Before you take Bendroflumethiazide Tablets

DO NOT TAKE Bendroflumethiazide Tablets:
- if you ever had an allergic reaction to bendroflumethiazide or any other thiazide diuretics, sulphonamides or to any of the other tablet ingredients
- if you have severe kidney or liver disease
- if you suffer from Addison's disease, a disease in which there is insufficient production of natural steroid hormones
- if you suffer from any of the following disorders which have not been successfully controlled by other medicines:
  - hypercalcaemia, that is a condition where there are high levels of calcium in your blood
  - hypokalaemia, a condition where there are low levels of potassium in the blood
  - hyponatraemia, a condition where there are low levels of sodium in the blood
- if you suffer problems caused by high levels of uric acid in the blood
- if you think you could be pregnant or you know you are pregnant
- if you wish to continue breast-feeding

Take special care with Bendroflumethiazide Tablets:
Tell you doctor before taking Bendroflumethiazide Tablets if you have or have had any medical condition, and especially if you have any of the following:
- kidney or liver problems, as your doctor may need to carry out additional check-ups
- you suffer from systemic lupus erythematosus (lupus), diabetes, gout, or cirrhosis of the liver

Your doctor may want to carry out blood tests, particularly if you are prescribed higher doses of Bendroflumethiazide Tablets or take this medicine over a long period of time.

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

Pregnancy: The use of Bendroflumethiazide Tablets in pregnancy is not recommended.

Breast-feeding: Bendroflumethiazide may pass into the mother's breast milk, and may also suppress the production of breast milk. It is recommended that mothers who wish to breast-feed do not take Bendroflumethiazide Tablets.

Driving and Using Machines: Dizziness and fainting are potential side effects of Bendroflumethiazide Tablets. As these side effects will affect your ability to drive or operate machinery, do not drive or use machinery if you experience any of these symptoms.

Taking other medicines with Bendroflumethiazide Tablets:
Please inform 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, as Bendroflumethiazide Tablets may interact with other drugs. Talk to you doctor if you are taking any of the following
- Medicines used to treat high blood pressure including ACE inhibitors, angiotensin-II antagonists, alpha blockers, beta-blockers, and calcium channel blockers.
- Medicines used for heart problems including amiodarone, digoxin, digitoxin, disopyramide, flecainide, lidocaine, mexilitine and quinidine.
- Medicines taken for depression including tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs) and reboxetine.
- Lithium used for depression or mania
- Non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen.
- Corticosteroids such as cortisone and hydrocortisone, used to treat inflammatory conditions.
- Acetazolamide, which is used to treat glaucoma, epilepsy or for preventing altitude sickness.
- Medicines used to treat circulatory problems, for example Raynaud's syndrome.
- The antihistamine, terfenadine.
- Amphotericin, an antibiotic used to treat fungal infections
- Vitamin supplements (in particular those containing Vitamin D) or calcium supplements.
- Carbenoxolone, which is used to treat mouth ulcers
- The hormone antagonists, aminoglutethimide and toremifene, which are used to treat certain breast and prostate cancers.
- If you are receiving adrenocorticotropic hormone (ACTH) treatment

SAME SIZE ARTWORK

- Oestrogens, as found in hormone replacement therapy or the contraceptive pill
- The local anaesthetic, lidocaine.
- Tizanidine, used to treat muscle spasm.
- The cholesterol-lowering medicines, colestipol and colestyramine.

As both these medicines can interfere with the absorption of Bendroflumethiazide Tablets, they should be taken either two hours before or after taking Bendroflumethiazide Tablets.

Any symptoms of dizziness or light-headedness experienced with Bendroflumethazide Tablets may be made worse if you also drink alcohol. This may also happen if you are also taking certain tranquilizers or sedatives known as barbiturates (for example, phenobarbital, which also may be used to control epileptic fits) or painkillers, such as codeine, which are also found in certain cough/cold remedies. Do not drive or operate machinery if you are affected in any way.

If you are having any tests performed, tell your doctor that you are taking Bendroflumethiazide Tablet as this medicine can potentially interfere with the results

If you see another doctor, dentist or go into hospital, especially if you are going to have an anaesthetic, let them know what medicines you are taking.

3. How to take Bendroflumethiazide Tablets

Always take Bendroflumethiazide Tablets exactly as directed by your doctor. If you do not understand these directions ask your pharmacist, nurse or doctor to explain them to you.

For high blood pressure:
The usual dose is 2.5 mg to 5 mg once daily. Your doctor may prescribe a lower dose if other blood pressure medication is also taken.

For fluid retention:
The usual dose is 5 mg to 10 mg once daily, or every other day. The usual maintenance dose is 5 mg to 10 mg once or twice weekly. The dose should be taken early in the morning.

For suppression of breast milk:
The usual dose is 5 mg taken in the morning and 5 mg taken at midday. Treatment usually lasts for approximately 5 days.

For children:
The dose for children depends how much they weigh. The starting dose is up to 400 micrograms per kilogram of body weight. The maintenance dose is 50 to 100 micrograms per kilogram of body weight. Your doctor will tell you how many tablets your child should take.

For elderly patients:
The dose of Bendroflumethiazide Tablets may be reduced in elderly people, and your doctor will tell you what you should take.

Take these tablets until your doctor tells you to stop. Don't stop taking these tablets because you feel better. If you stop taking these tablets too soon, your condition might get worse.

If you miss a dose you should take it as soon as you remember. Do not take a double dose to make up for a forgotten dose.

If you take an overdose of Bendroflumethiazide Tablets, contact a doctor immediately or go to your nearest hospital casualty department. Take the pack and any remaining tablets with you to show to the doctor.

4. Possible side effects

As with all medicines, bendroflumethiazide may cause side effects. Effects that may occur with Bendroflumethiazide Tablets include:

- headaches, feeling faint, light-headed or dizzy when you stand up
- upset stomach or stomach pains,
- weakness, muscle pains or cramps
- signs of gout (symptoms of which are pain and stiffness in the joints)
- the inability to get or maintain an erection
- skin rash, itching, unexplained bleeding or bruising under the skin, or an increased sensitivity of your skin to sunlight
- severe or sudden pains in your abdomen and/or lower back, nau sea, vomiting or fever
- worsening of your diabetes, in which case your doctor may need to alter your diabetes medication
- cough or shortness of breath
- a yellowing of the skin and/or eyes, also known a jaundice
- symptoms of anaemia, such as tiredness, being short of breath when exercising, or pale-looking

Tell your doctor or pharmacist if you experience any of these side effects.

This medicine may cause you to lose too much potassium or salt from your body, which can result in symptoms such as dryness of mouth and increased thirst, dizziness, tiredness, irritability, muscle cramps or stomach upset. You should tell your doctor if you experience any of these symptoms.

Always tell your doctor that you are taking Bendroflumethiazide Tablets before any blood tests are carried out, as this medicine may interfere with the results.

Rarely, people have an allergic reaction to bendroflumethiazide, symptoms of which may include rash, itching, inflamed or reddened skin. Very rarely, this allergic reaction may be serious and could result in a fall in blood pressure, feeling unwell, facial swelling and difficulty breathing. If you experience sudden wheeziness or difficulty in breathing, or swelling of the eyelids, lips, face or tongue, contact your doctor or casualty department of your hospital immediately.

If you think you have any other side effects not mentioned here, please tell your doctor or a pharmacist.

5. Storing Bendroflumethiazide Tablets

As with all medicines, keep your tablets out of the reach and sight of children.

Store in the original package to protect your tablets from light.

Keep the tablet container tightly closed to protect your tablets from moisture.

If your doctor tells you to stop taking Bendroflumethiazide Tablets, return any unused tablets to your pharmacist.

Do not take any Bendroflumethiazide Tablets after the expiry date as shown on the carton or label. Take any tablets remaining back to your pharmacist.

This leaflet was last approved in November 2006.

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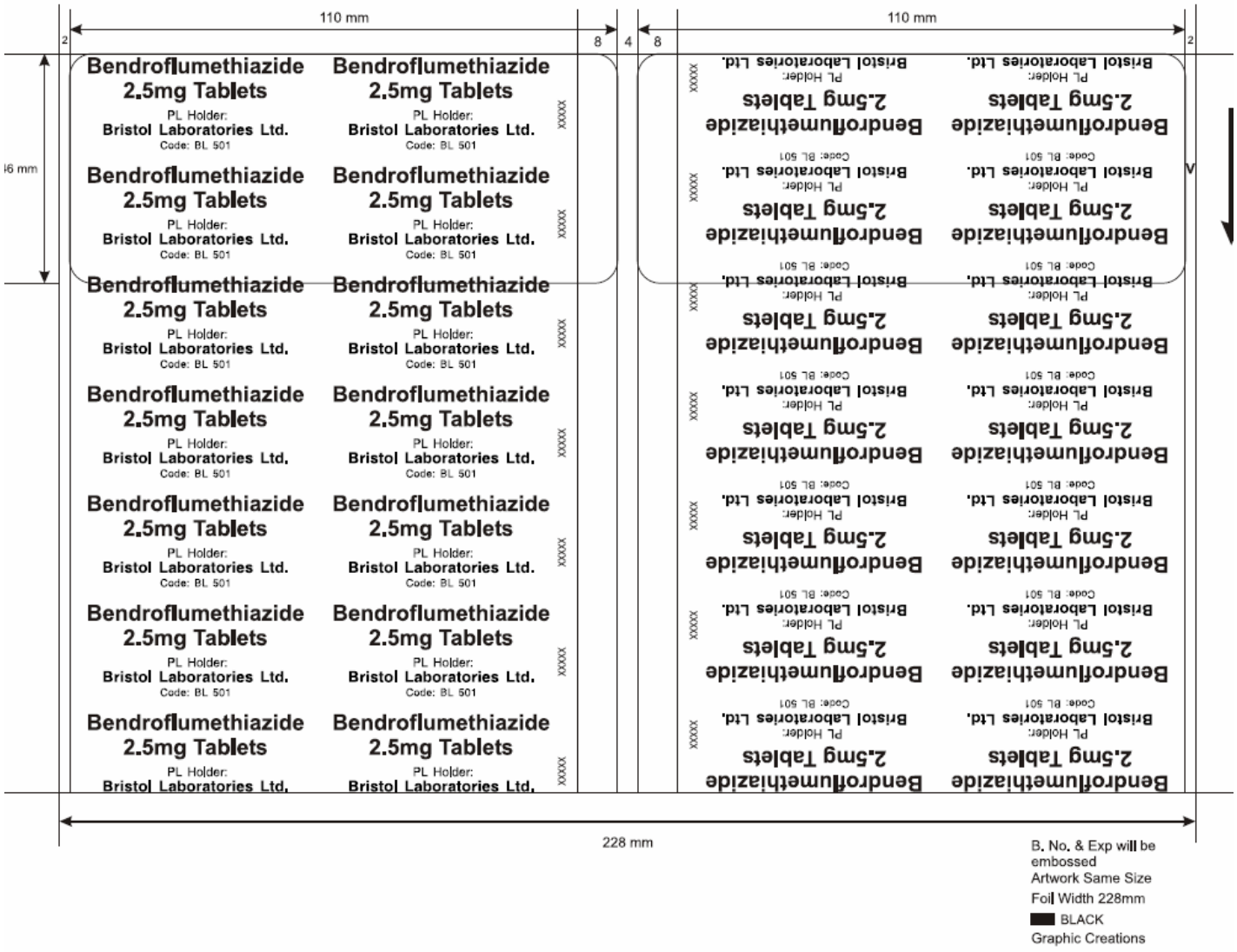
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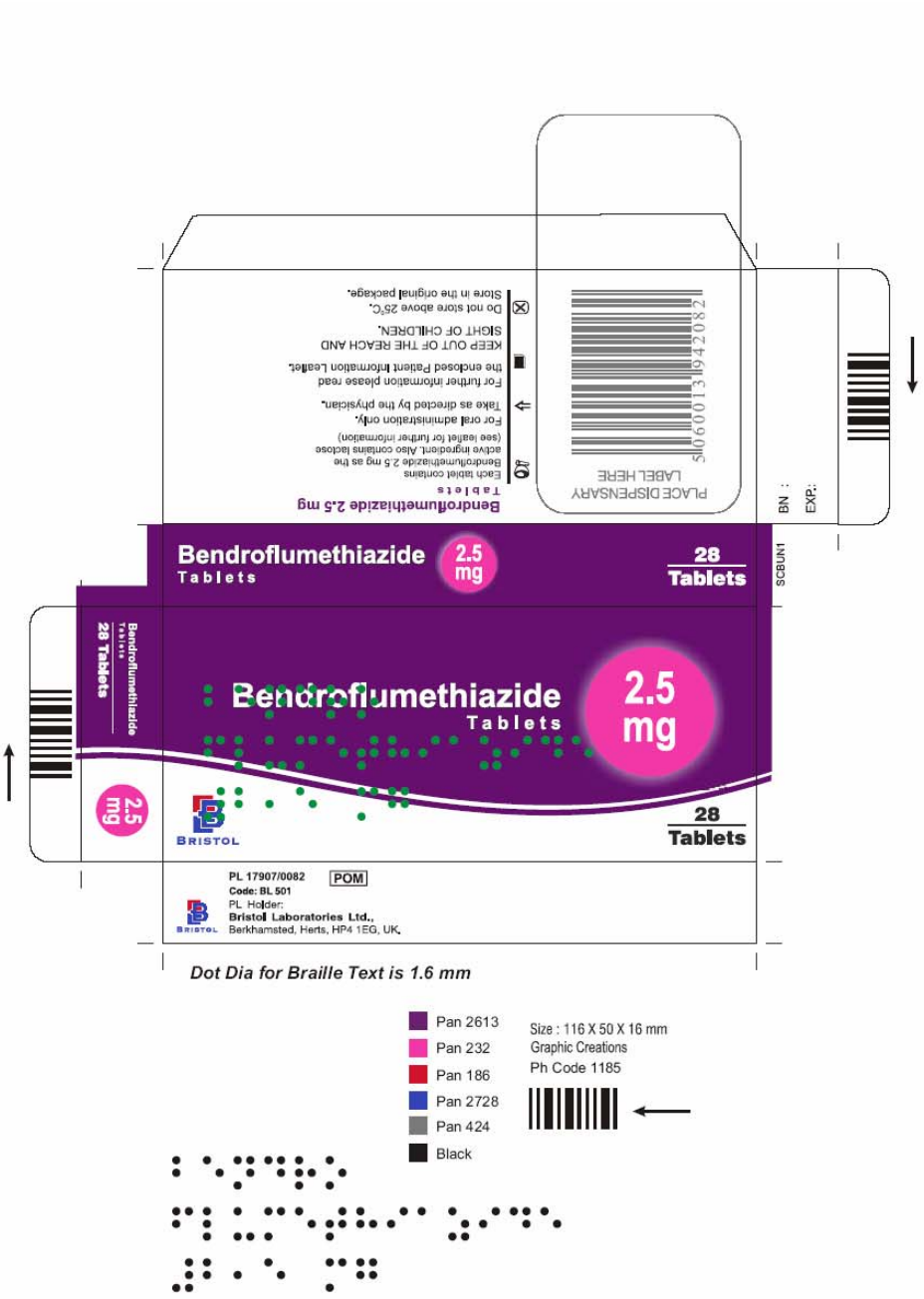
Bendroflumethiazide 2.5 mg
Tablets
Each tablet contains Bendroflumethiazide 2.5 mg as the active ingredient. Also contains lactose (see leaflet for further information)
For oral administration only.
Take as directed by the physician.
For further information please read the enclosed Patient Information Leaflet.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Do not store above 25°C.
Store in the original package.
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EXP.:
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Tablets
2.5 mg
28 Tablets
SCBUN1
Bendroflumethiazide
Tablets
2.5 mg
28 Tablets
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Bristol Laboratories Ltd.,
Berkhamsted, Herts, HP4 1EG, UK.
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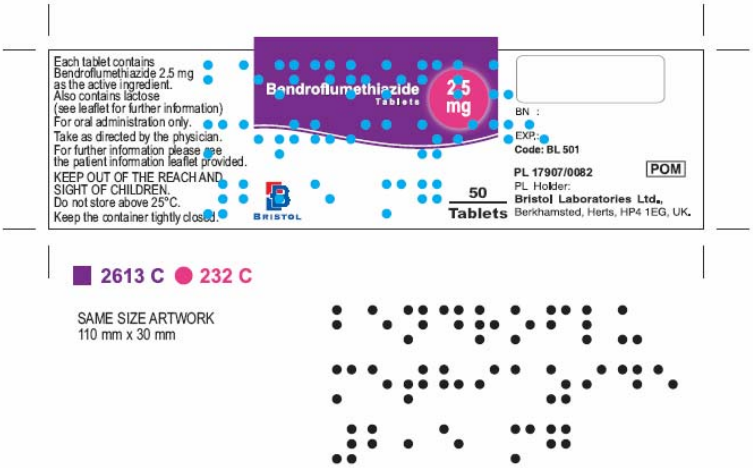

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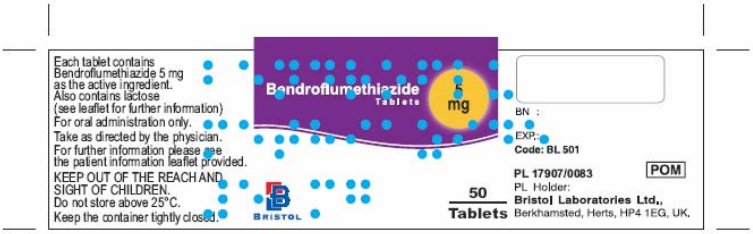

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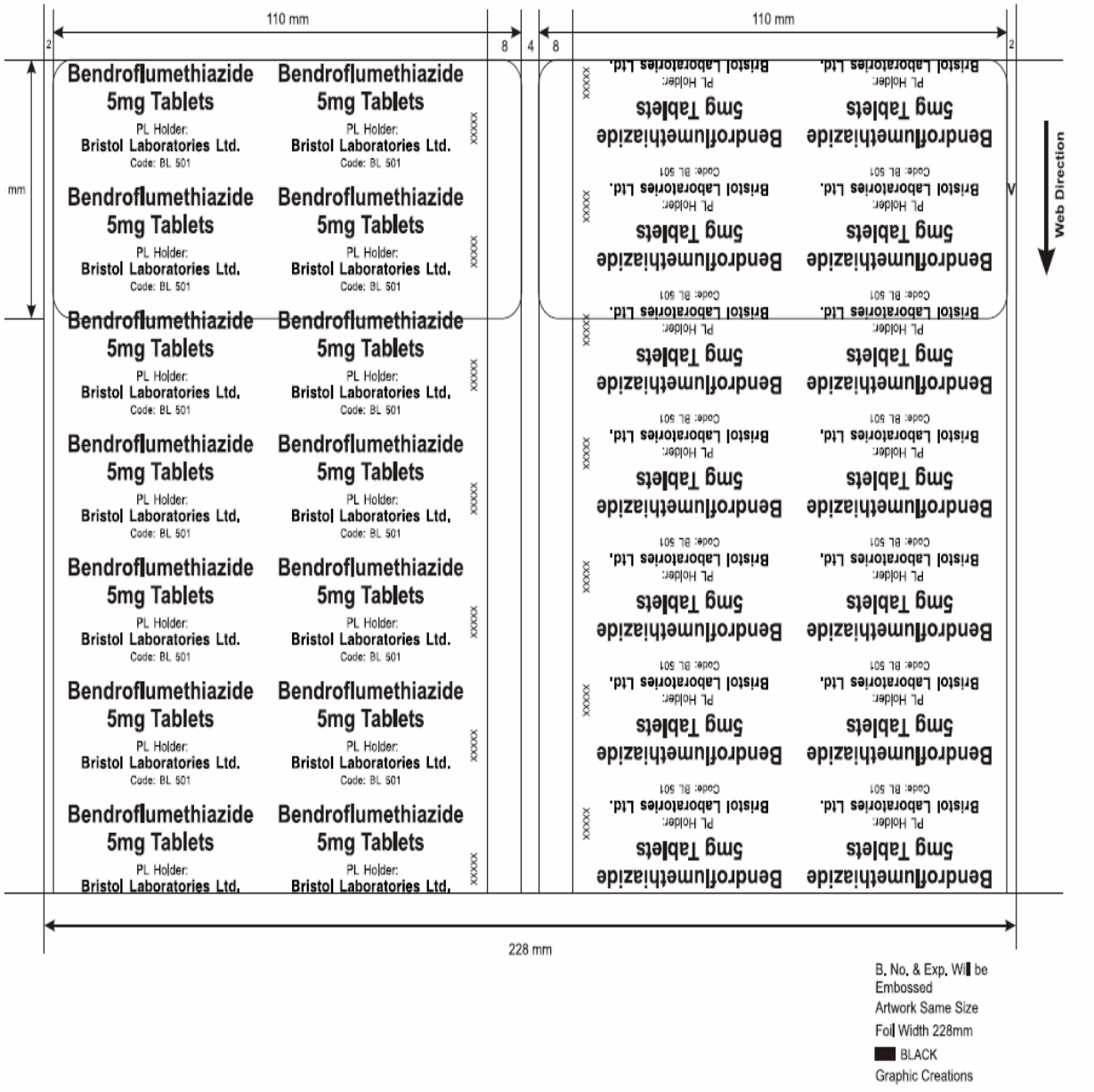
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Bendroflumethiazide 5mg Tablets
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Dot Dia for Braille Text is 1.5 mm

Pan 2613
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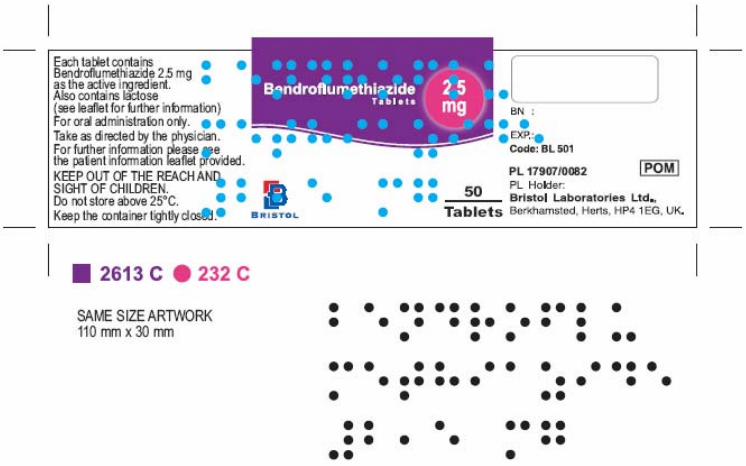
Graphic Creations



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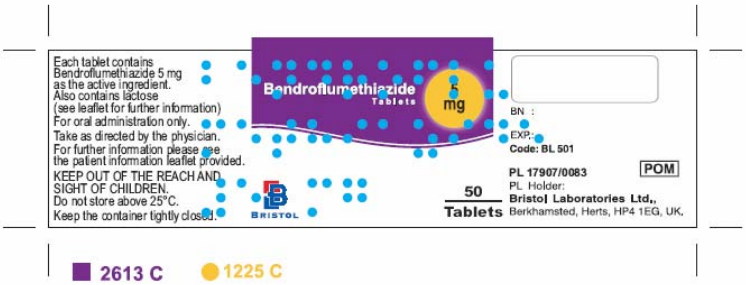

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