

Public Assessment Report

**Bendroflumethiazide 2.5mg Tablets
PL 04416/0529**

**Bendroflumethiazide 5mg Tablets
PL 04416/0530**

**BENDROFLUMETHIAZIDE 2.5MG TABLETS
PL 04416/0529**

**BENDROFLUMETHIAZIDE 5MG TABLETS
PL 04416/0530**

UKPAR

TABLE OF CONTENTS

	Page
Lay Summary	3
Scientific discussion	4
Steps taken for assessment	10
Steps taken after authorisation – summary	11
Summary of Product Characteristics	12
Patient Information Leaflet	30
Labelling	33

**BENDROFLUMETHIAZIDE 2.5MG TABLETS
PL 04416/0529**

**BENDROFLUMETHIAZIDE 5MG TABLETS
PL 04416/0530**

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) has granted Sandoz Limited Marketing Authorisations (licences) for the medicinal products Bendroflumethiazide 2.5mg Tablets/Bendroflumethiazide 5mg Tablets (PLs 04416/0529-30). These are prescription only medicines [POM] used to treat high blood pressure and to reduce swelling of any part of the body caused by heart, liver or kidney conditions.

Bendroflumethiazide works by increasing water loss through the kidneys, thus helping to remove excess fluids from the body.

These are simple applications that cross-refer to previously granted licences for Bendroflumethiazide 2.5mg Tablets/Bendroflumethiazide 5mg Tablets (PLs 12724/0028-9).

No new or unexpected safety concerns arose from these simple applications and it was therefore judged that the benefits of using Bendroflumethiazide 2.5mg Tablets/Bendroflumethiazide 5mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.

**BENDROFLUMETHIAZIDE 2.5MG TABLETS
PL 04416/0529**

**BENDROFLUMETHIAZIDE 5MG TABLETS
PL 04416/0530**

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

	Page
Introduction	5
Pharmaceutical assessment	6
Preclinical assessment	7
Clinical assessment	8
Overall conclusions and risk benefit assessment	9

INTRODUCTION

The UK granted marketing authorisations for the medicinal products Bendroflumethiazide 2.5mg Tablets/Bendroflumethiazide 5mg Tablets (PLs 04416/0529-30) to Sandoz Limited on 15 June 2006. The products are prescription only medicines [POM].

These applications were submitted as simple abridged applications according to Article 10.1(a)i of Directive 2001/83/EC, cross-referring to Bendroflumethiazide 2.5mg Tablets/Bendroflumethiazide 5mg Tablets (PLs 12724/0028-9, approved on 17 October 1994).

The products contain bendroflumethiazide. Bendroflumethiazide is a thiazide diuretic which reduces the reabsorption of electrolytes from the renal tubules, thereby increasing the excretion of sodium and chloride ions, and consequently of water. Bendroflumethiazide has, like other thiazides, a lowering effect on blood pressure which is considered to be due to sodium depletion; and it also enhances the effects of other antihypertensive agents.

No new data were submitted for these simple applications, nor were any necessary, as the data are identical to that of the previously granted cross-referenced products. As the cross-referenced products were granted prior to the introduction of current legislation, no public assessment reports were generated for them.

Bendroflumethiazide Tablets are indicated in the treatment of oedema associated with conditions such as congestive heart failure, nephrotic syndrome, cirrhosis of the liver. They may also be used as the sole antihypertensive agent or used concurrently with other specific hypotensive agents whose action it potentiates.

PHARMACEUTICAL ASSESSMENT

LICENCE NO: PLs 04416/0529-30
PROPRIETARY NAME: Bendroflumethiazide 2.5mg Tablets
Bendroflumethiazide 5mg Tablets
ACTIVE(S): Bendroflumethiazide
COMPANY NAME: Sandoz Limited
E.C. ARTICLE: 10.1(a)(i)
LEGAL STATUS: POM

INTRODUCTION AND BACKGROUND

These are national “informed consent” applications submitted under Article 10.1(a)(i) of Directive 2001/83/EC for tablets containing 2.5mg and 5mg of bendroflumethiazide.

These applications make reference to marketing authorisations held by Regent-GM Laboratories Ltd. (PLs 12724/0028-29) and a suitable letter of access to the data has been provided by them.

The applicant has confirmed that they have access to part II data concerning these products.

Licensing particulars are identical to respective strengths of reference products involving packaging; pack sizes; manufacturers of active ingredient and finished product; shelf lives; storage; finished product specification (FPS); drug substance specification (DSS) and method of manufacture.

The FPS and DSS for the products comply with the pharmacopoeial monographs.

Preclinical, pharmaceutical and clinical expert reports have been provided by suitably qualified experts. The experts confirm that the products are identical in composition, manufacture and pharmaceutical characteristics to the respective reference products and no toxicological or clinical issues arise.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPCs are consistent with those of the reference products.

PATIENT INFORMATION LEAFLET (PIL)

The PILs are consistent with those of the reference products and are therefore acceptable.

LABELLING

The labels generally comply with statutory requirements and best practice guidance.

CONCLUSIONS

A Marketing Authorisation may be granted.

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

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

OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY

The data for these applications are consistent with those previously assessed for the cross-referenced products and as such have been judged to be satisfactory.

PRECLINICAL

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

EFFICACY

These applications are identical to previously granted applications for Bendroflumethiazide 2.5mg Tablets/Bendroflumethiazide 5mg Tablets.

No new or unexpected safety concerns arose from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those of the cross-referenced products.

RISK-BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's products are identical to the cross-referenced products. Extensive clinical experience with the active ingredient bendroflumethiazide is considered to have demonstrated the therapeutic value of the compound. The risk-benefit assessment is therefore considered to be favourable.

**BENDROFLUMETHIAZIDE 2.5MG TABLETS
PL 04416/0529**

**BENDROFLUMETHIAZIDE 5MG TABLETS
PL 04416/0530**

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation applications for Bendroflumethiazide 2.5mg Tablets/Bendroflumethiazide 5mg Tablets on 24 March 2003.
2	The MHRA's assessment of the submitted data was completed on 25 June 2003.
3	Further information was requested from the company on 26 and 27 June 2003.
4	The applicant's response to further information request was received on 19 February 2004.
5	Further information was requested from the company on 8 June 2004.
6	The applicant's response to further information request was received on 10 November 2005.
7	Additional information was requested from the company on 10 November 2005.
8	The applicant's response to additional information request was received on 14 June 2006.
9	The MHRA completed its assessment of the application on 15 June 2006.
10	The application was determined on 15 June 2006.

**BENDROFLUMETHIAZIDE 2.5MG TABLETS
PL 04416/0529**

**BENDROFLUMETHIAZIDE 5MG TABLETS
PL 04416/0530**

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bendroflumethiazide 2.5mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Bendroflumethiazide 2.5 mg per tablet.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Bendroflumethiazide 2.5 mg tablets are presented as white flat bevelled edge tablets engraved with the company logo on one side and A268 on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Oedema:

Bendroflumethiazide is indicated in the treatment of oedema associated with conditions such as congestive heart failure, nephrotic syndrome, cirrhosis of the liver.

Essential hypertension:

Bendroflumethiazide may be used as the sole antihypertensive agent or used concurrently with other specific hypotensive agents whose action it potentiates.

4.2. Posology and method of administration

Route of administration: Oral

ADULTS:

Oedema:

5.0 - 10.0 mg once daily or on alternate days

Maintenance:

2.5 - 5.0 mg two or three times a week

Essential hypertension:

2.5 mg in the morning, alone or in conjunction with other antihypertensive agents in more severe hypertension.

The dosage should be reduced in the elderly with impaired renal function.

CHILDREN:

Diuretic - Initial: 0.4 mg per kg of body-weight per day.

Maintenance: 0.05 to 0.1 mg per kg of body-weight per day.

Antihypertensive: 0.05 to 0.4 mg/kg body-weight per day as a single dose or in two divided daily doses, adjusted according to response.

4.3. Contraindications

Bendroflumethiazide is contra-indicated in patients hypersensitive to this drug or any of the excipients and in patients with severe renal insufficiency, Addison's disease, refractory hypokalaemia, hyponatraemia, hypercalcaemia, serious hepatic disorders, symptomatic hyperuricaemia and acute porphyria.

4.4. Special warnings and precautions for use

When doses higher than those stated in Section 4.2 Posology and method of administration are given to patients being treated for hypertension, more marked changes in plasma potassium, uric acid, glucose and lipids may be experienced. There is also no advantage in the control of blood pressure at higher doses and therefore should not be used.

Patients receiving thiazides should be checked regularly for potassium deficiency. Thiazides may aggravate gout, Systemic Lupus Erythematosus (SLE), existing diabetes mellitus and cause symptoms in patients with latent diabetes.

Caution is required in treating patients with alcoholic cirrhosis as there is an increased risk of hypomagnesaemia with bendroflumethiazide.

Particular caution is required in patients with severe asthma who are taking bendroflumethiazide and beta₂ agonist therapy concomitantly because potentially serious hypokalaemia associated with beta₂ agonist therapy may be potentiated.

Particular caution is needed in the elderly because of their susceptibility to electrolyte imbalance. Electrolytes should be monitored regularly.

Renal function should also be monitored at regular intervals.

There is a risk of precipitating hepatic encephalopathy in patients with cirrhosis. Caution should be exercised when used in patients with diabetes, gout, SLE, hepatic impairment and renal impairment, porphyria, hyperlipidaemia, pancreatitis, cirrhosis and prostatic hypertrophy. ECG should be monitored in patients receiving cardiac glycosides.

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

4.5. Interactions with other medicinal products and other forms of interaction

Analgesics: Diuretics such as bendroflumethiazide increase the risk of nephrotoxicity associated with non-steroidal anti-inflammatory analgesics (NSAIDs). NSAIDs, particularly indometacin and ketorolac may antagonise the natriuresis and increase in plasma renin activity caused by thiazide diuretics. It may also reduce the antihypertensive effect and increase in urine volume caused by thiazide diuretics, possibly by inhibiting renal prostaglandin synthesis and/or by causing sodium and fluid retention. There have been occasional reports of decreased renal function when indometacin is given with triamterene. Concomitant use should therefore be avoided. There is an increased risk of ventricular arrhythmias with levacetylmethadol. Concomitant use with opiates leads to an increased risk of postural hypotension.

Anion-exchange resins: colestyramine and colestipol lead to decreased absorption of thiazides. It has been recommended that administration is at least 2 hours apart.

Antidiabetics: Concurrent administration of bendroflumethiazide in patients receiving sulphonylureas may impair control of diabetes by antagonising the hypoglycaemic effect. Chlorpropamide increases the risk of hyponatraemia associated with taking thiazides such as bendroflumethiazide in combination with potassium-sparing diuretics.

Antiepileptics: There is an increased risk of hyponatraemia with carbamazepine.

Antifungals: There is an increased risk of hypokalaemia if thiazides are given with amphotericin.

Antihistamines: Patients with hypokalaemia or other electrolyte imbalance have an increased risk of ventricular arrhythmias with terfenadine.

Antihypertensives: Concurrent use of bendroflumethiazide with antihypertensives enhances the hypotensive effect. There is an increased risk of first-dose hypotensive effect of post-synaptic alpha-blockers such as prazosin.

Antipsychotics: Patients with hypokalaemia have an increased risk of ventricular arrhythmias with pimozide. Concomitant use should be avoided.

Alprostadil: Concomitant use with alprostadil enhances the hypotensive effect.

Anti-arrhythmics: The cardiac toxicity associated with amiodarone, disopyramide, flecainide, and quinidine is increased if hypokalaemia occurs. The action of lidocaine and mexiletine is antagonised by hypokalaemia.

Antidepressants: There is a possible increased risk of postural hypotension with tricyclic antidepressants and of hypokalaemia if thiazides are given with reboxetine.

Beta-blockers: Use with bendroflumethiazide enhances the hypotensive effect. Patients with hypokalaemia have an increased risk of ventricular arrhythmias with sotalol.

Calcium salts: There is an increased risk of hypercalcaemia with thiazides such as bendroflumethiazide.

Calcium-channel blockers: Concomitant use with bendroflumethiazide enhances the hypotensive effect.

Cardiac glycosides: The concurrent use of cardiac glycosides with thiazide diuretics may enhance the possibility of cardiac toxicity associated with hypokalaemia, resulting in cardiac arrhythmias.

Corticosteroids: There is an increased risk of hypokalaemia with thiazides such as bendroflumethiazide and the diuretic effect is antagonised.

Cytotoxics: Concurrent use of diuretics such as bendroflumethiazide with cisplatin increases the risk of nephrotoxicity and ototoxicity.

Hormone Antagonists: There is an increased risk of hyponatraemia with aminoglutethimide. Thiazides such as bendroflumethiazide increase the risk of hypercalcaemia with toremifene.

Moxisylyte: Concomitant use with bendroflumethiazide enhances the hypotensive effect.

Muscle relaxants: An enhanced hypotensive effect is associated with concomitant use with baclofen and tizanidine. Bendroflumethiazide interacts with nondepolarising neuromuscular blocking drugs leading to prolonged neuromuscular blockade.

Oestrogens and Progestogens: The diuretic effect is antagonised with oestrogens and combined oral contraceptives.

Other diuretics: There is an increased risk of hypokalaemia if thiazides such as bendroflumethiazide, loop diuretics or acetazolamide are taken together.

Sympathomimetics: There is an increased risk of hypokalaemia if thiazides are given with high doses of bambuterol, fenoterol, formoterol, reproterol, ritodrine, salbutamol, salmeterol, terbutaline and tulobuterol. Potentially serious hypokalaemia may result from beta₂ agonist therapy.

Theophylline: There is an increased risk of hypokalaemia with thiazides such as bendroflumethiazide.

Ulcer-healing Drugs: There is an increased risk of hypokalaemia if thiazides are given with carbenoxolone. Carbenoxolone also antagonises the diuretic effect.

Other interactions: Interactions with lithium (leading to lithium toxicity due to reduced renal clearance of lithium), vitamin D (leading to increased risk of hypercalcaemia), alcohol, and barbiturates (leading to increased risk of postural hypotension) have also been reported.

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 hypovolaemia, increased blood viscosity and reduced placental perfusion.

There is inadequate evidence of safety in human pregnancy and some workers have described foetal bone marrow depression and blood disorders including neutropenia and thrombocytopenia. When given in late pregnancy, neonatal thrombocytopenia has been reported. Foetal and neonatal jaundice have also been described.

As diuretics pass into breast milk, they should be avoided in mothers who wish to breast-feed.

Bendroflumethiazide may suppress lactation.

4.7. Effects on ability to drive and use machines

None reported.

4.8. Undesirable effects

Impotence may occur and is reversible within a few weeks of stopping the treatment. Mild anorexia or indigestion which may occur occasionally can be avoided or reduced by taking the dose during or immediately after a meal.

Hypersensitivity reactions including pneumonitis, pulmonary oedema, and severe skin reactions have been reported.

Skin reactions have been reported in a few patients. Blood dyscrasias and pancreatitis have occurred rarely.

The intensive or continuous use of bendroflumethiazide may cause hypokalaemia and therefore potassium chloride supplements are strongly recommended in these circumstances. Higher doses cause more marked changes in plasma potassium.

Disturbances of electrolytes i.e. hypomagnesaemia, hyponatraemia, hypercalcaemia, hypochlorhaemic alkalosis, and acid/base balance, hyperglycaemia, lipids,

hyperuricaemia, nausea, vomiting, diarrhoea, constipation, thirst and polyuria, weakness, dizziness, muscle cramps, loss of libido, precipitation of gout, postural hypotension, photosensitivity, intra-hepatic cholestasis, and in cirrhosis, hepatic encephalopathy may occur.

4.9. Overdose

Signs and symptoms of overdosage are drowsiness, lethargy, coma, evidence of CNS depression with or without cardiovascular or respiratory depression and hypovolaemia.

Treatment should be symptomatic and aimed at fluid and electrolyte replacement. Gastric lavage should be carried out in the case of a recent excessive ingestion. Blood pressure monitoring is strongly advised.

During treatment, electrolyte and fluid status together with renal function should be carefully monitored. Hyponatraemia should be treated with water deprivation rather than salt addition. Cathartics should be avoided. There is no known specific antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic classification : Low-Ceiling Diuretics Thiazides -
Bendroflumethiazide

ATC code : C03A A01

Bendroflumethiazide is a thiazide diuretic which reduces the reabsorption of electrolytes from the renal tubules, thereby increasing the excretion of sodium and chloride ions, and consequently of water. Thiazides also reduce the carbonic anhydrase activity so that bicarbonate excretion is increased but this inhibitory action is weak as compared with the effect on chloride excretion and does not appreciably alter the pH of the urine. In response to the increased tubule load of sodium, the rate of tubular secretion of potassium and exchange with sodium is augmented and an increased amount of potassium is lost in the urine.

Diuresis is initiated after about 2 hours of bendroflumethiazide administration, the maximum diuresis occurs within 12 hours and a significant diuretic effect persists for 24 hours. In subjects with normal renal function; sodium and chloride output is increased twofold after 5 mg of bendroflumethiazide, 7.5 mg increases sodium output threefold and chloride output fourfold. 10 mg does not increase sodium and chloride output significantly more than 7.5 mg i.e. the dose response curve becomes flat. Potassium excretion is doubled after 5 mg of bendroflumethiazide, in normal subjects doubling this dose has no effect on potassium excretion.

Bendroflumethiazide has, like other thiazides, a lowering effect on blood pressure which is considered to be due to sodium depletion; and it also enhances the effects of other antihypertensive agents.

Bendroflumethiazide is used in oedema associated with congestive heart failure, renal and hepatic disorders.

In the treatment of oedema, the usual initial dose is 5 mg daily, reduced to a dose of 2.5 mg daily or 5 mg on alternative days. A suggested initial dose for children is up to 400 micrograms per kg body weight daily, reduced to 50 - 100 micrograms per kg for maintenance.

In the treatment for hypertension the usual dose is 2.5 mg to 10 mg daily either alone, or in conjunction with other antihypertensive agents.

5.2. Pharmacokinetic properties

Bendroflumethiazide is more completely absorbed from the gastro-intestinal tract than chlorothiazide, reflecting its greater lipid solubility. Maximum diuresis occurs within 12 hours of bendroflumethiazide administration, although a significant diuretic effect persists for 24 hours.

Bendroflumethiazide is fairly extensively metabolised: about 30% is excreted unchanged in the urine. It is estimated to have plasma half-life of about 3 or 4 hours.

5.3. Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose
Maize starch
Pregelatinised maize starch
Magnesium stearate
Starch 1500
Potable water

6.2. Incompatibilities

Bendroflumethiazide preparations should not be administered concurrently with lithium carbonate.

6.3. Shelf life

As packaged for sale:
3 years for opaque plastic containers.
2 years for blister packaging.

6.4. Special precautions for storage

Blister Packs: Do not store above 25°C, store in original package.
Plastic Containers: Do not store above 25°C, keep container tightly closed.

6.5. Nature and contents of container

Bendroflumethiazide tablets are packed in the following containers and closures.

1.	Opaque plastic containers composed of polypropylene tubes and polyethylene-made tamper-evident closures for pack sizes of 28, 30, 42, 50, 56, 60, 84, 90, 100, 112, 250, 500 and 1000 tablets.
2.	Opaque plastic containers composed of either high density polypropylene or high density polyethylene with a tamper-evident or child-resistant tamper-evident closure composed of high density polyethylene with a packing inclusion of standard polyether foam or polyethylene or polypropylene made filler in pack sizes of 28, 30, 42, 50, 56, 60, 84, 90, 100, 112, 250, 500 and 1000 tablets.
3.	Blister packs of aluminium/opaque PVC. It is subsequently packed in printed boxboard cartons in pack sizes of 28, 30, 42, 56, 60, 84, 90 and 112 tablets.

Not all pack sizes may be marketed.

6.6. Instructions for Use, Handling and Disposal

No special instructions for use/handling.

7. MARKETING AUTHORISATION HOLDER

Sandoz Ltd
Woolmer Way
Bordon
Hampshire
GU35 9QE

8. MARKETING AUTHORISATION NUMBER

PL 04416 / 0529

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

15/06/2006

10 DATE OF REVISION OF THE TEXT

15/06/2006

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bendroflumethiazide 5mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Bendroflumethiazide 5 mg per tablet.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Bendroflumethiazide 5 mg tablets are presented as white flat bevelled edge tablets engraved with the company logo on one side and A269 on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Oedema:

Bendroflumethiazide is indicated in the treatment of oedema associated with conditions such as congestive heart failure, nephrotic syndrome, cirrhosis of the liver.

Essential hypertension:

Bendroflumethiazide may be used as the sole antihypertensive agent or used concurrently with other specific hypotensive agents whose action it potentiates.

4.2. Posology and method of administration

Route of administration: Oral

ADULTS:

Oedema:

5.0 - 10.0 mg once daily or on alternate days

Maintenance:

2.5 - 5.0 mg two or three times a week

Essential hypertension:

2.5 mg in the morning, alone or in conjunction with other antihypertensive agents in more severe hypertension.

The dosage should be reduced in the elderly with impaired renal function.

CHILDREN:

Diuretic - Initial: 0.4 mg per kg of body-weight per day.

Maintenance: 0.05 to 0.1 mg per kg of body-weight per day.

Antihypertensive: 0.05 to 0.4 mg/kg body-weight per day as a single dose or in two divided daily doses, adjusted according to response.

4.3. Contraindications

Bendroflumethiazide is contra-indicated in patients hypersensitive to this drug or any of the excipients and in patients with severe renal insufficiency, Addison's disease, refractory hypokalaemia, hyponatraemia, hypercalcaemia, serious hepatic disorders, symptomatic hyperuricaemia and acute porphyria.

4.4. Special warnings and precautions for use

When doses higher than those stated in Section 4.2 Posology and method of administration are given to patients being treated for hypertension, more marked changes in plasma potassium, uric acid, glucose and lipids may be experienced. There is also no advantage in the control of blood pressure at higher doses and therefore should not be used.

Patients receiving thiazides should be checked regularly for potassium deficiency. Thiazides may aggravate gout, Systemic Lupus Erythematosus (SLE), existing diabetes mellitus and cause symptoms in patients with latent diabetes.

Caution is required in treating patients with alcoholic cirrhosis as there is an increased risk of hypomagnesaemia with bendroflumethiazide.

Particular caution is required in patients with severe asthma who are taking bendroflumethiazide and beta₂ agonist therapy concomitantly because potentially serious hypokalaemia associated with beta₂ agonist therapy may be potentiated.

Particular caution is needed in the elderly because of their susceptibility to electrolyte imbalance. Electrolytes should be monitored regularly.

Renal function should also be monitored at regular intervals.

There is a risk of precipitating hepatic encephalopathy in patients with cirrhosis. Caution should be exercised when used in patients with diabetes, gout, SLE, hepatic impairment and renal impairment, porphyria, hyperlipidaemia, pancreatitis, cirrhosis

and prostatic hypertrophy. ECG should be monitored in patients receiving cardiac glycosides.

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

4.5. Interactions with other medicinal products and other forms of interaction

Analgesics: Diuretics such as bendroflumethiazide increase the risk of nephrotoxicity associated with non-steroidal anti-inflammatory analgesics (NSAIDs). NSAIDs, particularly indometacin and ketorolac may antagonise the natriuresis and increase in plasma renin activity caused by thiazide diuretics. It may also reduce the antihypertensive effect and increase in urine volume caused by thiazide diuretics, possibly by inhibiting renal prostaglandin synthesis and/or by causing sodium and fluid retention. There have been occasional reports of decreased renal function when indometacin is given with triamterene. Concomitant use should therefore be avoided. There is an increased risk of ventricular arrhythmias with levacetylmethadol. Concomitant use with opiates leads to an increased risk of postural hypotension.

Anion-exchange resins: colestyramine and colestipol lead to decreased absorption of thiazides. It has been recommended that administration is at least 2 hours apart.

Antidiabetics: Concurrent administration of bendroflumethiazide in patients receiving sulphonylureas may impair control of diabetes by antagonising the hypoglycaemic effect. Chlorpropamide increases the risk of hyponatraemia associated with taking thiazides such as bendroflumethiazide in combination with potassium-sparing diuretics.

Antiepileptics: There is an increased risk of hyponatraemia with carbamazepine.

Antifungals: There is an increased risk of hypokalaemia if thiazides are given with amphotericin.

Antihistamines: Patients with hypokalaemia or other electrolyte imbalance have an increased risk of ventricular arrhythmias with terfenadine.

Antihypertensives: Concurrent use of bendroflumethiazide with antihypertensives enhances the hypotensive effect. There is an increased risk of first-dose hypotensive effect of post-synaptic alpha-blockers such as prazosin.

Antipsychotics: Patients with hypokalaemia have an increased risk of ventricular arrhythmias with pimozide. Concomitant use should be avoided.

Alprostadil: Concomitant use with alprostadil enhances the hypotensive effect.

Anti-arrhythmics: The cardiac toxicity associated with amiodarone, disopyramide, flecainide, and quinidine is increased if hypokalaemia occurs. The action of lidocaine and mexiletine is antagonised by hypokalaemia.

Antidepressants: There is a possible increased risk of postural hypotension with tricyclic antidepressants and of hypokalaemia if thiazides are given with reboxetine.

Beta-blockers: Use with bendroflumethiazide enhances the hypotensive effect. Patients with hypokalaemia have an increased risk of ventricular arrhythmias with sotalol.

Calcium salts: There is an increased risk of hypercalcaemia with thiazides such as bendroflumethiazide.

Calcium-channel blockers: Concomitant use with bendroflumethiazide enhances the hypotensive effect.

Cardiac glycosides: The concurrent use of cardiac glycosides with thiazide diuretics may enhance the possibility of cardiac toxicity associated with hypokalaemia, resulting in cardiac arrhythmias.

Corticosteroids: There is an increased risk of hypokalaemia with thiazides such as bendroflumethiazide and the diuretic effect is antagonised.

Cytotoxics: Concurrent use of diuretics such as bendroflumethiazide with cisplatin increases the risk of nephrotoxicity and ototoxicity.

Hormone Antagonists: There is an increased risk of hyponatraemia with aminoglutethimide. Thiazides such as bendroflumethiazide increase the risk of hypercalcaemia with toremifene.

Moxisylyte: Concomitant use with bendroflumethiazide enhances the hypotensive effect.

Muscle relaxants: An enhanced hypotensive effect is associated with concomitant use with baclofen and tizanidine. Bendroflumethiazide interacts with nondepolarising neuromuscular blocking drugs leading to prolonged neuromuscular blockade.

Oestrogens and Progestogens: The diuretic effect is antagonised with oestrogens and combined oral contraceptives.

Other diuretics: There is an increased risk of hypokalaemia if thiazides such as bendroflumethiazide, loop diuretics or acetazolamide are taken together.

Sympathomimetics: There is an increased risk of hypokalaemia if thiazides are given with high doses of bambuterol, fenoterol, formoterol, reproterol, ritodrine, salbutamol, salmeterol, terbutaline and tulobuterol. Potentially serious hypokalaemia may result from beta₂ agonist therapy.

Theophylline: There is an increased risk of hypokalaemia with thiazides such as bendroflumethiazide.

Ulcer-healing Drugs: There is an increased risk of hypokalaemia if thiazides are given with carbenoxolone. Carbenoxolone also antagonises the diuretic effect.

Other interactions: Interactions with lithium (leading to lithium toxicity due to reduced renal clearance of lithium), vitamin D (leading to increased risk of hypercalcaemia), alcohol, and barbiturates (leading to increased risk of postural hypotension) have also been reported.

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 hypovolaemia, increased blood viscosity and reduced placental perfusion.

There is inadequate evidence of safety in human pregnancy and some workers have described foetal bone marrow depression and blood disorders including neutropenia and thrombocytopenia. When given in late pregnancy, neonatal thrombocytopenia has been reported. Foetal and neonatal jaundice have also been described.

As diuretics pass into breast milk, they should be avoided in mothers who wish to breast-feed.

Bendroflumethiazide may suppress lactation.

4.7. Effects on ability to drive and use machines

None reported.

4.8. Undesirable effects

Impotence may occur and is reversible within a few weeks of stopping the treatment. Mild anorexia or indigestion which may occur occasionally can be avoided or reduced by taking the dose during or immediately after a meal.

Hypersensitivity reactions including pneumonitis, pulmonary oedema, and severe skin reactions have been reported.

Skin reactions have been reported in a few patients. Blood dyscrasias and pancreatitis have occurred rarely.

The intensive or continuous use of bendroflumethiazide may cause hypokalaemia and therefore potassium chloride supplements are strongly recommended in these circumstances. Higher doses cause more marked changes in plasma potassium.

Disturbances of electrolytes i.e. hypomagnesaemia, hyponatraemia, hypercalcaemia, hypochlorhaemic alkalosis, and acid/base balance, hyperglycaemia, lipids, hyperuricaemia, nausea, vomiting, diarrhoea, constipation, thirst and polyuria, weakness, dizziness, muscle cramps, loss of libido, precipitation of gout, postural

hypotension, photosensitivity, intra-hepatic cholestasis, and in cirrhosis, hepatic encephalopathy may occur.

4.9. Overdose

Signs and symptoms of overdosage are drowsiness, lethargy, coma, evidence of CNS depression with or without cardiovascular or respiratory depression and hypovolaemia.

Treatment should be symptomatic and aimed at fluid and electrolyte replacement. Gastric lavage should be carried out in the case of a recent excessive ingestion. Blood pressure monitoring is strongly advised.

During treatment, electrolyte and fluid status together with renal function should be carefully monitored. Hyponatraemia should be treated with water deprivation rather than salt addition. Cathartics should be avoided. There is no known specific antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic classification : Low-Ceiling Diuretics Thiazides -
Bendroflumethiazide
ATC code : C03A A01

Bendroflumethiazide is a thiazide diuretic which reduces the reabsorption of electrolytes from the renal tubules, thereby increasing the excretion of sodium and chloride ions, and consequently of water. Thiazides also reduce the carbonic anhydrase activity so that bicarbonate excretion is increased but this inhibitory action is weak as compared with the effect on chloride excretion and does not appreciably alter the pH of the urine. In response to the increased tubule load of sodium, the rate of tubular secretion of potassium and exchange with sodium is augmented and an increased amount of potassium is lost in the urine.

Diuresis is initiated after about 2 hours of bendroflumethiazide administration, the maximum diuresis occurs within 12 hours and a significant diuretic effect persists for 24 hours. In subjects with normal renal function; sodium and chloride output is increased twofold after 5 mg of bendroflumethiazide, 7.5 mg increases sodium output threefold and chloride output fourfold. 10 mg does not increase sodium and chloride output significantly more than 7.5 mg i.e. the dose response curve becomes flat. Potassium excretion is doubled after 5 mg of bendroflumethiazide, in normal subjects doubling this dose has no effect on potassium excretion.

Bendroflumethiazide has, like other thiazides, a lowering effect on blood pressure which is considered to be due to sodium depletion; and it also enhances the effects of other antihypertensive agents.

Bendroflumethiazide is used in oedema associated with congestive heart failure, renal and hepatic disorders.

In the treatment of oedema, the usual initial dose is 5 mg daily, reduced to a dose of 2.5 mg daily or 5 mg on alternative days. A suggested initial dose for children is up to 400 micrograms per kg body weight daily, reduced to 50 - 100 micrograms per kg for maintenance.

In the treatment for hypertension the usual dose is 2.5 mg to 10 mg daily either alone, or in conjunction with other antihypertensive agents.

5.2. Pharmacokinetic properties

Bendroflumethiazide is more completely absorbed from the gastro-intestinal tract than chlorothiazide, reflecting its greater lipid solubility. Maximum diuresis occurs within 12 hours of bendroflumethiazide administration, although a significant diuretic effect persists for 24 hours.

Bendroflumethiazide is fairly extensively metabolised: about 30% is excreted unchanged in the urine. It is estimated to have plasma half-life of about 3 or 4 hours.

5.3. Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose
Maize starch
Pregelatinised maize starch
Magnesium stearate
Starch 1500
Potable water

6.2. Incompatibilities

Bendroflumethiazide preparations should not be administered concurrently with lithium carbonate.

6.3. Shelf life

As packaged for sale:
3 years for opaque plastic containers.
2 years for blister packaging.

6.4. Special precautions for storage

Blister Packs: Do not store above 25°C, store in original package.
Plastic Containers: Do not store above 25°C, keep container tightly closed.

6.5. Nature and contents of container

Bendroflumethiazide tablets are packed in the following containers and closures.

1.	Opaque plastic containers composed of polypropylene tubes and polyethylene-made tamper-evident closures for pack sizes of 28, 30, 42, 50, 56, 60, 84, 90, 100, 112, 250, 500 and 1000 tablets.
2.	Opaque plastic containers composed of either high density polypropylene or high density polyethylene with a tamper-evident or child-resistant tamper-evident closure composed of high density polyethylene with a packing inclusion of standard polyether foam or polyethylene or polypropylene made filler in pack sizes of 28, 30, 42, 50, 56, 60, 84, 90, 100, 112, 250, 500 and 1000 tablets.
3.	Blister packs of aluminium/opaque PVC. It is subsequently packed in printed boxboard cartons in pack sizes of 28, 30, 42, 56, 60, 84, 90 and 112 tablets.

Not all pack sizes may be marketed.

6.6. Instructions for Use, Handling and Disposal

No special instructions for use/handling.

7. MARKETING AUTHORISATION HOLDER

Sandoz Ltd
Woolmer Way
Bordon
Hampshire
GU35 9QE

8. MARKETING AUTHORISATION NUMBER

PL 04416 / 0530

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

15/06/2006


10 DATE OF REVISION OF THE TEXT

15/06/2006


Patient Information Leaflet

BENDROFLUMETHIAZIDE 5MG TABLETS

PL 04416/0530

 <p>For oral administration, as directed by the doctor.</p> <p>For further information, see Patient Information Leaflet.</p> <p>KEEP OUT OF THE REACH AND SIGHT OF CHILDREN</p> <p>Do not store above 30°C. Keep container tightly closed.</p> <p>PL 04416/0530</p> <p>Sandoz Ltd, Woolston Way, Bordon, Hants, GU35 5GE</p> <p>500 tablets</p> <p>6290204LL01A</p>	<p>Antihypertensive (for lowering blood pressure) 0.05 to 0.4mg per kg of bodyweight daily as a single dose or in two divided daily doses, adjusted according to response.</p> <p>Effect:</p> <p>The dosage may need to be reduced, particularly when the patient is suffering from kidney disease.</p> <p>• Your doctor will decide the dose that is best for you. The pharmacist's label will also tell you how many tablets to take and how often. If you are not sure about anything ask your doctor or pharmacist.</p> <p>• Do not stop taking this medicine without consulting your doctor.</p> <p>• Try to take your medicine at the same time every day. If you miss a dose of this medicine, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and continue with the regular dosing schedule. DO NOT DOUBLE THE DOSES.</p> <p>• If you think you have taken too many tablets, contact your doctor straight away or go to the nearest hospital casualty department. Take with you any remaining tablets and the container so that the medicine can be identified.</p> <p>AFTER TAKING THIS MEDICINE</p> <p>• Along with the needed effects, this medicine may cause side effects in</p>	<p>certain patients. The more common side effects are impotence (difficulty in maintaining an erection), mild loss of appetite and indigestion may also occur but these can be reduced by taking the tablets during a meal or immediately after eating. Other side effects include: hypernatraemia.</p> <p>• Medicines such as propranolol (beta-blocker of the lungs), slow sodium to light, joint pain, lower back or side pain, disturbance of electrolyte and acid-base balance, faint, lightheadedness, weakness, dizziness, constipation, thirst and secretion of excessive amounts of urine, dark urine, light-coloured stools, difficult urination, fast breathing, sometimes with sweating, blue lips and fingernails, pale skin, increased sweating, dry mouth, increased thirst, irregular heartbeat, mood or mental changes, muscle cramps, weakness, joint pain, dizziness, headache, weakness, dizziness, muscle cramps, decreased sexual ability, gout, lightheadedness and, in patients with liver disease, hepatic encephalopathy (disturbance of the nervous system characterised by tremor and musty odour of breath) may occur. Rare side effects are skin reactions, pancreatitis (inflammation of the pancreas causing abdominal pain, back pain, fever and rapid pulse rate) and changes to blood cells. If you get a bad sore throat or high temperature or become more tired and pale, or you bruise or have nose bleeds more frequently, contact your doctor immediately.</p> <p>• As with all thiazides, Bendroflumethiazide increases the loss of potassium in the urine which can cause a variety of symptoms such as weakness and constipation. This imbalance can be corrected by taking potassium supplements or potassium</p>	<p>sparing diuretic. A diet that is rich in potassium (fresh fruit and vegetables) may be helpful.</p> <p>• You will need to have regular blood tests to check your levels of potassium and other electrolytes while you are taking Bendroflumethiazide.</p> <p>• Consult your doctor if any of these symptoms persist or become troublesome.</p> <p>• Tell your doctor straight away if you get a rash for the first time after taking the medicine as it may be a sign of allergy.</p> <p>• Tell your doctor or pharmacist if you notice any other unusual or unexpected symptoms.</p> <p>STORING THIS MEDICINE</p> <p>• Do not store above 30°C. Keep container tightly closed.</p> <p>• KEEP ALL MEDICINES OUT OF THE REACH AND SIGHT OF CHILDREN.</p> <p>• Unless your doctor tells you to, do not keep any tablets that you no longer need. Return them to the pharmacist.</p> <p>• Remember this medicine is for YOU. Do not give it to anyone else, even if their symptoms are the same as yours. This medicine may harm them.</p> <p>• Do not take the tablets if the expiry date on the label has passed.</p> <p>Date of revised leaflet: June 2006</p>
Page 1	Page 6	Page 7	Page 8

<p>PATIENT INFORMATION LEAFLET Bendroflumethiazide 5mg Tablets</p> <p>Please read this leaflet carefully before you start taking your tablets. If you have any questions or are not sure about anything, ask your doctor or pharmacist.</p> <p>WHAT YOU SHOULD KNOW ABOUT THIS MEDICINE</p> <p>The active ingredient in this medicine is bendroflumethiazide. This is the new name for bendroflumethiazide. The ingredient has not changed.</p> <p>• Bendroflumethiazide 5mg tablets contain 5mg of Bendroflumethiazide as the active ingredient. They also contain the following other ingredients: lactose, maize starch and magnesium stearate.</p> <p>• This medicine is available in pack sizes of 28, 56, 84, 112 or 500 tablets.</p> <p>• The product licence holder of this medicine is: Sandoz Ltd, Woolston Way, Bordon, Hants, GU35 5GE. The manufacturer of this medicine is: Crescent Pharma Ltd, Units 3 & 4, Guildenham Business Units, Polborough Lane, Overton, Hants, RG35 5ED.</p> <p>• This medicine belongs to a group of drugs known as thiazide diuretics. These are</p>	<p>used for increasing water loss through the kidneys; this makes you pass more water.</p> <p>• This medicine is used for reducing swelling of any part of the body caused by heart, liver or kidney conditions and is frequently used to treat high blood pressure, either alone or in combination with other drugs which lower blood pressure.</p> <p>WHAT YOU SHOULD CHECK BEFORE TAKING THIS MEDICINE</p> <p>• Do not take this medicine if you are allergic to Bendroflumethiazide or any of the ingredients listed above.</p> <p>• Do not take this medicine if you have: kidney disease (renal failure), adrenal gland hypersecretion (low levels of sodium in the blood), electrical hyperkalaemia (irregular problems with levels of potassium in the blood), hypernatraemia (high levels of sodium in the blood), systemic lupus erythematosus (high levels of uric acid in the blood), acute porphyria (blood metabolism disorder) or if you have long-term kidney or liver problems.</p> <p>• Tell your doctor or pharmacist if you are taking any other medicines, including any that you can buy without a prescription. This is particularly important if you are taking medicines known as non-steroidal anti-inflammatory drugs such as indomethacin, ibuprofen, naproxen, diclofenac or meloxicam; insulin, sulphonylureas e.g. chlorpropamide, gliclazide and glibenclamide for diabetes; ulcer healing drugs such as carbamazepine; pain relieving tablets such as levomefemibacil, lithium, calcium salts, vitamin D, amphotericin,</p>	<p>thiazides, benzofuran, carbamazepine, halothane, piroxicam, efavirenz, benzhexate, co-trimoxazole, aminoglycosides, tosylamide, metoprolol, metoprolol, medicines for high blood pressure including prazosin, cardiac glycosides such as digoxin, amiodarone, disopyramide, flecainide, quinidine, lidocaine and mexiletine, tricyclic antidepressants such as amitriptyline and nortriptyline, beta-blockers such as atenolol, medicines known as calcium-channel blockers such as verapamil, nifedipine, diltiazem, flunarizine, thiazidine and non-dihydropyridine calcium channel blockers such as flunarizine and diltiazem; oestrogens and combined oral contraceptives, acetazolamide and loop diuretics such as bumetanide, furosemide, spironolactone, bendroflumethiazide, frusemide, gentamicin, rifampicin, salicylates, tubuloin, and subcutaneous or tubalatin.</p> <p>• Consult your doctor before taking this medicine if you have diabetes, gout, porphyria (blood metabolism disorder), pancreatitis (inflammation of the pancreas), hypernatraemia (excessive sodium in the blood), systemic lupus erythematosus (a destructive skin condition), enlarged prostate, hyperlipidaemia (excessive fat in the blood), alcohol related liver problems, other liver problems, kidney problems or if you have severe asthma and are also taking beta2 agonist medicines such as salbutamol or terbutaline, or if you are pregnant or are breast feeding.</p> <p>• If you are going for an operation you should tell the doctor or dentist that you are taking this medicine.</p>	<p>• Alcohol consumption should be kept low as Bendroflumethiazide increases the likelihood of dehydration and hence other consumption of alcohol.</p> <p>• If you are taking the anti-exchange resin medicine colestyramine or colestipol, do not take at the same time as your Bendroflumethiazide medicine. Instead, take them 2 hours apart.</p> <p>• If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.</p> <p>HOW TO TAKE THIS MEDICINE</p> <p>• Swallow the tablets with water.</p> <p>DOSE:</p> <p>Adults:</p> <p>Initially: (for swelling of any part of the body) initially 5mg to 10mg in the morning daily or on alternate days. Maintenance: 0.5 to 5mg two or three times a week.</p> <p>Antihypertensive (for lowering blood pressure): 2.5mg in the morning, alone or in conjunction with other blood pressure lowering agents.</p> <p>Children:</p> <p>Duration: (for swelling of any part of the body): dosage in children may be up to 0.4mg per kg of bodyweight daily initially, reducing to 0.05 to 0.1mg per kg of bodyweight for maintenance.</p>
Page 2	Page 3	Page 4	Page 5

 <p>For oral administration, as directed by the doctor.</p> <p>For further information, see Patient Information Leaflet.</p> <p>KEEP OUT OF THE REACH AND SIGHT OF CHILDREN</p> <p>Do not store above 30°C. Keep container tightly closed.</p> <p>PL 04416/0530</p> <p>Sandoz Ltd, Woolston Way, Bordon, Hants, GU35 5GE</p> <p>500 tablets</p> <p>6290204LL01A</p>	<p>Job No.: 22559 Date: 12th June 2006</p> <p>PROOF 11 100% Label Code SZ90204LL01A</p> <p>Colour Reference: 201 Black</p>	<p>Base Label: 52mm x 125mm Leaflet Page 1: 52mm x 81mm</p> <p>Right Hand Opening <input type="checkbox"/></p> <p>Left Hand Opening <input checked="" type="checkbox"/></p> <p>Overall Leaflet Size: 52 x 316</p> <p>Page Widths: 81 79.5 78.5 77</p>
--	--	---

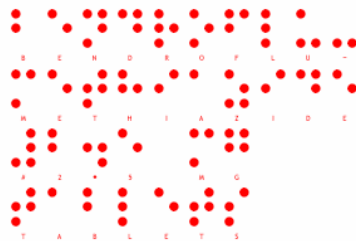
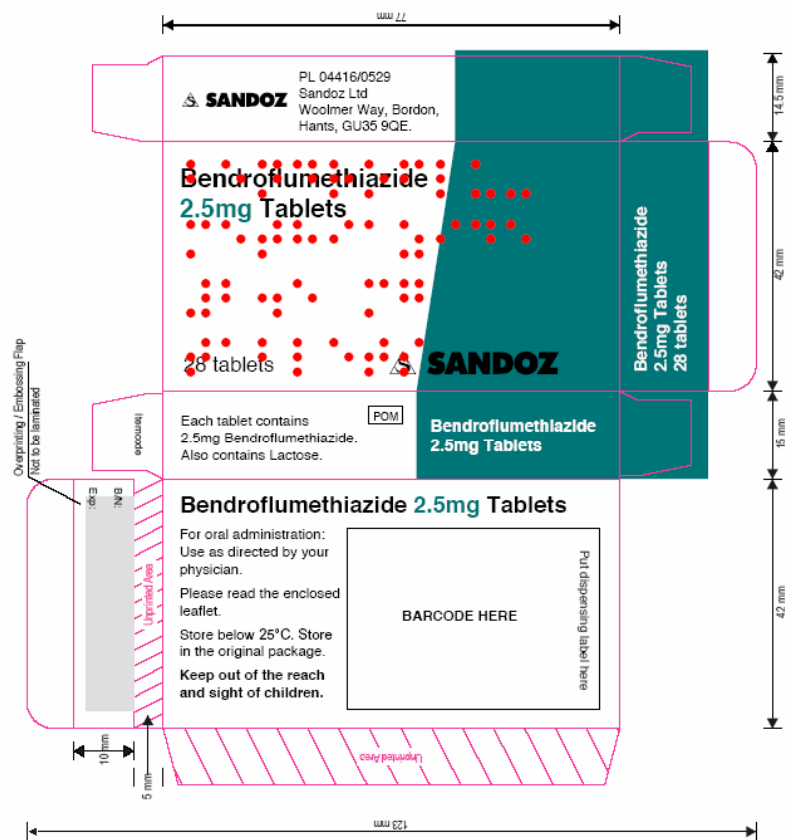
Labelling

BENDROFLUMETHIAZIDE 2.5MG TABLETS

PL 04416/0529

Bendroflumethiazide 2.5mg Tablets
PL 04416/0529

Colours: Black and PMS321
Dimensions: 42 x 15 x 77 mm



BENDROFLUMETHIAZIDE 5MG TABLETS

PL 04416/0530

Bendroflumethiazide 5mg Tablets
PL 04416/0530

Colours: Black and PMS201
Dimensions: 42 x 15 x 77 mm

