Safeguarding public health

MHRA

Public Assessment Report

Bendroflumethiazide 5mg Tablets

PL 13606/0127

Medicines and Healthcare products Regulatory Agency

BENDROFLUMETHIAZIDE 5MG TABLETS

PL 13606/0127

UKPAR

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BENDROFLUMETHIAZIDE 5MG TABLETS

PL 13606/0127

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) has granted Co-Pharma Limited a Marketing Authorisation (licence) for the medicinal product Bendroflumethiazide 5mg Tablets (PL 13606/0127). This is a prescription only medicine [POM] used to treat high blood pressure and to reduce the build-up of fluid in the tissues. It may also be used to help reduce the production of breast milk after pregnancy.

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

This is a simple application that cross-refers to a previously granted licence for Bendroflumethiazide Tablets BP 5mg (PL 17496/0005).

No new or unexpected safety concerns arose from this simple application and it was therefore judged that the benefits of using Bendroflumethiazide Tablets BP 5mg outweigh the risks, hence a Marketing Authorisation has been granted.

BENDROFLUMETHIAZIDE 5MG TABLETS

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SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted a marketing authorisation for the medicinal product Bendroflumethiazide 5mg Tablets (PL 13606/0127) to Co-Pharma Limited on 26 July 2006. The product is a prescription only medicine [POM].

This application was submitted as a simple abridged application according to Article 10.1(a)i of Directive 2001/83/EC, cross-referring to Bendroflumethiazide Tablets BP 5mg (PL 17496/0005, approved on 8 January 2001).

The product contains bendroflumethiazide. Bendroflumethiazide is a thiazide diuretic which acts by reducing re-absorption of electrolytes from renal tubules leading to increased excretion of sodium and chloride and hence water.

No new data were submitted for this simple application, nor were any necessary, as the data are identical to that of the previously granted cross-referenced product. As the cross-referenced product was granted prior to the introduction of current legislation, no public assessment report was generated for it.

Bendroflumethiazide 5mg Tablets is used as a diuretic in the treatment of essential hypertension and oedema. It may also be used in the suppression of unwanted lactation.

PHARMACEUTICAL ASSESSMENT

LICENCE NO: **PL 13606/0127**
PROPRIETARY NAME: **Bendroflumethiazide 5mg Tablets**
ACTIVE(S): **Bendroflumethiazide Ph.Eur.**
COMPANY NAME: **Co-Pharma Limited**
E.C. ARTICLE: **10.1(a)(i)**
LEGAL STATUS: **POM**

INTRODUCTION AND BACKGROUND

This is a national "informed consent" application that was submitted under Article 10.1(a)(i) of Directive 2001/83/EC, for tablets containing 5mg of bendroflumethiazide claimed to be identical to the marketing authorisation for Bendroflumethiazide Tablets BP 5mg PL 17496/0005, granted to Dalkeith Laboratories Limited on 8 January 2001.

A letter has been provided by Dalkeith Laboratories Limited confirming that Co-Pharma has access to all the available data.

The active ingredient manufacturer is identical to that of the reference product. A suitable letter from the active manufacturer has been provided stating their willingness to supply the active substance for this application.

Licensing particulars are identical to that of the reference product with regards to the packaging, pack sizes, shelf-life, storage, composition and finished product specification.

A letter has been provided confirming that the finished product manufacturer is willing to manufacture the finished product on behalf of the applicant.

Copies of the licences issued to all parties involved in the manufacturing process, giving them authority to carry out their respective functions at a particular site, have been provided.

COMPOSITION

Name of active substance	Quantity	Unit	Reference/Monograph standard
Bendroflumethiazide	5	mg	Ph.Eur.

Name of excipient	Reference / Monograph standard
Lactose	Ph.Eur.
Pre-gelatinised maize starch	Ph.Eur.
Sucrose (as syrup)	Ph.Eur.
Stearic acid	Ph.Eur.
Magnesium Stearate	Ph.Eur.

METHOD OF PREPARATION

A valid manufacturing licence is supplied, naming the sites of manufacture and assembly.

CONTROL OF STARTING MATERIALS

Active substance

A suitable letter authorising the MHRA to refer to the Drug Master File held by the active substance manufacturer, in relation to the present application, has also been provided.

Other ingredients

An assurance has been provided that the excipients satisfy current Ph.Eur. requirements.

It has been confirmed that the magnesium stearate is of vegetable origin.

A suitable declaration for lactose has been provided, declaring that the excipient is from cow milk, sourced from healthy animals in the same condition as milk collected for human consumption.

CONTROL TESTS ON INTERMEDIATE PRODUCTS/FINISHED MEDICINAL PRODUCT AND STABILITY

No specific details have been given in this simple application. However the pharmaceutical expert report does state that the materials, manufacturing process, quality control parameters and release specifications are the same as those which appear on the existing licence (PL 17496/0005).

With regard to the stability, no specific data have been supplied, although the current shelf life is 3 years for both the blister packs and containers.

EXPERT REPORTS

Expert reports have been provided by suitably qualified experts. These confirm that the quality, clinical and non-clinical details are identical to those for PL 17496/0005.

PRODUCT NAME AND APPEARANCE

The proprietary name is expressed in the form of the recommended International Non-proprietary Name (rINN). This is acceptable.

SUMMARY OF PRODUCT CHARACTERISTICS
PATIENT INFORMATION LEAFLET
LABELLING

Satisfactory.

CONCLUSION

A Marketing Authorisation may be granted.

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

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

OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY

The data for this application are consistent with those previously assessed for the cross-referenced product and as such have been judged to be satisfactory.

PRECLINICAL

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

EFFICACY

This application is identical to a previously granted application for Bendroflumethiazide Tablets BP 5mg.

No new or unexpected safety concerns arose from this application.

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

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's product is identical to the cross-referenced product. 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 5MG TABLETS

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STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application for Bendroflumethiazide 5mg Tablets on 2 June 2004.
2	The MHRA's assessment of the submitted data was completed on 13 January 2005.
3	Further information was requested from the company on 13 January 2005 and 4 February 2005.
4	The applicant responded to further information requests in a letter dated 9 September 2005.
5	Further information was requested from the company on 13 January 2006.
6	The applicant responded to further information request in a letter dated 16 February 2006.
7	Additional information was requested from the company on 20 February 2006 and 22 March 2006.
8	The applicant's response to additional information requests was received on 17 March 2006 and 27 March 2006.
9	The MHRA completed its assessment of the application on 14 July 2006.
10	The application was determined on 26 July 2006.

BENDROFLUMETHIAZIDE 5MG TABLETS

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bendroflumethiazide 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg Bendroflumethiazide.

For excipients see section 6.1

3 PHARMACEUTICAL FORM

Tablet.

Flat, white uncoated tablet with bevelled edge.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The tablets are intended solely for oral administration as a diuretic in the treatment of essential hypertension and oedema.

They may also be used in the suppression of unwanted lactation.

4.2 Posology and method of administration

For oral use.

Adults

Hypertension:

2.5mg in the morning. Higher doses are rarely necessary. The tablets may be used in conjunction with other anti-hypertensive agents (see BNF).

Oedema:

5 - 10 mg daily in the morning initially and a maintenance dose of 2.5 – 10mg up to three times a week.

Suppression of lactation:

5mg to be taken morning and midday for about five days.

Elderly

The dosage may need to be reduced particularly when renal function is impaired because of the possibility of electrolyte imbalance.

Children

Dosage can be up to 400µg/kg body weight daily initially with a maintenance dose of 50 – 100µg/kg daily.

4.3 Contraindications

Severe renal insufficiency and hypercalcaemia, hypersensitivity, hepatic failure, Addison's disease and concurrent lithium therapy.

4.4 Special warnings and precautions for use

Potassium depeletion is a particular risk in digitalized patients or patients with hepatic cirrhosis and/or ascites in patients with latent or overt diabetes. The dose of hypoglycaemic agents may need to be increased and when added to anti-hypertensive agents such as beta-blockers the combined hypotensive effect may require reduction in the dose of the anti-hypertensive agents.

The product may sometimes lower carbohydrate tolerance so that the insulin dosage of the diabetic patient may require adjustment. Care is therefore necessary when bendroflumethiazide is administered to those with a known predisposition of diabetes.

Patients with rare hereditary problems of fructose and galactose intolerance, the LAPP lactase deficiency, sucrase-isomaltase insufficiency or glucose-galactose malabsorption should not take this medicine.

Particular caution is needed in the elderly because of their susceptibility to electrolyte imbalance.

Caution in patients with hepatic or renal impairment.
Renal function should be monitored periodically during treatment

May cause exacerbation or activation of systemic lupus erythematosus in susceptible individuals.

4.5 Interaction with other medicinal products and other forms of interaction

May impair control of diabetes with sulphonylureas.

Non steroidal anti-inflammatory agents may blunt the diuretic and anti-hypertensive effects of thiazide diuretics.

Thiazide diuretics may enhance the neuro-muscular blocking effects of the non-depolarising muscle relaxants.

Increased sensitivity to digitalis glycosides by the hypokalaemic effect of concurrent bendroflumethiazide. Observe patients for digitalis intoxication, in particular if arrhythmias are observed the dose of the glycoside should be reduced temporarily and a potassium supplement given.

Lithium blood levels may be increased by concurrent use of thiazide diuretics.

Thiazides may enhance the effects of anti-hypertensive agents.

Postural hypotension associated with thiazide therapy may be enhanced by concomitant ingestion of alcohol, barbiturates or opioids.

ACTH, corticosteroids, acetazolamide and carbenoxolone may exacerbate the hypokalaemic effect.

Like all thiazides, it 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 some have described foetal bone marrow depression and thrombocytopenia. Foetal and neonatal jaundice have also been described.

As diuretics pass into breast milk and bendroflumethiazide can suppress lactation, avoid in mothers who wish to breast feed.

4.7 Effects on ability to drive and use machines

No or negligible influence.

4.8 Undesirable effects

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

Also reported are hyperglycaemia, hyperuricaemia and an increase in blood urea nitrogen. Thiazide diuretics may increase the serum uric acid levels with subsequent exacerbation of gout in susceptible subjects. Diabetes may be precipitated or aggravated.

Other occasional adverse reactions include skin rashes, photosensitivity, necrotising vasculitis, acute pancreatitis, impotence and aggravation of pre-existing myopia.

Rarely blood dyscrasias (including agranulocytosis, aplastic anaemia, thrombocytopenia and leucopenia) and pancreatitis have been reported with long term therapy.

4.9 Overdose

Symptoms include anorexia, nausea, vomiting, diarrhoea, diuresis, dehydration, hypotension, dizziness, weakness, muscle cramps, paraesthesia, tetany, gastrointestinal bleeding, hyponatraemia, hypo- or hyperglycaemia, hypokalaemia and metabolic alkalosis.

If appropriate treat either by emesis or gastric lavage initially, otherwise treatment should be symptomatic and aimed at fluid and electrolyte replacement. Blood pressure should be monitored following the overdose and throughout treatment. There is no specific antidote.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

C03A A01 – Low-ceiling diuretics, thiazides. Thiazides plain

Bendroflumethiazide is a thiazide diuretic which acts by reducing re-absorption of electrolytes from renal tubules leading to increased excretion of sodium and chloride and hence water. Potassium is less affected but hypokalaemia must be checked in prolonged treatment.

It reduces carbonic anhydrase activity and bicarbonate excretion may be increased but unlikely to be a problem.

Bendroflumethiazide has a slight direct hypotensive action and tends to potentiate effect of other antihypertensive drugs.

Diuresis is initiated in about 2 hours and lasts for 12-18 hours.

5.2 Pharmacokinetic properties

Bendroflumethiazide is readily absorbed from the gastro-intestinal tract and about 30% is excreted unchanged in the urine and has a plasma half life of about 4 hours.

5.3 Preclinical safety data

No data of relevance which is additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Pregelatinised Maize Starch
Sucrose (as syrup)
Stearic Acid
Magnesium Stearate (E572)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Tablet containers: Do not store above 25°C. Store in the original container. Keep the container tightly closed.

Blister packs: Do not store above 25°C. Store in the original package. Keep blister in the outer carton.

6.5 Nature and contents of container

HDPE tablet containers with PP caps of 500 and 1000 tablets.

PP tablet containers with LDPE caps of 500 and 1000 tablets.

Al/PVC/PVDC blister packs containing 28 or 56 tablets.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Co-pharma Limited
Unit 4, Metro Centre
Tolpits Lane
Watford
Hertfordshire
WD1 8SS

8 MARKETING AUTHORISATION NUMBER(S)

PL 13606/0127

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/07/2006

10 DATE OF REVISION OF THE TEXT

26/07/2006

Patient Information Leaflet

BENDROFLUMETHIAZIDE 5MG TABLETS

PL 13606/0127

Please read all of this leaflet carefully before you start taking this medicine.
Keep the leaflet, you may need to read it again.
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.
If you have any further questions, please ask your doctor or pharmacist.

The name of this medicine is
BENDROFLUMETHIAZIDE 5MG TABLETS

Each tablet contains Bendroflumethiazide 5 mg as the active substance. Other ingredients are Lactose, Pregelatinised Maize Starch, Sucrose, Stearic Acid and Magnesium Stearate.

Product Licence holder is **Co-pharma Ltd.**, Unit 4, Metro Centre, Tolpits Lane, Watford, Herts, WD1 8SS.
The tablets are manufactured by Surepharm Services Ltd., Bretby, Burton upon Trent, Staffs, DE15 0YZ.

What the tablets are and what they are used for
The tablets are flat, round and white in colour. Bendroflumethiazide belongs to a group of medicines called thiazide diuretics which work by causing an increase in the amount of urine passed (a diuretic action) thus helping to remove the excess fluids from the body.

The tablets are supplied to your pharmacist in packs of 28 or 56 tablets or in containers of 500 or 1000 tablets (not all packs may be marketed), who will then provide you with the required number of tablets as prescribed by your doctor.

Bendroflumethiazide Tablets are used to treat high blood pressure (hypertension) and reduce fluid build up in the tissues (oedema). They may also be used to help reduce the production of breast milk after pregnancy.

Before you take Bendroflumethiazide Tablets
Do not take if:
- You are allergic to bendroflumethiazide or any of the other ingredients.
- You suffer from severe liver or kidney problems.
- You are suffering from hypercalcaemia (an unusually high level of calcium in the blood).
- You suffer from Addison's disease.
- You are taking the drug lithium.
- You are pregnant or breastfeeding (unless considered essential by your doctor).

Take special care if:
- You suffer from diabetes.
- You are elderly.
- You suffer from impaired liver or kidney function.
- You suffer from SLE (systemic lupus erythematosus).

If you have been told by your doctor that you have an intolerance to some sugars, check with your doctor before taking this medicine as it contains sucrose and lactose.

You must make sure your doctor is aware that you are taking any other medicines especially any of the following:
- drugs for heart disease (e.g. digoxin).
- sulphonylurea drugs (e.g. chlorpropamide, glibenclamide) to treat diabetes.
- anti-hypertensive drugs (also to treat high blood pressure).
- non steroidal anti-inflammatory drugs (e.g. ibuprofen).
- muscle relaxants (e.g. atracurium, cisatracurium).
- corticosteroids or the drugs ACTH, acetazolamide (e.g. to treat glaucoma) and carbenoxolone (used to treat ulcers).
- sedative drugs or alcohol.

This medicine, like all diuretics may interfere with a number of laboratory tests.
Please speak to your doctor or pharmacist before taking if any of the above statements applies to you.

BENDROFLUMETHIAZIDE 5MG TABLETS

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Please inform your doctor or pharmacist if you are taking, or have recently taken any other medicine even those not prescribed, or any other medical conditions which you think may be affected.

How to take
The tablets should be swallowed with a drink of water. The usual dose is as follows:

Adults:
To treat high blood pressure: Take half a tablet each morning. Higher doses are rarely necessary.
To reduce fluid build up in the tissues: Take 1 or 2 tablets each morning initially. (Your doctor may then want you to continue with a dose of 2.5mg – 10 mg three times a week).
To reduce production of breast milk: Take 1 tablet each morning and 1 tablet at midday for about five days.

Elderly:
The dose may need to be reduced particularly if the patient suffers from kidney problems.

Children:
To be taken as instructed by a doctor, as the dose depends on the body weight of the child.

The dose your doctor prescribed you may be different to the usual dose given above; always follow your doctor's instructions for taking medicines.

If you take more tablets than you should:
In the case of an overdose, you should contact your doctor or go to your nearest hospital casualty department immediately, taking your tablets with you as you will need further treatment.

If you forget to take a dose of Bendroflumethiazide Tablets:
If you should miss a morning dose, do not take after midday; carry on with the normal routine.

Possible Side Effects
Like all medicines Bendroflumethiazide may sometimes cause side effects, and those which occasionally occur are:

- Hypokalaemia (low level of potassium in the blood), symptoms include an abnormal heartbeat and muscle weakness or numbness.
- Hyperglycaemia (high level of glucose in the blood), diabetes, hyperuricaemia (gout).
- Skin rashes, increased sensitivity to sunlight, blood vessel damage, severe abdominal pain, impotence and aggravation of pre-existing myopia (short sightedness).
- Blood disorders (symptoms of which include fever, tiredness, bruising and sometimes abnormal bleeding) have been reported during long term treatment.

If you do notice any side effects, including any not mentioned in this leaflet, please inform your doctor or pharmacist.

Storing the tablets
Keep out of the reach and sight of children.
Do not store above 25°C. Store in the original package or container. Keep blister in the outer carton or keep the container tightly closed, in order to protect the tablets from moisture.
Do not use the tablets after the expiry date shown on the label or carton.

Text prepared: November 2003.

Co-pharma

Labelling

BENDROFLUMETHIAZIDE 5MG TABLETS

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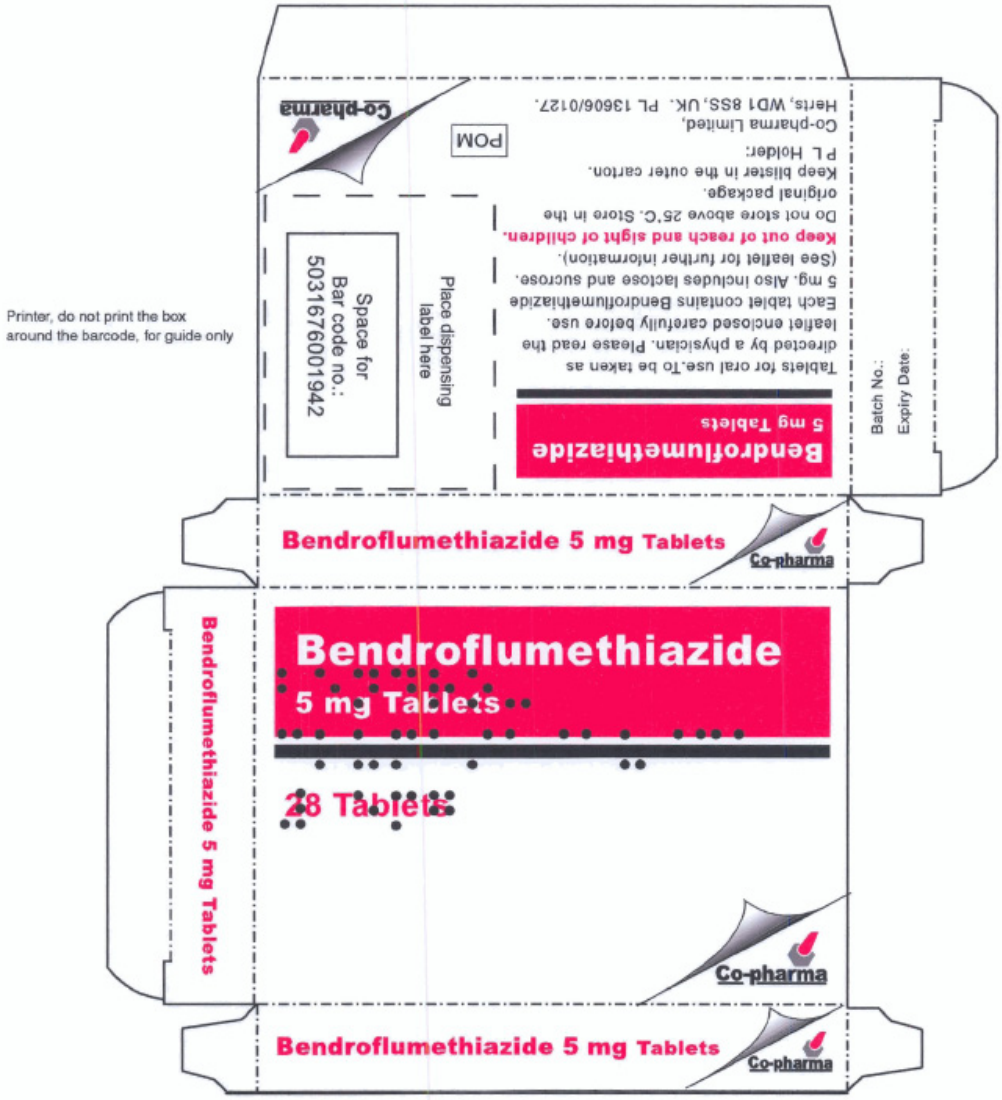

BENDROFLUMETHIAZIDE 5MG TABLETS

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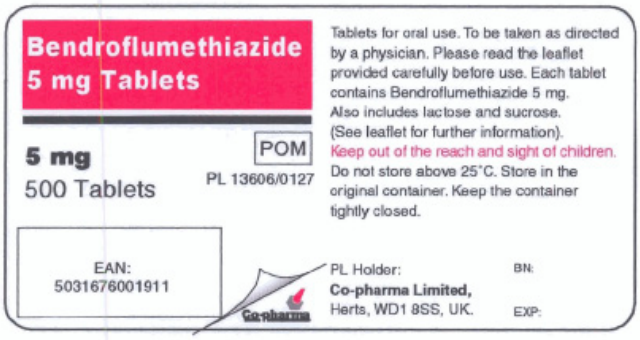

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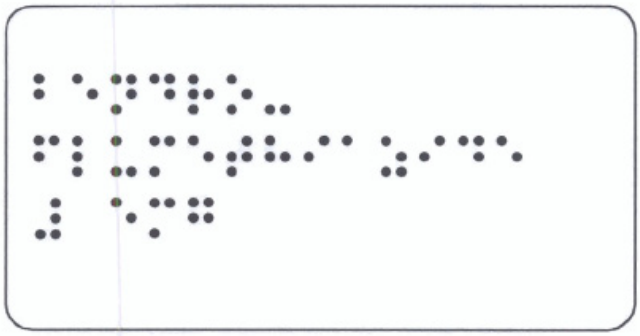

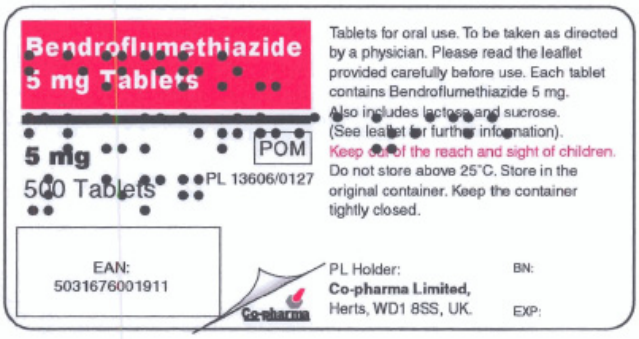

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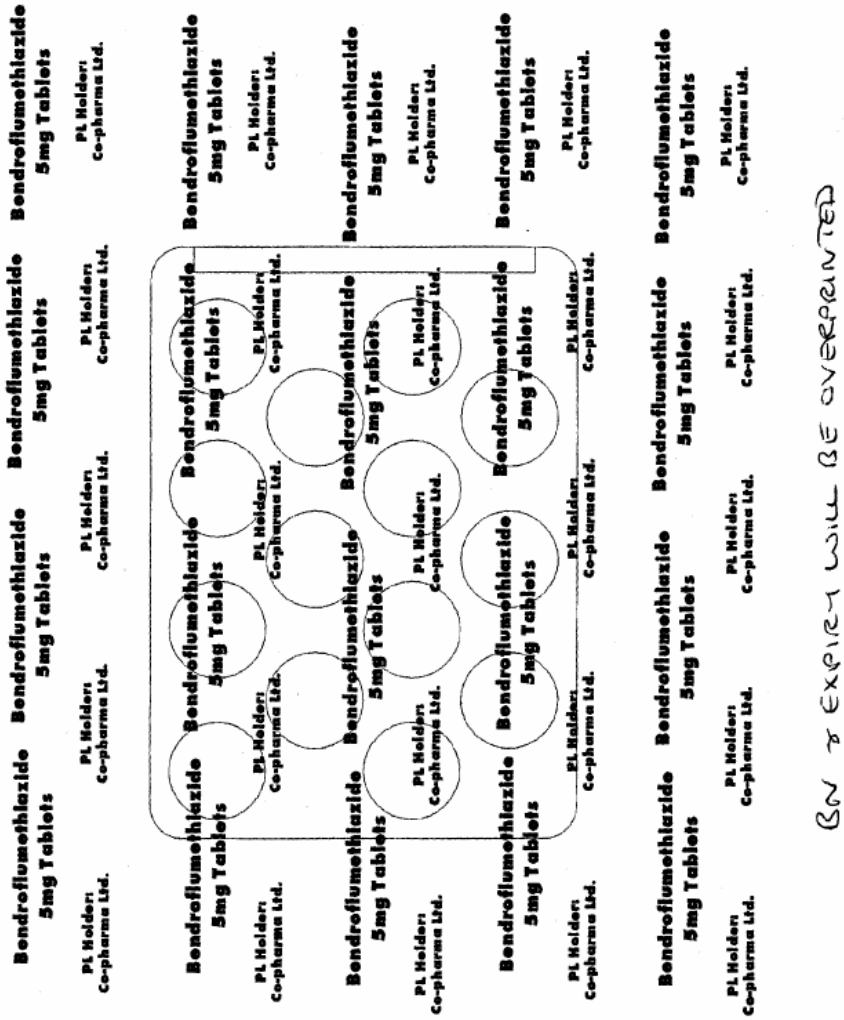
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