IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0046/018/002
Case No: 2052909

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Leo Laboratories Limited

Cashel Road, **Dublin 12**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Centyl 5 mg Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **18/07/2008**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Centyl 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5mg of bendroflumethiazide

Excipients: Lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
White, circular, flat, slightly bevelled tablet with a single scoreline engraved on one face and a central circular groove engraved on the other.
The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

As a diuretic in the management of oedema such as that which arises from cardiac, renal and hepatic origin.

In the management of hypertension alone or in combination with other antihypertensives.

4.2 Posology and method of administration

Adults:

Oedema
The usual initial dose is 2.5 to 10 mg as a single dose, with a maintenance dosage of 2.5 to 5mg daily, preferably in the morning.

Hypertension
2.5 to 5 mg once daily.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Severe electrolyte imbalance including hypercalcaemia, hyperchloraemia or hypokalaemia.
Severe renal impairment.
Severe hepatic impairment.
Addison’s disease.
Established gout.

As with other diuretics Centyl® should not be administered concurrently to patients taking lithium salts.

4.4 Special warnings and precautions for use

Considerations should be given to fluid and electrolyte status to avoid inadequate potassium supplementation or excessive loss of fluid especially in elderly patients. Concomitant medication should also be considered.

Bendroflumethiazide may provoke hyperglycaemia and glycosuria in diabetic and other susceptible patients. In case of reduced glucose tolerance, adjustments of anti-diabetic medicines may be necessary.

Thiazide diuretics should be used with caution in patients with renal or hepatic impairment and in patients with potential obstruction of the urinary tract or with disorders rendering their electrolyte balance precarious.

Thiazides may cause hyperuricaemia and precipitate or aggravate attacks of gout.

Bendroflumethiazide may cause exacerbation or activating of systemic lupus erythematous.

Bendroflumethiazide found in urine by doping test is cause for disqualification of athletes.

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

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant administration of this preparation with cardiac glycosides or hypotensive agents may necessitate adjustment of the dosage of those drugs.

Bendroflumethiazide may potentiate the effect of antihypertensive agents and drugs inducing postural hypotension e.g. tricyclic antidepressants.

Bendroflumethiazide may impair control by hypoglycaemic agents in cases of diabetes mellitus (c.f. section 4.4).

Non-steroidal anti-inflammatory drugs (NSAID) inhibit the effect of bendroflumethiazide.

Bendroflumethiazide reduces lithium clearance resulting in high serum levels of lithium, therefore concurrent use is contraindicated (c.f. section 4.3).

Probenecid inhibits the renal tubular secretion of bendroflumethiazide leading to a diminished natriuresis.

Cholestyramine and similar drugs reduces the absorption of thiazides.

Co-administration of bendroflumethiazide and other drugs known to cause photosensitivity reactions may increase the severity of these reactions.

Hypokalaemia (which may be induced by bendroflumethiazide) increases the sensitivity to digitalis glycosides and non-depolarising neuromuscular blocking agents.

The urinary excretion of calcium is reduced.

4.6 Pregnancy and lactation

Animal studies are insufficient with respect to effects on pregnancy. The potential risk for humans is unknown. Bendroflumethiazide should not be used during pregnancy unless clearly necessary.

Diuretics are excreted in breast milk and should not be used during lactation.

4.7 Effects on ability to drive and use machines

Bendroflumethiazide has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The most frequent undesirable effects are headache, dizziness, fatigue, postural hypotension and gastrointestinal symptoms. Electrolyte disturbances can occur especially during long term treatment.

Thiazide diuretics may cause a number of metabolic disturbances including reduced glucose tolerance and hyperuricaemia. Muscle cramps, various skin reactions, photosensitivity reactions and erectile dysfunction are less frequent. Vasculitis, blood dyscrasias, mainly affecting the platelets and acute pancreatitis, have also been reported.

Based on the clinical trial data for Centyl® K undesirable effects occurred in approximately 15% and are dose dependant.

Based on post-marketing data for both Centyl® and Centyl® K, the total “reporting rate” of undesirable effects is very rare being approximately 2:100,000 treatment months.

The undesirable effects are listed by MedDRA SOC and the individual undesirable effects are listed starting with the most frequently reported.

- Nervous system disorders

Headache
Dizziness
Vertigo
Syncope
Postural hypotension

- General disorders and application site conditions

Fatigue
Asthenia
Dry mouth
Thirst
Paraesthesia

- Gastrointestinal disorders

Nausea
Gastric irritation
Vomiting
Diarrhoea
Constipation

- Metabolism and nutrition disorder

Dehydration
Hyponatraemia
Hypokalaemia
Gout
Hyperuricaemia
Hyperglycaemia
Diabetes Mellitus
Metabolic alkalosis

Hypochloraemia
Hypocalcaemia
Hypomagnesaemia

- Musculoskeletal and connective tissue disorders

Myalgia
Muscle cramp

- Skin and subcutaneous tissue reactions

Rash
Photosensitivity reactions
Pruritus

- Reproductive and breast disorder

Erectile dysfunction

- Vascular Disorders

Hypotension
Vasculitis

- Blood and lymphatic system disorder

Thrombocytopenia
Granulocytopenia

4.9 Overdose

In high doses thiazide diuretics may cause electrolyte imbalance, dehydration and polyuria.

Symptoms of electrolyte imbalance include dry mouth, thirst, weakness, lethargy, drowsiness, gastrointestinal disturbances, restlessness, muscle pain and cramps, and seizures.

Treatment is adjustment of the fluid and electrolyte imbalance.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: C03A A01
Bendroflumethiazide is a thiazide diuretic which acts on both determinants of hypertension, i.e. cardiac output and peripheral resistance. Cardiac output is reduced due to the decrease in blood volume resulting from the diuretic effect. Centyl reduces peripheral resistance by a vasodilating effect, the mechanism of which is not completely understood. In oedematous conditions the diuretic action reduces extravascular fluid volume.

5.2 Pharmacokinetic properties

Bendroflumethiazide has been reported to be completely absorbed from the gastrointestinal tract and to have a half-life of about 3 or 4 hours. Plasma protein binding, as with most thiazides, is high. There is evidence that bendroflumethiazide is fairly extensively metabolised; about 30% is excreted unchanged in the urine.

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

Colloidal anhydrous silica
Gelatin
Maize starch
Lactose monohydrate
Talc
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Amber glass bottles of 100 and 500 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7 MARKETING AUTHORISATION HOLDER

LEO Laboratories Limited
285 Cashel Road
Dublin 12

8 MARKETING AUTHORISATION NUMBER

PA 46/18/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1978

Date of last renewal: 14 November 2007

10 DATE OF REVISION OF THE TEXT

February 2008