Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Centyl K 2.5 mg/573 mg modified-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5mg of bendroflumethiazide and 573mg of potassium chloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified-release tablet
Green, film-coated, oval shaped tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Centyl K is indicated as a diuretic:
• In the management of oedema such as that which arises from cardiac, renal or hepatic origin.
• In the management of hypertension alone or in combination with other antihypertensives.

4.2 Posology and method of administration

Posology
Hypertension: 1-2 tablets once daily.
Oedema: Initial dosage 1-4 tablets once daily. Maintain with 1-2 tablets daily.

Method of administration
For oral administration.
Centyl K should be taken in the morning to avoid nocturia.

The tablets should be taken with or after meals with at least a full glass of water or other fluid

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Addison's disease.
- Severe renal impairment or anuria (see section 4.4).
- Severe hepatic impairment (see section 4.4).
- Established arthritis urica.
- Severe dehydration electrolyte imbalance including hypercalcaemia, hyponatraemia, hyperchloraemia, hyperkalaemia or any situation which might lead to hyperkalaemia.
- Ulcer or obstruction of the gastrointestinal tract.

4.4 Special warnings and precautions for use

Hypersensitivity
Bendroflumethiazide is a sulphonamide, which should be considered by prescribers in relation to hypersensitivity.

Renal Impairment, Hepatic impairment and Urinary tract obstruction
Thiazide diuretics should be used with caution in patients with mild or moderate renal or hepatic impairment and in patients with potential obstruction of the urinary tract (see section 4.3).

Potassium levels

With long term treatment, potassium blood levels should be monitored and consideration should be given to fluid and electrolyte status especially in elderly patients. Depending on the results, potassium containing food or extra potassium supplementation might need to be recommended.

Hyponatraemia
Elderly patients may be particularly susceptible to hyponatraemia during treatment with bendroflumethiazide. Regular and continuous blood testing and monitoring should be carried out in this patient group.
The risk of hyponatraemia should also be considered in patients that are concomitantly treated with other medicinal products associated with reduced sodium levels (see section 4.5).

Hypercalcaemia
Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Diabetic patients
Thiazides may provoke hyperglycaemia and glucosuria in diabetic and other susceptible patients. In case of reduced glucose tolerance, adjustment of the anti-diabetic dose may be necessary (see section 4.5).

Hypotension
Thiazide diuretics should be used with caution in hypotensive patients.

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

Systemic Lupus Erythematosus
Thiazides may cause exacerbation or activation of systemic lupus erythematosus.

Athletes
Thiazide diuretics found in urine by doping tests is a cause for disqualification of athletes.

Lithium
Concomitant use of thiazides and lithium should be avoided (see section 4.5). Concomitant therapy requires close monitoring of serum lithium levels. If combination is still required, then lower lithium doses may be appropriate.

Potassium chloride administration
Potassium chloride should be administered with considerable care to patients with cardiac disease or conditions predisposing to hyperkalaemia such as renal or adrenocortical insufficiency, acute dehydration, or extensive tissue destruction as occurs with severe burns. Serum potassium should be monitored in patients with cardiac or renal impairment.

Potassium chloride may induce ulceration of the gastrointestinal tract in particular the small bowel. Potassium chloride should be administered with caution to patients in whom passage through the gastrointestinal tract may be delayed. Treatment should be discontinued if severe nausea, vomiting, or abdominal distress develops.

Choroidal effusion, acute myopia and secondary angle-closure glaucoma:
Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

4.5 Interaction with other medicinal products and other forms of interaction

Lithium
Bendroflumethiazide reduces lithium clearance resulting in increased lithium concentrations in serum and risk of lithium toxicity (weakness, tremor, excessive thirst, confusion) (see section 4.4). Concomitant therapy requires close monitoring of serum lithium levels. If combination is still required, then lower lithium doses may be appropriate.
NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) antagonise the diuretic effect of bendroflumethiazide by decreasing renal prostaglandin production. The effects of concurrent use should be monitored (e.g. blood pressure, signs of renal failure) and the dose of bendroflumethiazide modified if necessary. Diuretics may enhance the nephrotoxicity of NSAIDs.

Antiarrhythmics

Concomitant use of bendroflumethiazide and class Ic and III antiarrhythmic agents may result in increased risk of electrolyte imbalance and subsequent cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest). Patients should be monitored for electrolytes and symptoms of arrhythmias.

Digitalis glycosides

The hypokalaemic effect of bendroflumethiazide may enhance Na^+-K^+-ATPase inhibition by digitalis glycosides. Concomitant therapy may thus result in digitalis toxicity (nausea, vomiting, arrhythmias). Patients should be monitored for signs of potassium depletion. Potassium supplementation and lower digitalis glycoside dose should be considered.

Non-depolarising neuromuscular blocking agents

The hypokalaemic effect of bendroflumethiazide may enhance the neuromuscular blocking activity of non-depolarising muscle relaxants.

Beta-2 adrenergic agonists

The hypokalaemic effect of bendroflumethiazide may be enhanced by beta-2 adrenergic agonists.

Antihypertensives and drugs inducing postural hypotension

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

Drugs increasing potassium levels

Due to the content of potassium chloride concomitant treatment with drugs such as potassium-sparing diuretics, angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists increase the risk of hyperkalaemia.

Antidiabetics

Bendroflumethiazide can reduce the effects of the antidiabetics and impair the control of diabetes by raising blood glucose levels (see section 4.4). This effect appears to be dose related.

Drugs decreasing sodium levels

Concomitant administration of medicinal products that decrease sodium levels may increase the risk of hyponatraemia.

Calcium salts and drugs increasing calcium levels

Bendroflumethiazide can cause calcium retention by reducing its urinary excretion. Concomitant administration of calcium or any drugs that increase calcium levels may result in hypercalcemia

Photosensitising agents

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

Bile-acid binding resins

Cholestyramine and similar drugs reduce the absorption of bendroflumethiazide.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of bendroflumethiazide with potassium chloride in pregnant women. Animal studies are insufficient with respect to effects on pregnancy.

Thiazides cross the placenta and there have been reports of neonatal jaundice, thrombocytopenia, and electrolyte imbalance after maternal use. Reduction in maternal blood volume could also adversely affect placental perfusion. Bendroflumethiazide should not be used during pregnancyunless clearly necessary.

Breast-feeding

Bendroflumethiazide is excreted in human milk. Bendroflumethiazide should not be used during breast-feeding.

Fertility

There are no clinical studies with bendroflumethiazide regarding fertility.

4.7 Effects on ability to drive and use machines

Centy l K has no or negligible influence on the ability to drive and use machines. However, the patient should be informed that dizziness may occu r during treatment and take this into account while driving or using machines.

4.8 Undesirable effects

The estimation of the frequency of undesirable effects is based on a pooled analysis of data from clinical trials and spontaneous reporting.
Based on pooled data from clinical trials including more than 250 patients who received bendroflumethiazide, approximately 12% of patients can be expected to experience an undesirable effect.
The most frequently reported adverse reactions during treatment are dizziness (including orthostatic hypotension and vertigo) and headache both occurring in approximately 5% of patients and fatigue occurring in approximately 4% of patients.
Hypokalemia and electrolyte disturbances can occur especially during long term treatment.
Renal failure has been reported in post-marketing safety surveillance.

Undesirable effects are listed by MedDRA SOC and the individual undesirable effects are listed starting with the most frequently reported. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Very common ≥1/10
Common ≥1/100 and <1/10
Uncommon ≥1/1,000 and <1/100
Rare ≥1/10,000 and <1/1,000
Very rare <1/10,000
Not known (cannot be estimated from the available data)

Endocrine disorders	
Uncommon: (≥1/1,000 and <1/100)	Hyperparathyroidism
Metabolism and nutrition disorders	
Common: (≥1/100 and <1/10)	Hypokalaemia Hyperuricaemia and gout
Uncommon: (≥1/1,000 and <1/100)	Diabetes mellitus Acid base balance abnormal Dehydration Hypochloraemia Hyponatraemia Hypocalcaemia Hypomagnesaemia Weight increased
Not known (frequency cannot be estimated from the available data)	Hypercalcaemia
Nervous system disorders	
Common: (≥1/100 and <1/10)	Dizziness (including orthostatic hypotension and vertigo) Headache Fatigue
Uncommon: (≥1/1,000 and <1/100)	Syncope Ataxia Paraesthesia Dysgeusia
Psychiatric disorders	
Uncommon: (≥1/1,000 and <1/100)	Depression Confusional state Sleep disorder
Eye disorders	
Uncommon: (≥1/1,000 and <1/100)	Eye disorder and vision blurred
Cardiac disorders	
Uncommon: (≥1/1,000 and <1/100)	Palpitations and cardiovascular disturbance
Vascular disorders	
Uncommon: (≥1/1,000 and <1/100)	Hypotension Flushing Peripheral coldness
Respiratory, thoracic and mediastinal disorders	
Uncommon: (≥1/1,000 and <1/100)	Respiratory disorder Dyspnoea and wheezing

Gastrointestinal disorders	
Common: (≥1/100 and <1/10)	Gastrointestinal disturbances Nausea Dry mouth and thirst
Uncommon: (≥1/1,000 and <1/100)	Diarrhoea Vomiting Constipation Abdominal pain and discomfort
Skin and subcutaneous tissue disorders	
Common: (≥1/100 and <1/10)	Skin disorder (including rash, urticaria and eczema)
Uncommon: (≥1/1,000 and <1/100)	Photosensitivity reaction Pruritus Hyperhidrosis
Musculoskeletal and connective tissue disorders	
Common: (≥1/100 and <1/10)	Pain (including arthralgia and myalgia)
Uncommon: (≥1/1,000 and <1/100)	Muscle spasms and twitching
Renal and urinary disorders	
Uncommon: (≥1/1,000 and <1/100)	Renal impairment (including renal failure) Creatinine urine increased Polyuria and nocturia
Reproductive system and breast disorders	
Uncommon: (≥1/1,000 and <1/100)	Erectile dysfunction
General disorders and administration site conditions	
Common: (≥1/100 and <1/10)	Influenza like symptoms (including cough and rhinitis)
Uncommon: (≥1/1,000 and <1/100)	Oedema (including peripheral oedema and face oedema)

Blood dyscrasias including thrombocytopenia, leucopenia and granulocytopenia have been observed as class effects for thiazides.

Cases of choroidal effusion with visual field defect have been reported after the use of thiazide and thiazide-like diuretics.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie

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.

In addition, high doses of potassium may cause hyperkalaemia symptoms and effects on the heart such as hypotension, bradycardia, heart block and cardiac arrhythmia. Respiratory depression and gastric symptoms due to erosion and acidosis may develop.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: bendroflumethiazide and potassium, ATC code: C03A B01

Centyl K is a combination of a thiazide diuretic with a potassium supplement. Bendroflumethiazide acts on both determinants of hypertension i.e. cardiac output and peripheral resistance.
Cardiac output is reduce d due to a decrease in blood volume resulting from the diuretic effect. Peripheral resistance is reduced by a vasodilating effect, the mechanism of which is not completely understood. In oedematous conditions, the diuretic action reduces extravascular fluid volume.

Some degree of potassium depletion may be associated with prolonged thiazide therapy . A potassium supplement is therefore included in Centyl K to help counteract this. Because of the reported dangers of localised high concentrations of potassium salts in the small bowel, the potassium chloride in Centyl K is formulated in an inert wax core from which it is gradually released over several hours. The bendroflumethiazide is contained in a coat which surrounds the central core.

5.2 Pharmacokinetic properties

Bendroflumethiazide is well absorbed from the gastrointestinal tract after oral administration and the absorption is not affected by food. Plasma protein binding, as with most thiazides, is high. The plasma half-life averaged 3.9 hours after a 5 mg dose. There is evidence that bendroflumethiazide is fairly extensively metabolised; about 30% is excreted unchanged in the urine.

5.3 Preclinical safety data

No additional data.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Ethylcellulose
Glycerol
Stearyl alcohol
Magnesium stearate

Film Coating:
Glycerol
Hypromellose 15cps
Hypromellose 3cps
Citric Acid monohydrate
Saccharin sodium
Talc
Titanium dioxide (E171)
Polysorbate 20

Patent Blue V lake (E131)
Quinoline yellow lake (E104)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C. Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with a polypropylene (PP) tamper-evident closure with an integrated silica gel desiccant. Pack sizes of 100 or 250 modified-release tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

KARO PHARMA AB
Box 16184
103 24 Stockholm
Sweden

8 MARKETING AUTHORISATION NUMBER

PA22650/002/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1978
Date of last renewal: 14th November 2007

10 DATE OF REVISION OF THE TEXT

October 2023

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS