VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Bendroflumethiazide/ potassium chloride contains thiazide diuretic bendroflumethiazide that is used in therapy of oedema, arterial hypertension, diabetes insipidus as well as prevention of recurrent renal calculi containing calcium.

Hypertension is a worldwide disease; accordingly, its epidemiology has been well studied. In many countries, 50% of the population older than 60 years has hypertension. Overall, approximately 20% of the world's adults are estimated to have hypertension. The 20% prevalence is for hypertension defined as blood pressure in excess of 140/90 mm Hg. The prevalence dramatically increases in patients older than 60 years. Hypertension is a major risk factor for stroke, myocardial infarction, vascular disease, and chronic kidney disease. (Dreisbach AW, 2013)

Diabetes insipidus is defined as the passage of large volumes (>3 L/24 h) of dilute urine (< 300 mOsm/kg). Diabetes insipidus has 2 major forms: central and nephrogenic. Central diabetes insipidus is characterized by decreased secretion of antidiuretic hormone (ADH). Nephrogenic diabetes insipidus is characterized by a decrease in the ability to concentrate urine because of resistance to ADH action in the kidney. Diabetes insipidus is uncommon in the United States, with a prevalence of 3 cases per

100,000 population. With both central and nephrogenic diabetes insipidus, inherited causes account for approximately 1-2% of all cases (Khadori, 2013).

The majority of renal calculi contain calcium. The pain generated by renal colic is primarily caused by dilation, stretching, and spasm because of the acute ureteral obstruction. The annual incidence of urinary tract stones in the industrialized world is estimated to be 0.2%. Stone disease is rare in only a few areas, such as Greenland and the coastal areas of Japan. A lifetime risk of 2-5% has been noted for in Asia, 8-15% for the West, and 20% for Saudi Arabia (Wolf, 2013).

VI.2.2 Summary of treatment benefits

Based on the available data from clinical studies and clinical experience of several years, bendroflumethiazide represents an effective drug in the treatment of oedema, arterial hypertension, diabetes insipidus and the prevention of recurrent renal calculi containing calcium. Potassium chloride is used to counteract potassium depletion associated with prolonged thiazide therapy.
If administered as indicated in the Summary of Product Characteristics and taking into account the contra-indications, the warnings and precautions, bendroflumethiazide / potassium chloride can be considered effective in the approved indications and generally well tolerated.

VI.2.3 Unknowns relating to treatment benefits

Use in children

Bendroflumethiazide/ potassium chloride should not be used in children because clinical studies evaluating safety, efficacy and dosage in children were not performed.

Use in pregnant woman

Bendroflumethiazide/ potassium should only be used when urgently indicated during pregnancy. Experience of the use of bendroflumethiazide with potassium chloride in pregnant women is limited. Experience from animal experiments is inadequate, with regard to the effects on pregnancy. The potential risk for humans is unknown.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Fluid and salt balance disturbance	Very common side effect of bendroflumethiazide/ potassium chloride use is reduced potassium levels in the blood which may manifest themselves in weakness and weak muscles. Serious disturbances of the body's fluid and salt balance that manifest themselves in tiredness, listlessness, confusion, coma, muscle tension are rare side effects of bendroflumethiazide/ potassium chloride.	Bendroflumethiazide/ potassium chloride should not be used in patients that have serious disturbances of the body's fluid and salt balance (electrolyte disturbances). Blood levels of potassium and sodium should be checked regularly.

Risk	What is known	Preventability
Drug-drug interactions with the following compounds: medicines for high blood pressure (ACE inhibitors, angiotensin II receptor antagonists, antihypertensives), tacrolimus (treatment after transplantation), medicines that may lower blood pressure (e.g. tricyclic antidepressants), strong pain-killing medicines (opioids), alcohol, medicines for epilepsy (barbiturates), other diuretics (loop-diuretics), medicines for arthritis or pain (NSAIDs), heart medicine (digitalis glycosides), muscle relaxants (non-depolarising neuromuscular blockers), adrenocortical hormone (corticosteroids, corticotrophin), medicines for asthma (beta-2-agonists), medicine for fungal conditions (amphotericin B), calcium carbonate, vitamin D, vitamin D analogues, medicines for diabetes (antidiabetic therapy), medicines for manic states (lithium) and a medicine to treat cancer (cyclophosphamide)	If the patient is receiving treatment with lithium, he/she should not take bendroflumethiazide/ potassium chloride unless his/hers doctor checks his/hers treatment frequently. If, together with bendroflumethiazide/ potassium chloride, the patient takes alcohol, medicines for epilepsy (phenobarbital) or strong pain-killing medicines (opioids), the patient may be at risk of fainting and falling over as a result of blood pressure falling too low.	The doctor or pharmacist should be informed if the patient is taking/ using, have recently taken/used or might take/use any other medicines. The patient should talk to his/her doctor if he/she is taking: • Medicines for arthritis or pain (NSAIDs) • Cholesterol-lowering products (cholestyramine and colestipol). • Other diuretics. • Heart medicine (digoxin). • Muscle relaxants. • Medicines for high blood pressure. • Medicines for manic states (lithium). • Medicines for diabetes. • Adrenocortical hormone (corticosteroids). • Medicines for asthma (beta-2 agonists) • Medicine for fungal conditions (amphotericin B). • Calcium and/or vitamin D. • Medicines that may make your skin photosensitive. • Medicines that may lower blood pressure (e.g. tricyclic antidepressants). • Tacrolimus (treatment after transplantation).
Blood disorders (granulocytopaenia and thrombocytopaenia)	Serious changes in the blood that may manifest themselves in influenza-like symptoms, colds, high fever, tiredness, dizziness, spontaneous bleeding are rare side effects of bendroflumethiazide/ potassium chloride.	If the patient experiences any side effects, he/she should talk to his/her doctor or pharmacist.
Dizziness on standing up (orthostatic hypotension)	If, together with bendroflumethiazide/ potassium chloride, the patient takes alcohol, medicines for epilepsy (phenobarbital) or strong pain-killing medicines (opioids), he/she may be at risk of fainting and falling over as a result of blood pressure falling too low.	If the patient experiences any side effects, he/she should talk to his/her doctor or pharmacist.

Risk	What is known	Preventability
	Dizziness on standing up has been reported uncommonly with bendroflumethiazide/ potassium chloride use.	
Photosensitisation reactions	Increased sensitivity to light has been reported uncommonly with bendroflumethiazide/ potassium chloride use.	If the patient is taking medicines that may make his/her skin photosensitive, he/she should talk to his/her doctor. If the patient experiences any side effects, he/she should talk to his/her doctor or pharmacist.
Sensory disturbances of the skin (paraesthesia)	Sensory disturbances of the skin, e.g. formication, burning sensation, itching, pins and needles and prickling sensations have been reported uncommonly with bendroflumethiazide/ potassium chloride use.	If the patient experiences any side effects, he/she should talk to his/her doctor or pharmacist..

Important potential risks

Risk	Aggravation or activation of systemic lupus erythematosus
Aggravation or activation of systemic lupus erythematosus	Bendroflumethiazide/ potassium chloride may also exacerbate a connective tissue disease (systemic lupus erythematosus).

Missing information

Risk	What is known
Limited information on use in children	Bendroflumethiazide/ potassium chloride should not be used in children because safety, efficacy and dosage in children are not documented.
Limited information on use during pregnancy	Bendroflumethiazide/ potassium should only be used when urgently indicated during pregnancy. Experience of the use of bendroflumethiazide with potassium chloride in pregnant women is limited. Experience from animal experiments is inadequate, with regard to the effects on pregnancy. The potential risk for humans is unknown.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the risk management plan over time

Table 2. Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.2	02 Sept 2014	Important identified risks • Electrolyte disturbances including dehydration • Drug-drug interactions with the following compounds: ACE inhibitors, angiotensin II receptor antagonists, tacrolimus, antihypertensives, tricyclic antidepressants, opioids, alcohol, barbiturates, loop-diuretics, NSAIDs, digitalis glycosides, non-depolarising neuromuscular blockers, corticosteroids, corticotrophin, beta-2-agonists, amphotericin B, calcium carbonate, vitamin D, vitamin D analogues, antidiabetic therapy, lithium and cyclophosphamide • Blood disorders (granulocytopaenia and thrombocytopaenia) • Orthostatic hypotension • Photosensitisation reactions • Paraesthesia Important potential risks • Aggravation or activation of systemic lupus erythematosus Missing information • Use in children • Use during pregnancy	First approved version of RMP
2.0	09 Oct 2015	Not applicable No changes to safety concerns or risk minimisation measures have been done since the last version of the RMP	Not applicable