

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bendroflumethiazide Evolan 2.5 mg tablets

Bendroflumethiazide Evolan 5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Bendroflumethiazide in 2.5 mg or 5 mg dosages.

2.5 mg tablets contain 60 mg of lactose.

5 mg tablets contain 120 mg of lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

2.5 mg: white or almost white, circular and biconvex tablet (5,5 mm).

5 mg: white or almost white, circular with flat beveled-edge, with “5” embossed on one side of the tablet (7 mm).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension.

Treatment of oedema of cardiac, renal or hepatic origin.

4.2 Posology and method of administration

For oral administration.

Adults:

Oedema:

Initially 5 – 10 mg once daily or on alternate days; maintenance dose: 2.5 – 10 mg one to three times weekly.

Hypertension:

Usual dose of 2.5 mg administered in the morning. Rarely, higher doses are needed.

Children:

Initial dose of up to 400 µg/kg of body weight reducing to the maintenance dose of 50 – 100 µg/kg of body weight.

Elderly:

Dosage of thiazide diuretics may need to be reduced in the elderly, especially where there is impairment of renal function due to potential electrolyte imbalance.

4.3 Contraindications

Hypersensitivity to the active substance, other thiazide, or to any of the excipients listed in section 6.1.

Bendroflumethiazide Evolan tablets are also contra-indicated in patients with the following conditions:

- Refractory hypokalaemia, hyponatraemia, or hypercalcaemia
- Severe renal or hepatic insufficiency
- Symptomatic hyperuricaemia
- Addison's disease.

4.4 Special warnings and precautions for use

Bendroflumethiazide should be used with caution in patients with mild or moderate renal or hepatic dysfunction (avoid in case it is serious). Renal function should be continuously monitored during thiazide's administration. Thiazides diuretics may exacerbate or activate systemic lupus erythematosus in susceptible patients.

All thiazides diuretics can cause electrolyte imbalance which is more severe in patients with renal or hepatic impairment or in those receiving higher or prolonged doses. Plasma electrolytes should be monitored, in particular hypokalaemia and abnormalities corrected by adding potassium supplements to the regimen. Diabetes Mellitus and gout may be aggravated; increases the risk of hypomagnesaemia in alcoholic cirrhosis.

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.

Elderly patients and those on long term treatment with bendroflumethiazide need regular and continuous monitoring, as well as blood tests.

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

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

Allopurinol

Bendroflumethiazide may antagonise the action of allopurinol by causing retention of urate in the kidney. Caution is advised when using this combination.

Anion exchange resins

Colestipol and colestyramine may reduce the absorption of thiazide diuretics and should therefore be given 2 hours prior to, or after the ingestion of Bendroflumethiazide.

Anti-arrhythmics

The cardio toxicity of disopyramide, amiodarone, flecainide and quinidine is increased if hypokalaemia occurs. The action of lidocaine and mexiletine are antagonised by hypokalaemia.

Anti-depressants

There is an increased risk of postural hypotension if bendroflumethiazide is given with tricyclic antidepressants. There may be an risk of hypokalaemia if thiazides are given with reboxetine. Concomitant use with monoamine oxidase inhibitors (MAOIs), may result in an enhanced hypotensive effect.

Antidiabetics

Bendroflumethiazide antagonises the hypoglycaemic effects of sulfonylureas, with a potential loss of diabetic control

Anti-epileptics

Concomitant use of carbamazepine may increase the risk of hyponatraemia.

Anti-fungals

There is an increased risk of hyponatraemia if thiazides are given with amphotericin

Antihypertensives

Bendroflumethiazide may enhance the antihypertensive effect of ACE inhibitors and angiotensin-II antagonists. There is an increased risk of first dose hypotensive effect of post-synaptic alpha-blockers such as prazosin.

Antipsychotics

Hypokalaemia increases the risk of ventricular arrhythmias with pimozide or thioridazine; therefore, concomitant use should be avoided.

Calcium salts

Bendroflumethiazide reduces urinary excretion of calcium so there is an increase risk of hypercalcaemia when calcium salts are taken concurrently. Serum calcium levels should be monitored to ensure that they do not become excessive.

Calcium-channel blockers and peripheral vasodilators

The hypotensive effect of calcium channel blockers and moxislyte may be enhanced when coadministered with bendroflumethiazide.

Corticosteroids

Corticosteroids may exacerbate hypokalaemia associated with bendroflumethiazide and its diuretic activity may be antagonised.

Cytotoxics

Concomitant use with cisplatin can lead to an increased risk of nephrotoxicity and ototoxicity.

Digoxin

Sensitivity to digitalis glycosides may be increased by the hypokalaemic effect of concurrent bendroflumethiazide. Patients should be observed for signs of digitalis intoxication, in particular arrhythmias, and if these appear, the dose of the digoxin should be temporarily reduced and a potassium supplement given to restore stability.

Hormone antagonists

There is an increased risk of hyponatraemia when thiazides (bendroflumethiazide) are used concomitantly with aminoglutethimide. Thiazides can cause an increased risk of hypercalcaemia when co-administered with toremifene.

Lithium

Bendroflumethiazide inhibits the tubular elimination of lithium, resulting in an elevated plasma lithium concentration and risk of toxicity. Plasma lithium concentrations must be monitored when these drugs are given concurrently.

Muscle relaxants

The hypotensive activity of bendroflumethiazide may be increased by baclofen and tizanidine. Thiazide diuretics may enhance the neuromuscular blocking effects of the non-depolarising muscle relaxants, e.g. tubocurarine, gallamine, alcuronium and pancuronium.

NSAIDs

Diuretics may increase the risk of nephrotoxicity of NSAIDs. Indometacin and ketorolac antagonise the diuretic effect of bendroflumethiazide, this occurs to a lesser extent with ibuprofen, piroxicam and naproxen. The effects of concurrent use should be monitored and the dose of bendroflumethiazide modified if necessary.

Oestrogens and progestogens

Oestrogens and combined oral contraceptives antagonise the diuretic effect of thiazides.

Vitamins

The risk of hypercalcaemia is increased if bendroflumethiazide is given with vitamin D preparations.

Sympathomimetics

Sympathomimetics can cause hypokalaemia. The risk of serious heart arrhythmias in asthmatic patients may be increased if bendroflumethiazide is added to their medication.

Theophylline

Concomitant administration of theophylline and bendroflumethiazide increases the risk of hypokalaemia.

Ulcer healing drugs

There is an increased risk of hypokalaemia and a decrease in diuretic activity when carbenoxolone and bendroflumethiazide are taken together. Patients should be monitored and given potassium supplements when required.

Terfenadine

Hypokalaemia or other electrolyte imbalance also increases the risk of ventricular arrhythmias with terfenadine.

Alcohol, barbiturates or opioids:

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

Laboratory tests

Bendroflumethiazide may interfere with a number of laboratory tests, including estimation of serum protein-bound iodine and tests of parathyroid function.

Others

Xanthines, beta-agonists, acetazolamide and ACTH may exacerbate the hypokalaemia associated with thiazide use.

4.6 Fertility, pregnancy and lactation

Pregnancy

Diuretics should be avoided for the management of oedema or hypertension in pregnancy as its use may be associated with hypokalaemia, increased blood viscosity and reduced placental perfusion.

There is insufficient evidence of safety in human pregnancy and foetal bone marrow depression and thrombocytopenia. Neonatal jaundice has also been described.

Lactation

As diuretics pass into breast milk and bendroflumethiazide can suppresses lactation, its use should be avoided in mothers who wish to breastfeed.

4.7 Effects on ability to drive and use machines

The effects on the ability to drive and use machines are unknown.

4.8 Undesirable effects

The following undesirable effects, which are listed in system order class, have previously been associated with Bendroflumethiazide. Specific frequencies for the occurrence of these effects are not available.

Blood and lymphatic system disorders:

Rarely, blood dyscrasias including agranulocytosis, aplastic anaemia, neutropenia, thrombocytopenia (neonatal thrombocytosis is reported when given in late pregnancy) and leucopenia have been reported.

Immune system disorders:

Hypersensitivity reactions

Metabolism and nutrition disorders:

Bendroflumethiazide may lower carbohydrate tolerance and the insulin dosage of some diabetic patients may require adjustment.

Care is required when bendroflumethiazide is administered to patients with a known predisposition to diabetes (hyperglycaemia reported).

Bendroflumethiazide may raise serum uric acid levels and exacerbate gout in susceptible individuals (hyperuricaemia). Plasma lipids may be altered in patients taking bendroflumethiazide.

Cardiac and vascular disorders:

Postural hypotension

Respiratory, thoracic and mediastinal disorders:

Pneumonitis, pulmonary oedema

Gastrointestinal disorders:

Nausea, vomiting, diarrhoea, constipation and gastric irritation have all been reported

Hepatobiliary disorders:

Pancreatitis, intrahepatic cholestasis

Skin and subcutaneous tissue disorders:

Rash (including exfoliative dermatitis), photosensitivity, severe skin reactions also reported

Reproductive system and breast disorders:

Impotence (reversible on discontinuing the drug)

Investigations:

Hypokalaemia, hypomagnesaemia, hyponatraemia, hypercalcaemia, hypochloraemic alkalosis. Hypokalaemia may result in polyuria, malaise, muscle weakness or cramp, dizziness, nausea, anorexia or vomiting.

Description of selected adverse reactions:

Cases of acute angle-closure glaucoma, acute myopia and choroidal effusion, with visual field defect have been reported after the use of thiazide and thiazide-like diuretics.

4.9 Overdose

Overdose symptoms include anorexia, nausea, vomiting, diarrhoea, diuresis, dehydration, hypotension, dizziness, weakness, muscle cramps, parestesias, tetania, gastrointestinal bleeding, hyponatremia, hypo- or

hyperglycaemia, hypokalaemia and metabolic alkalosis. Initial treatment consists of vomit induction or gastric lavage, as appropriate.

On the contrary, treatment should be symptomatic and supportive, including fluid and electrolyte balance correction.

Blood pressure should be monitored. There is no specific antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 3.4.1.1 Thiazides and analogous, ATC code: C03A A01 Bendroflumethiazide.

Bendroflumethiazide is a thiazide diuretic. The mechanism whereby the thiazides exert their antihypertensive effect has not been clearly established.

Bendroflumethiazide inhibits the renal tubular absorption of salt and water by its action at the beginning of the distal convoluted tubule. Sodium and chloride ions are excreted in equivalent proportions. Because potassium excretion is promoted, metabolic alkalosis may occur secondary to hypokalaemia. There is no important effect upon carbonic anhydrase. Bendroflumethiazide exerts its diuretic effect in about 2 hours and this lasts for 12 to 18 hours or longer. The excretion of other electrolytes, notably potassium and magnesium, is also increased.

The excretion of calcium is reduced. Thiazides also reduce carbonic anhydrase activity so that bicarbonate excretion is increased, but this effect is generally small and does not appreciably alter the acid base balance or the pH of the urine. Thiazides also have a hypotensive effect, due to a reduction in peripheral resistance and enhance the effects of other antihypertensive agents.

5.2 Pharmacokinetic properties

Absorption: Bendroflumethiazide has been reported to be completely absorbed from the gastrointestinal tract and it is fairly extensively metabolised.. Diuresis is initiated in about 2 hours and lasts for 12-18 hours or longer About 30% is excreted unchanged in the urine. The onset of the hypotensive action is generally three or four days.

Distribution: Bendroflumethiazide is more than 90% bound to plasma proteins.

Metabolism: There are indications that it is fairly extensively metabolised. Peak plasma levels are reached in 2 hours and a plasma half- life of between 3 and 8.5 hours on average.

Elimination: About 30% is excreted unchanged in the urine with the remainder excreted as uncharacterized metabolites.

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

Pregelatinised maize starch

Talc

Stearic acid.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

HDPE bottles: Use within 6 months after opening.

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package.

6.5 Nature and contents of container

Packs containing 14, 28 or 56 or 98 tablets in PVDC/PVC/Alu blister and 100 or 500 tablets in HDPE bottles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7. MARKETING AUTHORISATION HOLDER

Evolan Pharma AB
Box 120
18212 Danderyd
Sverige

8. MARKETING AUTHORISATION NUMBER(S)

2,5 mg: 46483

5 mg: 46484

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10th October 2007

10. DATE OF REVISION OF THE TEXT

2021-07-07