

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Navispare tablets
Cyclopentiazide 0.25mg and Amiloride Hydrochloride 2.5mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

6-Chloro-3-(cyclopentylmethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (Cyclopentiazide B.P.) 0.25mg.

N-amindino-3,5-diamino-6-chloropyrazine-2-carboxamide dihydrate (Amiloride Hydrochloride Ph.Eur.) 2.5mg hydrochloride

3. PHARMACEUTICAL FORM

Coated tablets

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

For the treatment of mild to moderate hypertension.

4.2. Posology and Method of Administration

Adults: Usually 1 or 2 Navispare tablets taken once a day in the morning.

Use in the Elderly: Although no special dosage regime is necessary in the elderly, particular caution should be exercised in the elderly, since they are more susceptible to electrolyte imbalances.

Use in children: Navispare is not suitable for use in children.

4.3 Contraindications

Hypersensitivity to cyclopentiazide or other sulphonamide derivatives;

Addison's disease;
Hyperkalaemia;
In the presence of other potassium conserving agents or potassium supplements;
Anuria;
Severe renal and hepatic failure;
Diabetic Nephropathy;
Concurrent lithium therapy;
Refractory hypokalaemia and hyponatraemia;
Hypercalcaemia;
Symptomatic hyperuricaemia.

4.4. Special Warnings and Special Precautions for Use

4.4.1 Warnings

None known.

4.4.2 Precautions

Diabetes mellitus:

Hyperkalaemia has occurred in diabetic patients receiving amiloride hydrochloride, especially those with chronic renal disease or pre-renal azotaemia. The status of renal function should therefore be determined before use in a known or suspected diabetic patient. Navispare should be discontinued for at least three days before a glucose tolerance test.

Prolonged doses may bring about a decrease in glucose tolerance and precipitate a diabetic condition. In known diabetics the addition of a thiazide to the treatment regime may alter their antidiabetic requirement.

Metabolic or respiratory acidosis:

Potassium conserving therapy should be initiated with caution in patients in whom metabolic or respiratory acidosis may occur e.g. patients with cardiopulmonary disease or decompensated diabetes. Shifts in acid-base balance of extracellular potassium and the development of acidosis may be associated with rapid increase in plasma potassium.

Electrolyte considerations:

In patients with renal impairment, a rise in blood urea can occur. In such cases, either the dose should be reduced or the treatment interrupted temporarily. Thiazides may precipitate an attack of gout in patients predisposed to this condition.

The elderly, especially those suffering from chronic disease and patients with hepatic cirrhosis are more susceptible to a lack of electrolyte and fluid balance homeostasis. During treatment with thiazides hyponatraemia accompanied by neurological symptoms has been observed in isolated cases. In the elderly and

patients with hepatic cirrhosis, the serum electrolytes should be monitored at more frequent intervals.

Patients receiving relatively high doses of thiazides may develop hypomagnesaemia accompanied by signs and symptoms such as nervousness, muscle spasms and cardiac arrhythmias.

Miscellaneous:

In patients with hyperlipidaemia, the serum lipids should be regularly monitored. In the event of a rise in serum lipids, withdrawal of the thiazide medication should be considered. Lupus erythematosus may possibly become activated under treatment with thiazides.

4.5. Interactions with other Medicinal Products and other Forms of Interaction

The concomitant administration of thiazides with other antihypertensive agents (e.g. beta-blockers, vasodilators, calcium antagonists) may necessitate adjustment of the dosage of those drugs.

The concomitant administration of potassium-sparing agents such as amiloride and ACE inhibitors may increase serum potassium levels and is not to be recommended. However, if the concomitant use of these agents is deemed appropriate, they should be used with caution and with frequent monitoring of plasma potassium.

NSAIDs may attenuate the antihypertensive effect of thiazide diuretics.

Thiazide containing drugs may increase the responsiveness to tubocurarine.

Orthostatic hypotension may occur and may be potentiated by alcohol, barbiturates and narcotics.

4.6. Pregnancy and Lactation

Diuretics are best avoided for the management of oedema or hypertension in pregnancy as their use may be associated with hypovolaemia, increased blood viscosity and reduced placental perfusion.

There is inadequate evidence of safety in human pregnancy and there have been reports of foetal bone marrow depression, thrombocytopenia, and foetal and neonatal jaundice reported with the use of thiazide diuretics.

As cyclopentiazide passes into breast milk, Navispare should be avoided in mothers who wish to breast-feed. It is not known whether amiloride hydrochloride passes into breast milk.

4.7. Effects on Ability to Drive and Use Machines

None stated.

4.8. Undesirable Effects

Navispare is generally well tolerated. Reported side-effects of the combination include rare cases of dizziness, headache, lightheadedness, tiredness, nausea and vomiting, discomfort/pain in the chest. However, the following side-effects of cyclopenthiiazide and amiloride as single agents have been reported:

Cyclopenthiiazide:

Skin:

Occasional: allergic urticaria (nettle rash) and other forms of skin rash.

Rare: photosensitisation. Isolated cases: necrotising vasculitis.

Gastro-intestinal tract:

Occasional: loss of appetite, mild nausea, vomiting.

Rare: gastrospasm, diarrhoea or possibly constipation. Isolated cases: pancreatitis.

Central nervous system:

Rare: headache, muzziness, dizziness, sleep disturbances, depression and paraesthesiae.

Blood:

Rare: thrombocytopenia sometimes with purpura. In isolated cases: leucopenia, agranulocytosis, anaemia and bone marrow depression.

Electrolytes:

Frequent: hypokalaemia.

Occasional: hyponatraemia, hypomagnesaemia.

Rare: hypercalcaemia. If hypercalcaemia occurs, further diagnostic clarification is necessary (e.g. possibility of hyperparathyroidism).

In isolated cases: hypochloraemic alkalosis.

Liver:

Rare: intrahepatic cholestasis or jaundice.

Miscellaneous:

Occasional: impotence.

Metabolic:

Occasional: hyperuricaemia. Rare: hyperglycaemia, glycosuria. Gout or diabetes may be precipitated or aggravated. Increased blood lipid levels in response to higher doses.

Cardiovascular system:

Occasional: postural hypotension, which may be aggravated by alcohol, anaesthetics or sedatives.

Rare: cardiac arrhythmias.

Amiloride:

Gastro-intestinal tract:

Rare: anorexia, nausea, vomiting, abdominal pain.

In isolated cases: diarrhoea, constipation, GI bleeding, jaundice, thirst, dyspepsia, heartburn, flatulence.

Central nervous system:

Rare: dizziness, paraesthesiae, tremors, mental confusion.

In isolated cases: encephalopathy, nervousness, insomnia, decreased libido, depression, somnolence, vertigo.

Cardiovascular system:

Rare: palpitation.

In isolated cases: angina pectoris, orthostatic hypotension, arrhythmias.

Respiratory:

Rare: cough, dyspnoea.

Urogenital:

Rare: frequency or micturition.

In isolated cases: impotence, polyuria, dysuria.

Musculoskeletal:

Rare: joint pain.

In isolated cases: muscle cramps.

Skin and appendages:

Rare: pruritus, rash, alopecia.

In isolated cases: dryness of mouth.

4.9. Overdose

Signs and Symptoms

Signs: In cases of overdosage the following signs and symptoms may occur. Dizziness, nausea, somnolence, hypovolaemia, hypotension and electrolyte disturbances associated with cardiac arrhythmias and muscle spasms.

Treatment:

Emesis should be induced or gastric lavage performed. Intravenous fluid and electrolyte replacement may be indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

ATC code: C03E A07

Mode of action:

Cyclopenthiazide is a benzothiadiazine (thiazide) diuretic.

Cyclopenthiazide is a thiazide diuretic which exerts diuretic effect by inhibiting the reabsorption of sodium chloride and water probably at the distal renal tubules.

Amiloride hydrochloride is a mild potassium-sparing diuretic, belonging to the pyrazine carboxamide class, which acts mainly on the distal part of the renal tubule. It increases the excretion of sodium and chloride and reduces the excretion of potassium.

5.2. Pharmacokinetic Properties

The lipophilic thiazides - such as cyclopenthiazide - attain higher concentration in the cells and thus have a larger distribution volume than the hydrophilic derivatives. Their protein binding rate is also greater, amounting to approximately 92%. They therefore exert a more prolonged action than the more hydrophilic thiazides.

Amiloride is completely absorbed from the GI tract; peak serum concentrations are achieved about 3 and 4 hours after oral administration. It is excreted unchanged in the urine and has been estimated to have a serum half life of about 6 hours.

5.3. Pre-clinical Safety Data

Cyclopenthiazide: In reproduction toxicity studies with mice, rats, and rabbits, no teratogenic effects were observed.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

The coated tablets contain lactose, wheat starch, polyvinylpyrrolidone (K90), stearic acid, talc, sodium starch glycollate, titanium dioxide (E171), yellow iron oxide (E172), polyethoxylated hydrogenated castor oil, hydroxypropylmethylcellulose and water.

6.2. Incompatibilities

None known.

6.3. Shelf Life

Three years.

6.4. Special Precautions for Storage

Protect from moisture. Store below 25°C.

Medicines should be kept out of reach of children.

6.5. Nature and Contents of Container

All tablets are packed in PVC/PVDC packs of 28 tablets.

6.6. Instructions for Use/Handling

None.

7. MARKETING AUTHORISATION HOLDER

Goldshield Pharmaceuticals Limited
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UK

8. MARKETING AUTHORISATION NUMBER(S)

PL 12762/0216

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF
AUTHORISATION**

30/01/2006

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27/07/2007