

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF MEDICINAL PRODUCT

Navidrex 0.5mg Tablets

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cyclopentiazide BP 0.5mg.

### 3. PHARMACEUTICAL FORM

White, flat, round tablets with bevelled edges, pressed '055' on one side, and the letters 'GS' on each side of a breakline on the other.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

Treatment of mild to moderate hypertension; in more severe hypertension Navidrex may be used in conjunction with other antihypertensive agents.

Stable, chronic heart failure of mild to moderate degree (functional class II, III), as long as creatinine clearance is > 30ml/min.

Oedema of specific origin:

- fluid retention in pre-menstrual syndrome only as short-term therapy and only if the gain in weight is the main symptom and is well documented,
- ascites due to cirrhosis of the liver in stable patients under close control.
- oedema associated with renal disease.

#### 4.2 Posology and method of administration

The dosage of Navidrex should be individually titrated to give the lowest effective dose; this is particularly important in the elderly. Navidrex should be taken orally: a single dose of up to 1mg given in the morning is recommended.

Adults:

*Hypertension:* Initially 0.25mg daily; if necessary the dosage may be raised to 0.5mg daily. For a given dose, the full effect is reached after 4 to 6 weeks. If the decrease in blood pressure proves inadequate with 0.5mg/day, combined treatment with other antihypertensive drugs such as  $\beta$ -blocker (if necessary, a  $\alpha$ -blocker and vasodilator), or an ACE inhibitor is recommended. It is recommended that diuretics (Navidrex) should be withdrawn for several days before starting the ACE inhibitor.

*Stable, chronic heart failure (NYHA class II, III):* Initially 0.25 to 0.5mg daily. If necessary the dose may be titrated up to 1mg/day; higher doses rarely achieve any further benefit. The lowest effective dose should be used for maintenance therapy. If the response proves inadequate, a positive inotropic drug (e.g. digitalis), possibly combined with an ACE inhibitor may be added. In the latter case a reduction in the dose of Navidrex may be necessary.

*Oedema:* The lowest effective dose should be determined by titration and administered over limited periods only. Doses should not exceed 0.5mg/day.

*Children:* Adequate experience regarding the dosage in children is lacking.

*Elderly:* Particular caution should be exercised since the elderly are more susceptible to electrolyte imbalances (see Section 4.4 'Special warnings and precautions for use').

*Patients with renal impairment:* There is no evidence on the effect of renal impairment on the excretion of cyclopentiazide, but experience with other thiazide diuretics indicates that a 50% reduction of the normal adult dose may be appropriate.

### 4.3 Contraindications

Anuria, severe renal and hepatic failure. Hypersensitivity to cyclopentiazide and other sulphonamide derivatives. Refractory hypokalaemia, hyponatraemia and hypercalcaemia. Symptomatic hyperuricaemia (history of gout or uric acid calculi). Hypertension during pregnancy. Creatinine clearance lower than 30ml/min. Conditions involving enhanced potassium loss, e.g. salt-losing nephropathies and prerenal (cardiogenic) impairment of kidney function. Untreated Addison's disease. Concomitant lithium therapy.

### 4.4 Special warnings and precautions for use

Navidrex should be used with caution in patients with renal disease or with impaired hepatic function (see Section 4.3 'Contra-indications' and below under 'other precautions').

#### *Electrolytes:*

As with all thiazide diuretics, potassium loss induced by Navidrex is dose dependent. With daily doses of 125 and 500µg. given for 8 weeks, the decreases in serum potassium concentrations averaged 0.2 and 0.6mmol/l, respectively. For chronic treatment, serum potassium concentrations should be checked initially and then after 3 to 4 weeks. Thereafter (if the potassium balance is not disturbed by additional factors, e.g. vomiting, diarrhoea, change in renal function etc..) checks should be carried out every 4 to 6 months.

Titrated co-administration of an oral potassium salt (e.g. KCl) may be considered in patients receiving digitalis, glucocorticoids or ACTH; in patients exhibiting signs of coronary heart disease, unless they are also receiving an ACE inhibitor; in patients on high doses of a  $\alpha$ -adrenergic agonist; and in all cases where plasma concentrations are  $< 3.0$ mmol/l. If oral potassium preparations are not tolerated, Navidrex may be combined with a potassium-sparing diuretic (e.g. amiloride). Combined treatment consisting of Navidrex and a potassium salt or a potassium-sparing diuretic must be avoided in patients also receiving ACE inhibitors.

In all cases of combined treatment, maintenance or normalisation of the potassium balance should be checked closely. If hypokalaemia is accompanied by clinical signs (e.g. muscular weakness, paresis and EGG alteration), Navidrex should be discontinued.

There have been isolated reports of hyponatraemia with neurological symptoms (e.g. nausea, debility, progressive disorientation and apathy).

Serum electrolyte levels should be monitored particularly in the elderly, and in patients with ascites due to liver cirrhosis and in patients with oedema due to nephrotic syndrome. For the latter condition, Navidrex should be used only under close control in normokalaemic patients with no signs of volume depletion or severe hypoalbuminaemia.

As with other diuretics, Navidrex may cause disturbances in the electrolyte balance during prolonged treatment. Since the excretion of electrolytes is increased, a very strict low salt diet should be avoided.

#### *Metabolic effects:*

Navidrex may raise the serum uric acid level and provoke attacks of gout in predisposed patients. Glucose intolerance may occur (this may manifest as hypoglycaemia and glycosuria) but diabetes mellitus very seldom occurs under treatment.

In patients with hyperlipidaemia, serum lipids should be monitored regularly. Small and partly reversible increases in plasma concentrations of total cholesterol, triglycerides or low density lipoprotein cholesterol have been reported in patients during long term treatments with thiazides and thiazide-like diuretics. The clinical relevance of these findings is not clear. Withdrawal of Navidrex should be considered if serum lipids rise further.

Navidrex should not be used as first line therapy for long-term treatment in patients with overt diabetes mellitus or in subjects receiving therapy for hypercholesterolaemia (diet or combined).

*Other precautions:*

Navidrex may accumulate in patients with impaired renal function. At creatinine clearance levels of <30ml/min (or at serum creatinine levels of > 2.5mg/100ml), cyclopentiazide will not exert a diuretic effect. In such cases, loop diuretics are indicated.

The antihypertensive effect of ACE inhibitors is potentiated by diuretics that increase plasma renin activity. A cautious dosage schedule should therefore be adopted when an ACE inhibitor is added to a diuretic agent.

As with all antihypertensive agents, a cautious dosage schedule is indicated in patients with severe coronary or cerebral arteriosclerosis.

Lupus erythematosus may possibly become activated under treatment with thiazides.

#### **4.5 Interactions with other medicinal products and other forms of interaction**

*Curare derivatives and antihypertensive drugs:* Diuretics potentiate the action of these drugs (e.g. guanethidine, methyldopa,  $\alpha$ -blockers, vasodilators, calcium antagonists and ACE inhibitors).

*Lithium:* Diuretics raise the blood level of lithium. Where lithium has produced polyuria, diuretics may exert a paradoxical antidiuretic effect. (see Section 4.3 "Contra-indications").

*Corticosteroids, ACTH, amphotericin and carbenoxolone:* These may increase the hypokalaemic effect of diuretics.

*Anti-diabetic agents:* It may prove necessary to adjust the dosage of insulin and oral antidiabetic agents.

*Digitalis:* Hypokalaemia or hypomagnesaemia possibly occurring as unwanted effects may cause onset of digitalis-induced cardiac arrhythmias.

*Non-steroidal anti-inflammatory agents:* Concomitant administration of certain NSAIDs (e.g. indomethacin) may reduce the diuretic and antihypertensive activity of Navidrex; there have been isolated reports of a deterioration in renal function in predisposed patients.

*Allopurinol:* Co-administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol. (see Section 4.3 "Contra-indications").

*Amantadine:* Co-administration of thiazide diuretics may increase the risk of adverse effects from amantadine.

*Antineoplastic agents (e.g. cyclophosphamide, methotrexate):* Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance the myelosuppressive effects.

*Anticholinergic agents (e.g. atropine, biperiden):* The bioavailability of thiazide type diuretics may be increased by anticholinergic agents, apparently due to a decrease in gastrointestinal motility and stomach emptying rate.

*Cholestyramine:* Absorption of thiazide diuretics is decreased by cholestyramine. A decrease of the pharmacological effect may be expected.

*Vitamin D:* Concomitant use of thiazide diuretics may decrease urinary excretion of calcium, and coadministration of Vitamin D may potentiate the increase in serum calcium.

*Cyclosporin:* Concomitant treatment with diuretics may increase the risk of hyperuricaemia and gout type complications.

*Calcium salts:* Concomitant use of thiazide type diuretics may cause hypercalcaemia by increasing tubular calcium resorption.

*Diazoxide:* Thiazide diuretics may enhance the hyperglycaemic effect of diazoxide.

*Methyldopa*: There have been reports in the literature of haemolytic anaemia occurring with concomitant use of a thiazide diuretic and methyldopa.

#### **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.

Diuretics do not prevent or alter the course of oedema, proteinuria or hypertension during pregnancy (pre-eclampsia). Cyclopentiazide must not be used to treat hypertension during pregnancy (see Section 4.3 “Contraindications”), and the use of Navidrex for other indications (e.g. heart disease) during pregnancy should be avoided unless there are no safer alternatives. There have been reports of foetal bone marrow depression, thrombocytopenia, and foetal and neonatal jaundice associated with the use of thiazide diuretics.

Cyclopentiazide may be excreted into the breast milk and thus mothers taking Navidrex should refrain from breast-feeding their infants.

#### **4.7 Effects on ability to drive and use machines**

Patients should be warned of the potential hazards of driving or operating machinery if they experience side effects such as dizziness, sleep disturbances or visual disturbances.

#### **4.8 Undesirable effects**

*Electrolytes and metabolic disorders*: Frequent: mainly at higher doses, hypokalaemia, and rise in blood lipids (see Section 4.4 “Special warnings and precautions for use”). Occasional: hyponatraemia, hypomagnesaemia and hyperuricaemia. Rare: hypercalcaemia, hyperglycaemia, glycosuria, worsening of diabetic metabolic state. Isolated cases: hypochloroemic alkalosis.

*Skin*: Occasional: urticaria and other forms of skin rash. Rare: photosensitisation. Isolated cases: necrotising vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus like reactions, reactivation of cutaneous lupus erythematosus.

*Gastro-intestinal tract*: Occasional: loss of appetite, mild nausea and vomiting. Rare: abdominal distress, constipation, diarrhoea and gastrointestinal discomfort. Isolated cases: pancreatitis.

*Liver*: Rare: intrahepatic cholestasis.

*Cardiovascular system*: Occasional: postural hypotension, which may be aggravated by alcohol, anaesthetics or sedatives. Rare: cardiac arrhythmias.

*Central nervous system*: Rare: headache, dizziness or muzziness, sleep disturbance, depression and paraesthesia.

*Special senses*: Visual disturbances, particularly in the first few weeks of treatment.

*Blood*: Rare: thrombocytopenia, sometimes with purpura. Isolated cases: leucopenia, agranulocytosis, bone marrow depression and haemolytic anaemia.

*Other effects*: Occasional: impotence. Isolated cases: hypersensitivity reactions – respiratory distress including pneumonitis and pulmonary oedema. Gout may be precipitated or aggravated in susceptible patients or those with a history of the illness, but there have been only isolated reports of attacks occurring during chronic therapy.

#### **4.9 Overdose**

*Symptoms*: Dizziness, nausea, somnolence, hypovolaemia, hypotension and electrolyte disturbances associated with cardiac arrhythmias and muscle spasms.

*Treatment*: There is no specific antidote to Navidrex. Gastric lavage, emesis or activated charcoal should be employed to reduce absorption. Blood pressure and fluid and electrolyte balance should be monitored and appropriate corrective measures taken. Intravenous fluid and electrolyte replacement may be indicated.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Cyclopenthiiazide is a benzothiadiazine (thiazide) diuretic.

Thiazide diuretics act primarily on the distal renal tubule (early convoluted part), inhibiting NaCl reabsorption (by antagonising the NaCl-cotransporter), promoting Ca<sup>2+</sup> reabsorption (by an unknown mechanism). The enhanced delivery of Na<sup>+</sup> and water to the cortical collecting tubule and/or the increased flow rate leads to increased secretion and excretion of K<sup>+</sup> and H<sup>+</sup>.

In healthy volunteers or in patients with oedema, cyclopenthiiazide administration results in a dose dependent increase in urinary excretion of sodium and chloride and a less prominent dose dependent increase in potassium excretion. The diuretic and natriuretic effect appears within 1 to 3 hours and subsides within 24 hours.

Thiazide-induced diuresis initially leads to a decrease in plasma volume, cardiac output and systemic blood pressure. The renin-angiotensin aldosterone system may possibly become activated. On continued administration the hypotensive effect is maintained, probably due to the fall in peripheral resistance; cardiac output returns to pretreatment values, plasma volume remains somewhat reduced and plasma renin activity may be elevated.

During repeated administration of Navidrex the antihypertensive effect is dose dependent from 125 to 500 µg/day. The maximum hypotensive effect is reached with 500 µg in most patients. In chronic heart failure, daily doses of 1 mg may enhance the therapeutic benefit but at higher doses the expected benefit must be balanced by the increased risk of sideeffects.

As with other diuretics, when Navidrex is given as monotherapy, blood pressure control is achieved in about half of patients with mild to moderate hypertension. In general the elderly and black patients are found to respond well to diuretics as primary therapy.

Combined treatment with other antihypertensives has an additive effect and in a large proportion of patients failing to respond to monotherapy, a further decrease in blood pressure can thus be achieved.

### 5.2 Pharmacokinetic properties

Based on limited pharmacokinetic data, the variability of the amount of Cyclopenthiiazide absorbed appears to be low. After oral administration of single doses of 0.5 or 1.0mg cyclopenthiiazide, peak plasma levels of about 3 and 7ng/ml respectively were reached after an average of 3 to 4 hours. Twelve hours after the administration of 1mg cyclopenthiiazide, the plasma concentration decreases to about 25% of the peak concentration.

In rats, cyclopenthiiazide is excreted mainly by tubular secretion. In humans receiving cyclopenthiiazide the drug can be detected in the urine. At 24 hours after the administration of a 0.5mg dose, for instance, the concentration in the urine is about 400 ng/ml.

### 5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to those already included in other sections of the Summary of Product Characteristics.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Lactose  
Wheat starch  
Gelatin  
Stearic acid  
Talc

## **6.2 Incompatibilities**

None known

## **6.3 Shelf life**

3 Years (PVC/PVdC blister packs)

## **6.4. Special precautions for storage**

Protect from heat and moisture. Store below 25°C.

## **6.5 Nature and contents of container**

PVC/PVdC/Aluminium blister packs of 28 tablets.

## **6.6 Instruction for use/handling**

None

## **7. MARKETING AUTHORISATION HOLDER**

Goldshield Pharmaceuticals Ltd  
NLA Tower  
Croydon  
CR0 0XT  
United Kingdom

## **8. MARKETING AUTHORISATION NUMBER**

PL 12762/0076

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

24th July 2000

## **10. DATE OF REVISION OF THE TEXT**

September 2008