NOVARTIS

Esidrex®

Composition

Active substance: Hydrochlorothiazide
Excipients: Tableting excipients

Pharmaceutical form and quantity of active substance per unit

Scored tablets of 25 mg

Indications / Potential uses

Hypertension: As monotherapy and in combination with other antihypertensives (e.g. beta-blockers, vasodilators, calcium antagonists, ACE inhibitors, reserpine).
Heart failure
Oedema due to heart failure or mild to moderate kidney or liver failure
Nephrogenic diabetes insipidus
Idiopathic hypercalciuria and prevention of recurrent calcium oxalate calculi

Dosage and Administration

The dosage depends on the clinical picture and the patient's response. Where a single daily dose is prescribed, this is best taken in the morning with breakfast.
In the case of long-term therapy, the lowest dose compatible with maintenance of optimum effect should be given, particularly in elderly patients.

Hypertension
Adults: The initial dosage is usually 25–50 mg daily, taken in the morning or in two divided doses. For long-term treatment 12.5–25 mg every morning is often sufficient. If blood pressure reduction is not adequate, co-medication with another antihypertensive (e.g. betablocker, vasodilator, calcium antagonist, ACE inhibitor, reserpine) is recommended. This way the dosage of each substance can often be kept lower.

Heart failure and oedema
Adults: The initial dosage is 25–75 mg daily, given in 1–2 doses. In isolated cases this can be increased, but doses exceeding 100 mg rarely result in an additional increase in efficacy. If the effect is inadequate, positive inotropic substances and vasodilators should be used. Once the patient has begun to respond satisfactorily, 25 mg daily – or possibly every other day – is usually adequate for maintenance therapy.
The mean dosage in children is usually up to 2 mg/kg daily, depending on the clinical picture.

Nephrogenic diabetes insipidus
Adults: The initial dosage is 100 mg daily, given in 2–4 single doses. Later the dosage may be reduced. Experience in children is limited to isolated cases and dosage should therefore be determined on an individual basis in hospital.

Idiopathic hypercalciuria and prevention of recurrent calcium oxalate calculi
Adults: 25–50 mg twice daily.

Contraindications

Anuria, severe renal and hepatic failure. Hypersensitivity to hydrochlorothiazide and other sulphonamide derivatives. Refractory hypokalaemia, hyponatraemia and hypercalcaemia.
Symptomatic hyperuricaemia (history of gout or uric acid calculi).
Hypertension during pregnancy.
Creatinine clearance below 30 ml/minute.
Conditions associated with increased potassium loss, e.g. salt- losing nephropathies and prerenal (cardiogenic) kidney dysfunction.

Warnings and Precautions

Esidrex should be used with caution in patients with renal disease or impaired liver function (see **Contraindications** and **Dosage and Administration**).

Electrolytes
Like all thiazide diuretics, Esidrex causes dose-dependent kaliuresis. During 6 months of treatment with 12.5 mg daily, serum potassium concentrations decrease by an average of 0.36 mmol/litre. Serum potassium concentrations should be checked at the beginning of longterm therapy and again 3–4 weeks later. Thereafter they should be measured every 4–6 months, unless the potassium balance is disturbed by other factors, such as vomiting, diarrhoea, change in renal function, etc.
Concomitant administration of an oral potassium salt (e.g. KCl) in an individually adapted dosage may be considered in patients receiving digitalis or showing signs of coronary heart disease, unless they are also receiving an ACE inhibitor. The same applies to patients receiving high doses of beta-adrenergic agonists and in all patients in whom serum potassium concentrations are below 3.0 mmol/litre. If oral potassium preparations are not tolerated, Esidrex can be combined with a potassium-sparing diuretic.
Whenever combination treatment is given, the patient should be closely monitored to ensure maintenance or normalization of the potassium balance. If hypokalaemia is accompanied by clinical signs of potassium depletion (e.g. muscle weakness, paresis or ECG changes), Esidrex should be discontinued.

Patients who are also receiving an ACE inhibitor should not be given Esidrex in combination with a potassium salt or a potassium- sparing diuretic.
Hyponatraemia accompanied by neurological symptoms (nausea, weakness, progressive disorientation, apathy) has been observed in isolated cases.
Monitoring of serum electrolytes is particularly called for in elderly patients, patients with ascites due to liver cirrhosis, and patients with oedema due to nephrotic syndrome. In the case of oedema due to nephrotic syndrome, Esidrex should not be used unless the patient is normokalaemic and there are no signs of volume depletion or severe hypoalbuminaemia; if it is used, close surveillance is indicated.

Metabolic effects
Like other diuretics, Esidrex can raise serum uric acid levels, but attacks of gout are seldom seen during prolonged treatment.
As with all thiazide diuretics, glucose tolerance may change during long-term treatment with Esidrex; this effect is less pronounced with lower doses. Thiazides rarely cause frank diabetes mellitus, especially if there are no predisposing factors.
Slight and partly reversible increases in plasma concentrations of total cholesterol, triglycerides, or low-density-lipoprotein cholesterol have been observed during long-term treatment with thiazides and thiazide-like diuretics. The clinical relevance of these findings is disputed.
Esidrex should not be used as a first-line drug for long-term treatment of patients with overt diabetes mellitus or patients receiving treatment for hypercholesterolaemia (diet alone or diet combined with drug therapy).
Thiazides reduce calcium excretion. During long-term treatment with thiazides, pathological changes in the parathyroid gland accompanied by hypercalcaemia and hypophosphataemia have been observed in a few patients. If hypercalcaemia occurs, further diagnostic clarification is necessary. The complications that usually arise with hyperparathyroidism, e.g. nephrolithiasis, bone resorption and peptic ulcer, have not been seen.

Efficacy, dosage and renal function
Patients with renal failure: It is recommended that the dosage be halved in patients with kidney failure (creatinine clearance of 30–70 ml/minute).
Thiazide diuretics, including Esidrex, lose their diuretic effect when creatinine clearance is below 30 ml/minute (or when serum creatinine levels are above 2.5 mg/100 ml). In such cases a loop diuretic is indicated.

Other
Substances that increase plasma renin activity (i.e. diuretics) potentiate the antihypertensive effect of ACE inhibitors. The dosage should therefore be carefully adjusted if an ACE inhibitor is given in addition to treatment with a diuretic.
Lupus erythematosus may be activated during treatment with thiazides.

Interactions

Since diuretics can raise blood lithium levels, these must be monitored in patients receiving lithium during treatment with Esidrex. If lithium has induced polyuria, diuretics may have a paradoxical antidiuretic effect.
Thiazides potentiate the effect of curare derivatives and antihypertensive drugs (e.g. guanethidine, methyldopa, beta-blockers, vasodilators, calcium antagonists and ACE inhibitors).
The hypokalaemic effect of diuretics may be potentiated by corticosteroids, ACTH, amphotericin and carbenoxolone (not approved in Switzerland).
It may be necessary to adapt the dosage of insulin and oral antidiabetic agents.
Hypokalaemia or hypomagnesaemia, which can occur as adverse effects of thiazide treatment, may promote the onset of digitalis-induced cardiac arrhythmias (see **Warnings and Precautions**).
Concomitant administration of certain non-steroidal anti-inflammatory agents (e.g. indometacin) may reduce the diuretic and antihypertensive effects of diuretics. Isolated cases of deterioration in renal function have been reported in predisposed patients.

Allopurinol
Concomitant treatment with thiazide diuretics may increase the frequency of hypersensitivity reactions to allopurinol.

Amantadine
Concomitant use of thiazide diuretics may increase the risk of adverse effects caused by amantadine.

Antineoplastic agents (e.g. cyclophosphamide, methotrexate)
Concomitant use of thiazide diuretics with antineoplastic agents may reduce renal excretion of the cytotoxic agents and potentiate their myelosuppressive effects.

Anticholinergic agents (e.g. atropine, biperiden)
The bioavailability of thiazide-like diuretics may be increased by anticholinergic agents, apparently owing to reduced gastrointestinal motility and slower gastric emptying.

Colestyramine
The absorption of thiazide diuretics is decreased by colestyramine, which means that their pharmacological effect is likely to be reduced during co- medication.

Vitamin D
The increase in serum calcium is potentiated when thiazide diuretics, which may lower urinary calcium excretion, are administered together with vitamin D.

Ciclosporin
Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-like complications.

Calcium salts
Concomitant treatment with calcium salts may lead to hypercalcaemia due to the increase in tubular calcium reabsorption.

Diazoxide
Thiazide diuretics can potentiate the hyperglycaemic effect of diazoxide.

Methyldopa
There have been reports in the literature of haemolytic anaemia occurring during concomitant treatment with hydrochlorothiazide and methyldopa.

Pregnancy and Lactation

Hydrochlorothiazide crosses the placental barrier. Although no reprotoxic effects have been observed in animal studies, it is suspected that in humans, use during the second half of pregnancy may cause thrombocytopenia in neonates. Esidrex should therefore not be used during pregnancy unless clearly necessary.
In addition, Esidrex – like other diuretics – may reduce placental perfus ion. Since these drugs do not prevent or influence the course of pre-eclampsia or EPH (oedema-proteinuriahypertension) gestosis, they should not be used to treat hypertension in pregnant women.
Since hydrochlorothiazide passes into the breast milk and can suppress lactation, it should not be taken by breast-feeding women.

Effects on ability to drive and use machines

Esidrex may impair the reactions, particularly at the start of treatment. Patients who drive vehicles or use machines should therefore be made aware of this effect.

Adverse effects

Frequency
"Very common" (>1/10), "common" (>1/100 to <1/10), "uncommon" (>1/1000 to <1/100), "rare" (>1/10 000 to <1/1000), "very rare" (<1/10 000).

Blood
Rare: Thrombocytopenia, sometimes with purpura.
Very rare: Leucopenia, agranulocytosis, bone-marrow depression, haemolytic anaemia.

Immune system
Very rare: Hypersensitivity reactions.

Electrolyte and metabolic disturbances
Common: Hypokalaemia, especially with higher doses; increase in blood lipid levels.
Uncommon: Hyponatraemia, hypomagnesaemia and hyperuricaemia.
Rare: Hypercalcaemia, hyperglycaemia, glycosuria, deterioration of diabetic metabolic status.
Very rare: Hypochloraemic alkalosis.

Nervous system
Rare: Headache, dizziness or light-headedness, sleep disturbances, depression and paraesthesias.

Eye disorders
Disturbances of vision, particularly during the first few weeks of treatment.

Cardiovascular system
Uncommon: Orthostatic hypotension, which may be aggravated by alcohol, anaesthetics or sedatives.
Rare: Cardiac arrhythmias.

Respiratory tract
Very rare: Respiratory symptoms including pneumonitis and pulmonary oedema.

Gastrointestinal tract
Uncommon: Appetite loss, mild nausea and vomiting.
Rare: Abdominal symptoms, constipation, diarrhoea and gastrointestinal symptoms.
Very rare: Pancreatitis.

Liver
Rare: Intrahepatic cholestasis or jaundice.

Skin
Uncommon: Urticaria and other types of rash, including erythema, sometimes associated with pruritus.
Rare: Photosensitivity.
Very rare: Necrotizing vasculitis, toxic epidermal necrolysis, lupus-erythematosus-like reactions, reactivation of cutaneous lupus erythematosus.

Reproductive system
Uncommon: Impotence.

Overdose

Signs and symptoms
The following signs and symptoms may occur following overdosage: dizziness, nausea, somnolence, hypovolaemia, hypotension, and electrolyte disturbances associated with cardiac arrhythmias and muscle spasm.

Management
Induce vomiting or perform gastric lavage, and give activated charcoal. Intravenous fluids and electrolyte replacement may be indicated.

Properties and Actions

ATC code: C03AA03

Mechanism of action
Hydrochlorothiazide, the active substance of Esidrex, is a benzothiadiazine (thiazide) diuretic. Thiazide diuretics act mainly on the distal renal tubule (early convoluted part), inhibiting NaCl reabsorption (by antagonising the Na^+-Cl^- cotransporter), and promoting Ca^{++} reabsorption (by an unknown mechanism). The enhanced delivery of Na^+ and water to the cortical collecting tubule and/or the higher flow rate lead to increased secretion and excretion of K^+ and H^+.

In patients with normal renal function, diuresis is induced by administering as little as 12.5 mg Esidrex. The resulting increase in urinary excretion of sodium and chloride and the less marked increase in kaliuresis are dose-dependent. The diuretic and natriuretic effect sets in 1–2 hours after oral administration, reaches a peak after 4–6 hours, and can last for 10–12 hours.
Thiazide- induced diuresis initially results in decreased plasma volume, cardiac output and systemic blood pressure. The renin-angiotensin-aldosterone system may be activated. The maintenance of the antihypertensive effect during continued administration is probably due to a fall in peripheral vascular resistance. Cardiac output returns to the pretreatment level, plasma volume remains slightly reduced, and plasma renin activity may be increased.

During prolonged administration the antihypertensive effect of Esidrex is dose-dependent in the range from 12.5 mg/day to 50–75 mg/day. In most patients the maximum antihypertensive effect is reached with 50 mg/day.
Daily doses above 50 mg may in rare cases enhance the therapeutic benefit, but they increase the risk of metabolic side effects.
Like other diuretics, when given as monotherapy Esidrex brings blood pressure under control in about 40–50% of patients with mild to moderate hypertension. Elderly and black patients usually respond particularly well to diuretics as primary therapy.
Combined treatment with other antihypertensives promotes the blood-pressure-lowering effect. This makes it possible to achieve a further reduction in blood pressure in many patients who fail to respond adequately to monotherapy.
Because thiazide diuretics, including Esidrex, reduce Ca^{++} excretion, they have been used to prevent the recurrent formation of renal calcium oxalate stones.
During long-term treatment, patients receiving thiazides showed considerably higher bone mineral levels than patients not receiving thiazides. It has also been observed that in elderly patients, long-term treatment with thiazides substantially reduces the risk of hip fracture, a serious clinical complication of osteoporosis.
In nephrogenic diabetes insipidus, hydrochlorothiazide reduces urinary volume and raises the osmolality of the urine.

Pharmacokinetics

Absorption
About 70% of hydrochlorothiazide is absorbed when administered in tablet form. Variations in absorption owing to fasting or food intake are of little clinical significance. Absorption is reduced in patients with congestive heart failure.
After oral administration of single doses of 12.5 mg, 25 mg, 50 mg, and 75 mg, mean peak plasma concentrations of 70, 142, 260, and 376 ng/ml, respectively, are reached after an average of 2 hours. The systemic availability of hydrochlorothiazide is dose-proportional within the therapeutic dose range.
The pharmacokinetics of hydrochlorothiazide do not change during long-term administration. After 3 months of treatment with 50 mg hydrochlorothiazide daily no differences in absorption, elimination or excretion were observed compared with short-term treatment.
During repeated administration of hydrochlorothiazide, e.g. 75 mg daily for 6 weeks, mean plasma steady-state concentrations of 111 ng/ml were observed.

Distribution
Hydrochlorothiazide accumulates in the erythrocytes, peak concentrations being attained 4 hours after oral administration. After 10 hours, concentrations in the erythrocytes are about three times higher than plasma concentrations. About 40–70% of hydrochlorothiazide binds to plasma proteins. The apparent volume of distribution is estimated at 5–6 litres/kg.
Hydrochlorothiazide crosses the placenta and reaches concentrations in the umbilical vein approaching those in the maternal blood. The substance accumulates in the amniotic fluid, reaching concentrations up to 19 times higher than in umbilical vein plasma.
Hydrochlorothiazide passes into the breast milk. With a daily intake of about 600 ml breast milk, the infant ingests no more than 0.05 mg of the substance.

Elimination
During the terminal elimination phase, hydrochlorothiazide is eliminated from the plasma with a mean half- life of 9.5 to 13 hours. 60–80% of a single oral dose is excreted in the urine within 72 hours, 95% in unchanged form and about 4% as the hydrolysate 2-amino-4-chlorom- benzenedisulfonamide (ACBS). Up to 24% of an oral dose is found in the faeces, and a negligible amount is eliminated via the bile.

Pharmacokinetics in special patient populations
Steady-state concentrations of hydrochlorothiazide are higher, and systemic clearance is significantly slower, in elderly patients compared with young patients. Careful medical surveillance is therefore called for when treating elderly patients with Esidrex.
In patients with impaired renal function, mean peak plasma concentrations and AUC values of hydrochlorothiazide are increased and urinary excretion is reduced. In patients with kidney failure (creatinine clearance of 30–70 ml/minute) the mean elimination half- life is almost doubled, and renal clearance of hydrochlorothiazide is significantly reduced compared with renal clearance in patients with normal kidney function (about 300 ml/minute). It is therefore recommended that the dosage be halved in patients with kidney failure (creatinine clearance of 30–70 ml/minute).
Liver disease does not significantly alter the pharmacokinetics of hydrochlorothiazide, and usually no dosage reduction is necessary.

Preclinical data

Hydrochlorothiazide
Acute toxicity tests in animals indicated no particular sensitivity, and long-term studies yielded no unusual findings apart from changes in the electrolyte balance.
Hydrochlorothiazide did not display any mutagenic or tumorigenic potential.

Other information

Special precautions for storage:
See folding box.

Pack sizes

Country Specific pack sizes

Manufacturer
See folding Box

Information last revised

October 2004

Approval date (text)

5 January 2005

® = registered trademark

Novartis Pharma AG, Basle, Switzerland

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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