ZAROXOLYN
5mg tablets
ZAROXOLYN
10 mg tablets
Metolazone

PHARMACOTHERAPEUTIC CATEGORY
Diuretic with minor diuretic action, non-associated.

THERAPEUTIC INDICATIONS
Zaroxolyn is indicated in the treatment of hypertension by itself or, in more severe forms, associated with other antihypertensive drugs. Zaroxolyn is also indicated as a diuretic, in all cases of fluid and salt retention.

CONTRAINDICATIONS
Hypersensitivity to the active substance or any one of the excipients. Liver or severe renal failure. Refractory hypokalaemia, symptomatic hyperuricaemia, Addison’s disease.

PRECAUTIONS FOR USE
Electrolytic imbalance
The product should be administered with care in cases of hypokalaemia, hyponatraemia, hypercalcaemia and hyperchloraemic alkalosis. Measurements of serum electrolytes (sodium, potassium, chlorine, calcium) must be made at regular intervals to detect possible imbalances. These checks are particularly important if the patient vomits excessively or is being treated with fluids by parenteral route. Blood nitrogen, uric acid and sugar should also be periodically checked during diuretic therapy. All patients being treated with Zaroxolyn should be kept under observation in order to detect clinical signs of fluid-salt imbalance (hypokalaemia, hyponatraemia, hypochloraemic alkalosis). Some treatments, such as digitalis for example, can also be influenced by the effects of the diuretic on serum electrolytes. The first signs of hydroelectrolytic imbalance, regardless of the cause, are as follows: dryness of the mouth, thirst, weakness, lethargy, drowsiness, irritability, muscular pains or cramps, muscular exhaustion, hypotension, oliguria, tachycardia and gastrointestinal disorders (nausea, vomiting, etc). In the case of hypokalaemia a potassium supplement or administration of a potassium sparing drug is indicated. Hypokalaemia can also occur more often when diuretic therapy has been intense and extended, with concomitant steroid or ACTH therapy with inadequate intake of salts. Patients with hyperuricaemia and hyperglycaemia
Care should be taken with these patients. In subjects with latent diabetes hyperglycaemia and glycosuria can occur. In diabetic patients Zaroxolyn can interfere with the antidiabetic therapy. Liver or renal failure
In liver failure, diuretic-driven hypokalaemia can lead to encephalopathy. Caution should be taken in administering Zaroxolyn to patients with reduced renal function. As the majority of the drug is excreted via the kidneys, the plasma levels of this drug can increase with poor renal function.
**Other situations**
Chlorides deficit and hyperchloremic alkalosis can occur. A hyposaline syndrome can occur in patients with conspicuous oedemas associated with heart or renal failure; a warm climate and a low salt diet can contribute to this. Marked diuresis can cause acute hypotension.

**INTERACTIONS**
Associating Zaroxolyn with the following drugs requires particular precautions or an adjustment of the dosage:
- Diuretics: increased risk of hypokalaemia; administration of metolazone with furosemide causes prolific diuresis which should be carefully monitored.
- Other antihypertensives: increased hypotensive effect; suitable monitoring of blood pressure is required, especially in the initial phase, in order to modify doses quickly, if necessary.
- Barbiturates and opioid analgesics: increased hypotensive effect.
- Cyclosporin: increased serum creatinine, if associated with metolazone.
- Captopril: deterioration of renal function, which improves by suspending metolazone.
- Digitalis: increased toxicity with risk of severe arrhythmias, in particular in the case of hypokalaemia.
- Corticosteroids and ACTH: increased risk of hypokalaemia and fluid/salt retention.
- Lithium: elimination of lithium is reduced as plasma concentrations and toxicity risk increase.
- Neuromuscular blockers: increased effect of the neuromuscular block with respiratory depression up to apnoea; therefore it is necessary to suspend Zaroxolyn at least 3 days before surgery.
- Non-steroidal anti-inflammatory drugs (NSAIDS): increased risk of nephrotoxicity of the NSAIDS. NSAIDS can attenuate the antihypertensive effect of Zaroxolyn.
- Sympathomimetics: metolazone can reduce the response to norepinephrine, without however impeding its efficacy as a vasopressor.
- Antidiabetics: reduction of the hypoglycaemic effect. The need to increase the dose of hypoglycaemics should be considered.
- Anticoagulants: increased bleeding time has been observed with warfarin. Zaroxolyn, as with other thiazide diuretics, can also change the hypoprothrombinaemic response, it would therefore be necessary to adjust its dose.
Alcohol can increase the hypotensive effect of metolazone.
Inform your doctor or pharmacist if you are taking or have recently taken any other medicinal product, including those without medical prescription.

**SPECIAL WARNINGS**
As for other diuretics, the highest doses can cause a marked change in the plasma potassium, uric acid, glucose and lipids. Hypokalaemia can occur, with the associated symptoms of asthenia, cramps and cardiac arrhythmias.
Hypokalaemia is particularly dangerous in patients being treated with digitalis, as it can cause dangerous or lethal arrhythmias.
Hyperazotaemia and hyperuricaemia can be induced or aggravated by administering Zaroxyln (rare cases of gout attacks have been reported in patients with a history of gout). Zaroxyln must be suspended, if hyperazotaemia and oliguria deteriorate during treatment of patients with renal failure. When Zaroxyln and furosemide are administered simultaneously there can be significant and protracted results on urinary hydroelectrolytic excretion; it is therefore recommended that co-administration of these diuretics for treatment of resistant oedemas is initiated in a hospital environment, so that adequate monitoring can be provided. If Zaroxyln is used together with other antihypertensive drugs, it is necessary to pay particular attention especially during the early phases of therapy. The dosage regimen of other antihypertensive agents must be reduced appropriately. Zaroxyln can be administered, when indicated, together with a potassium sparing diuretic. In this case the diuresis could be enhanced and the dosage should be reduced. There is a potential for potassium retention and hyper-kalaemia: serum potassium must be measured frequently.

A supplemented intake of potassium is contraindicated when a potassium-sparing diuretic is administered.

For people taking part in sports: the use of the drug without therapeutic need forms doping and can therefore cause a positive dope test.

PREGNANCY AND LACTATION
Metolazone crosses the placental barrier and its use is therefore not recommended during pregnancy; there have been reports of neonatal jaundice and thrombocytopenia in newborns from mothers who have taken the drug. Metolazone passes into breast milk, therefore breastfeeding must be suspended. Ask your doctor or pharmacist for advice before taking any medicinal product.

EFFECTS ON CAPACITY TO DRIVE VEHICLES AND USE MACHINES
There are no known effects of metolazone on the capacity to drive and use machines.

DOSE, METHOD AND TIME OF USE
Hypertension: The initial recommended dose is 2.5 mg (the equivalent of half a tablet) or 5 mg a day, in the morning.
Heart failure-related oedema: 5-10 mg once a day, in the morning.
Renal failure-related oedema: 5-20 mg once a day, in the morning. After having obtained the desired therapeutic effect, it is usually appropriate to reduce the dose of Zaroxyln to lower, maintenance levels (2.5 or 5 mg on alternate days). The length of the initial treatment with the highest, loading dosage can vary from a few days for oedema, to 3-4 weeks when treating hypertension. The elderly: lower initial doses must be used given that they are more susceptible to the undesirable effects. Patients with renal failure: the dosage regimen must be altered based on renal function. Paediatric age: the product is not recommended.

OVERDOSE
With overdose there is a risk of dehydration and electrolytic depletion. Treatment of overdose must target fluid reintegration and correction of the electrolytic imbalance.
In the case of accidentally taking an excessive dose of the medicine, immediately inform your doctor or attend the closest hospital.

**UNDESIRABLE EFFECTS**
As with other medicinal products, this can also cause undesirable effects even if not all people experience them.

During treatment with Zaroxylyn headaches, anorexia, vomiting, abdominal disorders, muscle cramps and vertigo have been reported occasionally. Hyperuricaemia hyperazotaemia have been reported especially in patients with altered renal function.

The undesirable effects reported with metolazone and listed below, based on system organ class, are considered rare (<0.1%) or very rare (<0.01%):
- Blood and lymphatic system disorders: leucopenia, aplastic anaemia, thrombocytopenia.
- Metabolism and nutrition disorders: gout.
- Nervous system disorders: dizziness, drowsiness, headache, paraesthesia, irritability, insomnia, syncope.
- Ocular disorders: blurred vision.
- Heart disorders: palpitations, chest pain.
- Vascular disorders: orthostatic hypotension, hypovolaemia, venous thrombosis, haemoconcentration.
- Gastrointestinal system disorders: constipation, dryness of the mouth, nausea, vomiting, anorexia, diarrhoea, flatulence, epigastric pain, pancreatitis.
- Hepatobiliary system disorders: intrahepatic cholestasis, hepatitis.
- Alterations of the skin and subcutaneous tissue: exanthema, severe skin rash.
- Disorders of the musculoskeletal system and connective tissue: cramps, muscle spasms.
- Diagnostic investigations: hypokalaemia, hyponatraemia, hypochloraemia, hypochloraemic alkalosis, hypophosphataemia, glycosuria, increased azotaemia and creatinine, hyperuricaemia, hyperglycaemia.
- General disorders and changes to the administration site, hypersensitivity reactions: hives, purpura, necrotising angiography. Shivers, asthenia.

When moderate or severe side-effects arise the dose of Zaroxylyn must be reduced or the treatment discontinued.

*Following the instructions in the information leaflet reduces the risk of undesirable effects.*

*If any one of the undesirable effects deteriorates, or if an undesirable effects not listed on this information leaflet appears, inform your doctor or pharmacist.*

**EXPIRY DATE AND STORAGE**

**Expiry date:** see the expiry date indicated on the pack.

**Storage:** Store away from light.

Do not use the medicinal product after the expiry date indicated on the pack. The expiry date refers to the product, correctly stored, in complete packaging. Keep the medicinal product out of the site and reach of children. Medicinal products must not be discarded in domestic waste or waste water. Ask your pharmacist how to dispose of medicinal products you no longer use. This will help to protect the environment.
COMPOSITION
One 5 mg tablet contains:
Active substance: metolazone 5mg
Excipients: Microcrystalline cellulose, magnesium stearate
One 10 mg tablet contains:
Active substance: metolazone 10 mg
Excipients: Microcrystalline cellulose, magnesium stearate, E127 (under the form of aluminium lake 15%).

PHARMACEUTICAL FORM AND CONTENT
50 tablets of 5 mg
50 tablets of 10 mg

MARKET AUTHORISATION HOLDER
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