Lodoz® 2.5 mg/6.25 mg, film-coated tablet
Lodoz® 5 mg/6.25 mg, film-coated tablet

Bisoprolol fumarate
Hydrochlorothiazide

QUALITATIVE AND QUANTITATIVE COMPOSITION
Lodoz 2.5 mg/6.25 mg, film-coated tablet:
Bisoprolol fumarate 2.5 mg
Hydrochlorothiazide 6.25 mg

Lodoz 5 mg/6.25 mg, film-coated tablet:
Bisoprolol fumarate 5 mg
Hydrochlorothiazide 6.25 mg

PHARMACEUTICAL FORM
Lodoz 2.5 mg/6.25 mg, film-coated tablet:
Film coated tablet
Yellow, round, biconvex upper side embossed heart, downside embossed 2.5.

Lodoz 5 mg/6.25 mg, film-coated tablet:
Film coated tablet
Pastel-pink, round, biconvex, upper side embossed heart, downside embossed 5.

ROUTE OF ADMINISTRATION
Oral

CLINICAL PARTICULARS
Therapeutic indications
Mild to moderate hypertension.

Posology and method of administration
For individual therapy Lodoz is available in the strengths:
Lodoz 2.5/6.25 mg, film-coated tablets
Lodoz 5/6.25 mg, film-coated tablets

The initial dosage is one tablet containing bisoprolol 2.5 mg + hydrochlorothiazide 6.25 mg once daily.

If inadequate response to treatment is obtained, the dosage should be increased to one tablet containing bisoprolol 5 mg + hydrochlorothiazide 6.25 mg in a once daily dose. If latter proves to be insufficiently effective, the dosage may be increased to bisoprolol 10 mg + hydrochlorothiazide 6.25 mg once daily.

If discontinuation is necessary, gradual discontinuation of bisoprolol treatment is recommended, since abrupt withdrawal of bisoprolol may lead to an acute deterioration of the patient's condition, in particular in patients with ischaemic heart disease.

Lodoz should be swallowed in the morning and can be taken with food. The film-coated tablets should be swallowed with some liquid and not be chewed.

No dose adjustment is necessary in patients with mild-to-moderate hepatic impairment or mild-to moderate renal impairment (creatinine clearance > 30 mL/min).

Elderly: No dose adjustment is normally required

Paediatric population
Experience with Lodoz in paediatric patients is limited, therefore its use cannot be recommended in this population.

Contraindications
Lodoz is contraindicated in patients with hypersensitivity to bisoprolol, hydrochlorothiazide, other thiazides, sulphonamides, or any of the excipients.

Bisoprolol
Bisoprolol is contraindicated in any of the following conditions:

- Severe asthma
- Heart failure not controlled by therapy
- Cardiogenic shock;
- Sick-sinus syndrome (including SA block)
- Second or third degree AV block (without pacemaker);
- Symptomatic bradycardia;
- Pheochromocytoma (except after prior alpha-receptor blocker therapy);
- Severe forms of Raynaud's syndrome and severe peripheral arterial occlusive disease;
- Metabolic acidosis;
- In combination with sultopride

Hydrochlorothiazide
Hydrochlorothiazide is contraindicated in any of the following conditions:

- Severe renal impairment (creatinine clearance ≤ 30 mL/min).
- Severe hepatic impairment
- Refractory hypokalaemia

Special warnings and precautions for use

Warnings

Bisoprolol

Never stop bisoprolol abruptly in patients with coronary artery disease (angina pectoris). Abrupt cessation of therapy may cause serious cardiac arrhythmias, myocardial infarction, or sudden death.

Hydrochlorothiazide

Lodoz must be used with caution in patients with impaired liver function.

In patients with liver disease, thiazide diuretics and related drugs may trigger hepatic encephalopathy. Should this happen, diuretic therapy must be stopped immediately. This medication should not be taken in lactating women.

Precautions for Use

Bisoprolol

Asthma and Chronic Obstructive Pulmonary Disease

Although cardioselective (beta1) beta-blockers may have less effect on lung function than non-selective beta-blockers, as with all beta-blockers, these should be avoided in patients with obstructive airways diseases, unless there are compelling clinical reasons for their use. Where such reasons exist, Lodoz may be used with caution. In patients with obstructive airways diseases, the treatment with bisoprolol should be started at the lowest possible dose and patients should be carefully monitored for new symptoms (e.g. dyspnea, exercise intolerance, cough). In bronchial asthma or other chronic obstructive lung diseases, which may cause symptoms, bronchodilating therapy should be given concomitantly. Occasionally an increase of the airway resistance may occur in patients with asthma, therefore the treatment of $beta_2$-stimulants may have to be adapted.

Cardiac Failure

Patients with compensated cardiac failure who require beta-blocker therapy may be administered bisoprolol using a very low starting dose, to be increased gradually with close medical monitoring.

First Degree AV Block

Having negative dromotropic activity, beta-blockers should be used cautiously in patients with first degree AV block.

Prinzmetal's Angina

Beta-blockers may increase the frequency and length of vasospastic episodes in patients with Prinzmetal's angina. Cases of coronary vasospasm have been observed. Despite its high beta1-selectivity, angina attacks cannot be completely excluded when bisoprolol is administered to patients

with Prinzmetal's angina. A β1-selective beta-blocker may be used in minor or mixed clinical presentations of Prinzmetal‘s angina if a vasodilator is used concurrently.

Peripheral Arterial Occlusive Disease
Beta-blockers may aggravate the symptoms of peripheral arterial occlusive disease (PAOD) or Raynaud‘s syndrome. Such patients should preferably be prescribed a β1-selective beta-blocker.

Pheochromocytoma
In patients with pheochromocytoma Lodoz must not be administered until after alpha-receptor blockade. Blood pressure response should be closely monitored.

Elderly
No dose adjustment is normally required. However, elderly patients should be closely monitored (see paragraph: Fluid and electrolyte balance)

Diabetics
Diabetic patients should be aware of the risk of hypoglycemic episodes and of the increased need for careful home glucose monitoring in the initial phase of therapy. The warning signs of hypoglycemia, particularly tachycardia, palpitations, and sweating, may be masked.

Psoriasis
There have been reports of beta-blockers being associated with worsening of psoriasis, thus patients with psoriasis should receive bisoprolol only if clearly needed.

Hypersensitivity Reactions
In patients at risk of severe anaphylactic reaction to whatever allergen, particularly when using iodine-containing contrast materials or during specific immunotherapy (desensitisation), beta-blockers may aggravate the anaphylactic reaction and cause unresponsiveness to the usual doses of epinephrine used to treat hypersensitivity reactions.

General Anesthesia
In patients undergoing general anaesthesia beta-blockade reduces the incidence of arrhythmias and myocardial ischaemia during induction and intubation, and the post-operative period. It is currently recommended that maintenance beta-blockade be continued peri-operatively. The anaesthetist must be aware of beta-blockade because of the potential for interactions with other drugs, resulting in bradyarrhythmias, attenuation of the reflex tachycardia and the decreased reflex ability to compensate for blood loss. If it is thought necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.

Thyrotoxicosis
Beta-blockers may mask the cardiovascular signs of hyperthyroidism.

Competitive athletes
Competitive athletes should be aware that this medicinal product contains an agent that may give a positive reaction in doping tests.

Strict fasting
Lodoz must be used with caution in patients under strict fasting

Combination with verapamil, diltiazem or bepridil
Such combinations require a close clinical and ECG monitoring, notably in the elderly and at the beginning of the treatment.

Hydrochlorothiazide
Non-melanoma skin cancer
An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC. (see also Section Undesirable effects).

Fluid & Electrolyte Balance
During long term-therapy with Lodoz, periodic monitoring of serum electrolytes (especially potassium, sodium, calcium), creatinine and urea, the serum lipids (cholesterol and triglycerides), uric acid as well as blood glucose is recommended.

Long-term, continuous administration of hydrochlorothiazide may lead to fluid and electrolyte disturbances, in particular to hypokalaemia and hyponatraemia, also to hypomagnesaemia and hypochloraemia, and hypercalcaemia.

Plasma Sodium
Plasma sodium should be determined before and periodically during therapy. Any diuretic therapy may give rise to hyponatremia, with serious consequences in some cases.
As hyponatremia may initially be asymptomatic, periodic monitoring is indispensable and should be more frequent in high-risk populations, i.e., the elderly and patients with cirrhosis of the liver.

Plasma Potassium

Potassium loss resulting in hypokalemia is the greatest risk associated with thiazide diuretics and related drugs.

The risk of hypokalemia (< 3.5 mmol/L) should be anticipated in certain high-risk populations, i.e., elderly and/or malnourished and/or taking multiple drugs, and patients with coronary artery disease or heart failure, where hypokalemia increases the cardiotoxicity of digitalis glycosides and the risk of cardiac arrhythmia. Also at risk are patients with long QT syndrome, either congenital or iatrogenic. Hypokalemia (as well as bradycardia) facilitates the development of severe arrhythmias, particularly torsade de pointes, which maybe fatal.

More frequent plasma potassium monitoring is indicated in all of the above populations, starting within the week after initiation of therapy.

Plasma Calcium

Thiazide diuretics and related drugs may reduce urinary calcium excretion, resulting in mild, transient hypercalcemia. Significant hypercalcemia may be related to undiagnosed hyperparathyroidism. Therapy must be interrupted before performing parathyroid function tests.

Combination with lithium

Due to the diuretic, this combination should be avoided.

Blood Glucose

In diabetics, blood glucose must be monitored, especially in the presence of hypokalemia.

Uric Acid

In patients with hyperuricemia, the risk for attacks of gout may be increased. Dosage should be adjusted as a function of uric acid plasma concentrations.

Kidney Function & Diuretics

Full benefit from thiazide diuretics can be derived only if kidney function is normal or almost normal (serum creatinine < 25 mg/L, or 220 µmol/L, in adults).

Serum creatinine needs to be corrected for age, weight, and gender, using Crockroft's formula for instance:

ClCr = (140 – Age) x Weight/0.814 x Serum Creatinine

Where Age is indicated in years

Weight in kg, and Serum Creatinine in µmol/L.

The above formula gives ClCr for elderly male subjects, and needs to be corrected for elderly female subjects by multiplying by 0.85.

Hypovolemia secondary to diuretic-induced water and sodium loss at the start of therapy reduces glomerular filtration, which may result in blood urea nitrogen and serum creatinine increases. This transient functional renal impairment is not relevant in patients with normal kidney function but may worsen pre-existing renal insufficiency.

Combination with other Antihypertensive Drugs
It is advisable to reduce the dosage when this medicinal product is combined with another antihypertensive, at least in the initial phase of therapy.

Photosensitivity
Photosensitivity reactions have been reported with thiazide diuretics in rare cases. If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of treatment is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA-light.

Competitive athletes
Competitive athletes should be aware that this medicinal product contains an agent that may give a positive reaction in doping tests.

Choroidal effusion, acute myopia and secondary angle-closure glaucoma
Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in effusion with visual field defect, acute 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 hydrochlorothiazide 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.

Acute respiratory toxicity

Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Lodoz should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Interactions with other medicinal products and other forms of interaction
1 - Interactions related to bisoprolol
Contra-indication

- sultopride
  Increased risk of ventricular arrhythmias, notably torsades de pointes.

Not recommended combinations

- verapamil, diltiazem
  Risk of bradycardia, as well as negative effects on heart contractility and auriculo-ventricular conduction. Such a combination requires a close clinical and ECG monitoring, notably in the elderly and at the beginning of the treatment.

- bepridil
  Risk of bradycardia, as well as negative effects on heart contractility and auriculo-ventricular conduction. Additionally, increased risk of ventricular arrhythmias, notably torsades de pointes. Such a combination requires a close clinical and ECG monitoring, notably in the elderly and at the beginning of the treatment.

Combinations requiring a caution for use

- Centrally-acting antihypertensive drugs (e.g. clonidine, methyldopa, moxonidine, rilmenidine):
  Concomitant use of centrally-acting antihypertensive drugs with bisoprolol may further decrease the central sympathetic tonus and may thus lead to an additive reduction in heart rate and cardiac output and to vasodilatation/hypotension.
  Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase the risk of 'rebound hypertension'. Avoid any sudden interruption of the centrally-acting antihypertensive agent.

- propafenone, cibenzoline, flecainide
  Risk of bradycardia, as well as negative effects on heart contractility and auriculo-ventricular conduction. Clinical monitoring and ECG, if appropriate, are required.

- lidocaine
  Increased lidocaine plasma levels increasing the likelihood of neurologic and cardiac side-effects, due to reduced hepatic blood flow by the beta-blocking agent and subsequent reduced clearance of lidocaine. Clinical and biological monitoring and ECG, if appropriate, are required, with dosage adjustment of lidocaine if necessary.

- Antidiabetics (insulin, sulphonylureas, glinides)
  All beta-blockers may mask warning signs of hypoglycemia, notably palpitations and tachycardia. Diabetic patients should be aware of the risk of hypoglycemic episodes and of the increased need for careful home glucose monitoring, especially in the initial phase of therapy.

- Other bradycardia-inducing drugs (anticholinesterases , digitalis glycosides, mefloquine…)
  Increased risk of bradycardia. A regular clinical monitoring should be made.

- Calcium channel blockers of the dihydropyridine type (e.g. nifedipine, amlodipine) Concomitant use may increase the risk of hypotension, and a further risk of deterioration of the ventricular pump function in patients with heart failure cannot be excluded.

- Topical beta-blockers (e.g. eye drops for glaucoma treatment) They may add their effects to the systemic ones of bisoprolol.

2 - Interactions related to hydrochlorothiazide

Not recommended combinations

- lithium
  Increased lithium plasma levels with signs of overdosage, as occur on a low-sodium diet, due to reduced urinary lithium excretion. If this combination cannot be avoided, provide close lithium plasma level monitoring and adjust dosage as necessary.

Combinations requiring a caution for use

- NSAIDs (systemic), acetylsalicylic acid at anti-inflammatory dosage regimen
  Acute renal failure in dehydrated patients (NSAIDs reduce glomerular blood flow by inhibiting vasodilatory prostaglandins). Patients should be rehydrated and the kidney function monitored at the start of the therapy.

- Potassium-sparing diuretics (alone or combined)
  Such a combination, possibly useful, does not preclude hypo- or hyperkaliemia, the latter being more frequent in case of diabetes or renal impairment. Kaliemia should be monitored and, if appropriate, ECG. Treatment may possibly have to be reconsidered.

- Hypokaliemic drugs (IV amphotericin, systemic corticosteroids, tetracosactide, stimulating laxatives): Increased risk of hypokalaemia. Monitor and, if appropriate, correct plasma potassium. This is notably of importance with the concomitant use of digitalis glycosides. Rather use non stimulating laxatives.

- Angiotensin Converting Enzyme Inhibitors (ACEI),
- Angiotensin II receptors antagonists (AIIA):
  Risk of significant blood pressure decrease and/or acute renal failure during initiation of ACEI therapy in patients with pre-existing sodium depletion (particularly in patients with renal artery stenosis). If prior diuretic therapy may have produced sodium depletion, either stop the diuretic 3 days before starting ACEI or AIIA therapy and reintroduce the diuretic later if necessary, or start patient on a reduced ACEI or AIIA dose to be gradually increased thereafter.

- Carbamazepine
  Risk of symptomatic hyponatremia.

Clinical and biological monitoring is required. Another class of diuretics should be eventually used.

- Iodinated contrast media
  In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of the iodine product. Patients should be rehydrated before the administration.

- Resins
  Reduction of the absorption of hydrochlorothiazide.
  A time-interval of at least two hours should separate the resin intake from Lodoz administration

- Uric acid-lowering agents
  Their effect may be attenuated with the concomitant administration of hydrochlorothiazide.

- Calcium salts
  Risk of hypercalcemia due to reduced urinary excretion.

- Cyclosporine
  Risk of increased creatininemia without change of cyclosporine levels, even out of any sodium depletion.

3 - Interactions related to both bisoprolol and hydrochlorothiazide

Combinations requiring a caution for use

- Antiarrhythmic drugs inducing torsades de pointes (agents of the subclass IA: quinidine, hydroquinidine, disopyramide, and of the subclass III: amiodarone, sotalol, dofetilide, ibutilide):
  Increased risk of ventricular arrhythmias, notably torsades de pointes, favoured by bradycardia and/or hypokalemia. Clinical and ECG monitoring are required.

- Non antiarrhythmic drugs inducing torsades de pointes (e.g. astemizole, bepridil, cisapride, diphemanil, IV erythromycin, halofantrine, lumefantrine, methadone, moxifoxacin, pentamidine, sotalol, IV spiramycin, sparfloxacin, terfenadine, vincamine, some antipsychotics like pimozide, haloperidol, benzamides):
  Increased risk of ventricular arrhythmias, notably torsades de pointes, favoured by bradycardia and/or hypokalemia. Clinical and ECG monitoring are required.

- Digitalis glycosides
  Due to hydroclorothiazide, there is a risk of hypokaliemia, which may facilitate the toxic effects of cardiac glycosides. Due to bisoprolol, there is a risk of bradycardia and negative effect on AV conduction. A regular clinical monitoring should be made. Plasma potassium should be monitored and, if appropriate, ECG.

Combinations to be taken into account

- Other antihypertensive agents, tricyclics, phenothiazines, baclofene, amifostine
  Concomitant use with these drugs that lower blood pressure, as main or side-effect, may increase the risk of hypotension.

- NSAIDs
  Reduced antihypertensive efficiency by inhibition of vasodilatory prostaglandins (pyrazole derivatives also induce sodium retention)

- Corticosteroids, tetracosactide
  Reduced antihypertensive efficiency by a sodium retention effect.

Pregnancy and lactation

Pregnancy
Lodoz is not recommended during pregnancy

Bisoprolol
Animal studies did not show any teratogenic effect. To date, results of well-controlled prospective studies with some betablockers did not show any birth defect in newborns. In neonates born from mothers treated with betablockers, betablocking activity persists for several days post-partum and may induce bradycardia, respiratory distress and hypoglycaemia. In most cases, this impregnation is without any clinical consequences. Nevertheless, heart failure may occur, necessitating intensive care unit management, avoiding plasma expanders (risk of acute pulmonary oedema).

Hydrochlorothiazide
Diuretics may give raise to foetoplacental ischemia with the attendant risk of foetal hypotrophy. Rare cases of severe neonate thrombocytopenia have been reported.

Lactation
It is not known if bisoprolol is excreted in human milk. Thiazide diuretics are excreted in human milk in minimal amounts. Thus, this medication should not be given to lactating women.

Bisoprolol
The risk for hypoglycaemia and bradycardia in suckling infant has not been evaluated.

Hydrochlorothiazide
Thiazide diuretics may produce:

- Decrease or even suppression of milk secretion
- Adverse biological effects (hypokalemia)
- Hemolysis (G6PD defect) and hypersensitivity due to sulphonamide properties.

Fertility

No human data on fertility are known for the combination product. Bisoprolol or hydrochlorothiazide had no influence on fertility or on general reproduction performance in animal studies.

Effects on ability to drive and use machines

Depending on the individual patient's response to Lodoz treatment the ability to drive and use machines may be impaired. This should be particularly considered at the start of treatment as well as in conjunction with alcohol.

Undesirable effects

Common (≥ 1% and < 10%), uncommon (≥ 0.1% and < 1%), rare (≥ 0.01% and < 0.1%), very rare (< 0.01%) including isolated cases.

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Not known: Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)

Description of Selected Adverse Reactions

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide and NMSC has been observed. (see also sections Special warnings and precautions for use and Pharmacodynamic properties)

Blood and lymphatic system disorders

Rare: leucopenia, thrombocytopenia

Very rare: agranulocytosis

Metabolism and nutrition disorders

Uncommon: loss of appetite, hyperglycaemia, hyperuricaemia, disturbances of fluid and electrolyte balance (in particular hypokalaemia and hyponatraemia, also hypomagnesaemia and hypochloraemia as well as hypercalcaemia)

Very rare: metabolic alkalosis

Psychiatric disorders

Uncommon: depression, sleep disorder

Rare: nightmare, hallucination

Nervous system disorders

Common: dizziness*, headache*

Eye disorders
Rare: reduced tear flow (to be taken into consideration in patients wearing contact lenses), visual disturbances
Very rare: conjunctivitis
Not known: choroidal effusion, acute myopia, acute angle-closure glaucoma

Ear and labyrinth disorders
Rare: hearing disorders

Cardiac disorders
Uncommon: bradycardia, AV-conduction disturbances, worsening of pre-existing heart failure

Vascular disorders
Common: feeling of coldness or numbness in extremities,
Uncommon: orthostatic hypotension
Rare: syncope

Respiratory, thoracic and mediastinal disorders
Uncommon: bronchospasm in patients with bronchial asthma or history of obstructive airways disease
Rare: allergic rhinitis
Very rare: acute respiratory distress syndrome (ARDS) (See Precautions for Use.)

Gastrointestinal disorders
Common: gastrointestinal complaints such as nausea, vomiting, diarrhoea, constipation
Uncommon: abdominal complaints
Very rare: pancreatitis

Hepatobilary disorders
Rare: hepatitis, jaundice

Skin and subcutaneous tissue disorders
Rare: hypersensitivity reactions such as pruritus, flush, rash and angioedema, photodermatitis, purpura, urticaria.
Very rare: anaphylactic reactions, toxic epidermic necrolysis (Lyell syndrome), alopecia, cutaneous lupus erythematosus. Beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash.

Musculoskeletal and connective tissue disorders
Uncommon: muscle weakness, muscle cramps

Reproductive system and breast disorders
Rare: erectile dysfunction

General disorders
Common: fatigue*
Uncommon: asthenia
Very rare: chest pain

Investigations:
Uncommon: increase in amylase, reversible increase of serum creatinine and urea, increased triglyceride and cholesterol levels, glucosuria,
Rare: increase in liver enzymes (ASAT, ALAT)

*These symptoms occur in particular at the start of treatment. They are generally mild and mostly disappear within 1-2 weeks.

Overdose
The most common signs expected with overdose of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. There is a wide inter-individual variation in sensitivity to one single high dose of bisoprolol and patients with heart failure are probably very sensitive.

The clinical picture in acute or chronic overdose of hydrochlorothiazide is characterised by the extent of fluid and electrolyte loss.

Most common signs are dizziness, nausea, somnolence, hypovolaemia, hypotension, hypokalaemia.

In general, if overdose occurs, discontinuation of Lodoz and supportive and symptomatic treatment is recommended.

Bradycardia: Administer intravenous atropine. If the response is inadequate, isoprenaline or another agent with positive chronotropic properties may be given cautiously. Under some circumstances, transvenous pacemaker insertion may be necessary.

Hypotension: intravenous fluids and vasopressors should be administered.

AV block (second or third degree): Patients should be carefully monitored and treated with isoprenaline infusion or intravenous cardiac pacemaker insertion.
Acute worsening of heart failure: Administer I.V. diuretics, inotropic agents, vasodilating agents.
Bronchospasm: Administer bronchodilator therapy such as isoprenaline, beta-2-sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: administer I.V. glucose.

Limited data suggest that bisoprolol is hardly dialyzable. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Combination of an adrenoceptor blocking agent (β1-selective) and a thiazide diuretic.

ATC code: C07BB07

Clinical studies have shown that the antihypertensive effects of these two drugs are additive, and the efficacy of the lowest dose, 2.5 mg/6.25 mg, in the treatment of mild-to-moderate essential hypertension has been demonstrated.

The pharmacodynamic effects, including hypokalemia (hydrochlorothiazide), and bradycardia, asthenia, and headache (bisoprolol) are dose-related.

Combining both drugs at one-fourth/half the doses used in single-agent therapy (2.5 mg/6.25 mg) aims to reduce those effects.
Bisoprolol is a highly β1-selective adrenoceptor blocking agent with no intrinsic sympathomimetic activity and without significant membrane-stabilizing activity.

As with other β1-receptor blocking drugs, the mechanism of bisoprolol's antihypertensive effect has not been completely established. However, it has been shown that the drug produces a marked decrease in plasma renin and a reduction in heart rate.

Hydrochlorothiazide is a thiazide diuretic with antihypertensive activity. Its diuretic effect is due to inhibition of active Na+ transport from the renal tubules to the blood, affecting Na+ reabsorption.

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High hydrochlorothiazide use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to hydrochlorothiazide: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg). (see also section Special warnings and precautions for use)

Pharmacokinetic properties

Bisoprolol

- Absorption: T_{max} varies from 1-4 hours.
- Bioavailability is high (88%); hepatic first-pass extraction is very low; and absorption is not affected by the presence of food. Kinetics are linear for doses from 5-40 mg
- Distribution: Plasma protein binding is 30%, and the volume of distribution is high (approximately 3 L/kg)
- Biotransformation: 40% of a bisoprolol dose is metabolized in the liver. Bisoprolol metabolites are inactive.
- Elimination: The plasma elimination half-life is 11 hours. Renal clearance and hepatic clearance are approximately comparable, and half of a dose (unchanged) as well as the metabolites are excreted in urine. The total clearance is approximately 15 L/h.

Hydrochlorothiazide

- Absorption: The bioavailability of hydrochlorothiazide shows between-subject variability and ranges from 60-80%. T_{max} varies from 1.5-5 hours (mean ≈4 hrs).
- Distribution: Plasma protein binding is 40%.
- Elimination: Hydrochlorothiazide is not metabolized and is excreted almost entirely as unchanged drug by glomerular filtration and active tubular secretion. The terminal t1/2 of hydrochlorothiazide is approximately 8 hours.
- The renal clearance of hydrochlorothiazide is reduced and the elimination half-life prolonged in patients with renal and/or cardiac insufficiency. The same applies to elderly subjects, who also show an increase in C_{max}.
- Hydrochlorothiazide crosses the placental barrier and is excreted in human milk.

Preclinical safety data

Bisoprolol or hydrochlorothiazides have not been found to be hazardous to humans according to the standard preclinical toxicity tests (long-term toxicity, mutagenicity, genotoxicity and carcinogenicity tests). Like other beta-blockers, bisoprolol at high doses has been found in animal experiments to cause toxic effects to the mother (decreased food intake and body weight gain) and to the embryo/foetus (increased late resorptions, reduced birth weight of the offspring, retardation of the physical development up to the end of lactation). However, bisoprolol as well as hydrochlorothiazide were not teratogenic. There was no increase in toxicity when both components were given in combination.

PHARMACEUTICAL PARTICULARS

List of excipients

Lodoz 2.5 mg/6.25 mg, film-coated tablet.

Tablet core

Magnesium Stearate, Crospovidone, Maize Starch, Pregelatinized maize starch, Microcrystalline Cellulose, Calcium-hydrogen phosphate, anhydrous

Lodoz 5 mg/6.25 mg, film-coated tablet.
Tablet core
Silica, colloidal anhydrous, Magnesium Stearate, Microcrystalline Cellulose, Maize Starch, Calcium hydrogen phosphate, anhydrous

Shelf-life
Lodoz 2.5 mg/6.25 mg, film-coated tablet:
2 years
Lodoz 5 mg/6.25 mg, film-coated tablet:
4 years

Special precautions for storage
Do not store above 30°C

Nature and contents of container
Aluminium / aluminium blister.

Packs containing 30, 50, 60, 90 or 100 tablets.

Not all strengths and pack sizes are marketed.

NAME AND ADDRESS OF MANUFACTURER
Merck Healthcare KGaA,
Frankfurter Strasse 250,
64293 Darmstadt,
Germany

PRODUCT REGISTRATION HOLDER
Merck Sdn Bhd
B-23A-1, Level 23A, The Ascent Paradigm
No.1, Jalan SS7/26A, Kelana Jaya,
47301 Petaling Jaya, Selangor,
Malaysia

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