# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Lodoz 2.5 mg/6.25 mg, film-coated tablet
Lodoz 5 mg/6.25 mg, film-coated tablet
Lodoz 10 mg/6.25 mg, film-coated tablet.

## 2. 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

Lodoz 10 mg/6.25 mg, film-coated tablet:
Bisoprolol fumarate 10 mg
Hydrochlorothiazide 6.25 mg

For the full list of excipients, see section 6.1.

## 3. 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.

Lodoz 10 mg/6.25 mg, film-coated tablet:
Film-coated tablet
White, round, biconvex, upper side embossed heart, downside embossed 10.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Mild to moderate essential hypertension.

### 4.2 Posology and method of administration

Posology

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
Lodoz 10/6.25 mg, film-coated tablets

The usual starting dose is one bisoprolol 2.5 mg / hydrochlorothiazide 6.25 mg tablet once daily.

If the antihypertensive effect of this dosage is inadequate, the dose will be increased to one bisoprolol 5 mg / hydrochlorothiazide 6.25 mg tablet once daily and, if response is still inadequate, to one bisoprolol 10 mg / hydrochlorothiazide 6.25 mg tablet 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.

*Patients with renal or hepatic impairment*

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 (see section 4.4).

*Paediatric population*

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

Method of administration

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.

## 4.3 Contraindications

Lodoz is contraindicated in patients with

- hypersensitivity to bisoprolol, hydrochlorothiazide, other thiazides, sulphonamides, or to any of the excipients listed in section 6.1
- acute heart failure or during episodes of heart failure decompensation requiring intravenous inotropic therapy
- cardiogenic shock
- second or third degree AV block
- sick sinus syndrome
- sinoatrial block
- symptomatic bradycardia
- severe bronchial asthma
- severe forms of peripheral arterial occlusive disease or severe forms of Raynaud's syndrome
- untreated phaeochromocytoma
- severe renal impairment (creatinine clearance ≤ 30 ml/min)
- severe hepatic impairment
- metabolic acidosis
- refractory hypokalaemia

## 4.4 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 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 (see section 4.6).

***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 $\beta_1$-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 $\beta_1$-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 (see 4.5) 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 (see section 4.5).

*Hydrochlorothiazide*

*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 may be 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 (see section 4.5).

*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 yrs
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 bu 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 non relevant in patients with normal kidney function but may worsen preexisting 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 (see section 4.8). 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.

*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 exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of hydrochlorothiazide could act as a possible mechanism for NMSC. Patients taking hydrochlorothiazide 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 hydrochlorothiazide may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

*Competitive athletes*

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

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in 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.

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

***Combinations not recommended***

Lithium: Lodoz may intensify the cardiotoxic and neurotoxic effect of lithium through a reduction of lithium excretion.

Calcium antagonists of the verapamil type and the diltiazem type: Negative effect on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients on ß-blocker treatment may lead to profound hypotension and atrioventricular block.

Centrally-acting antihypertensive agents: Concomitant use of centrally-acting antihypertensive agents may lead to a further reduction in heart rate and cardiac output and to vasodilatation. Abrupt withdrawal, may increase the risk of 'rebound hypertension'.

***Combinations to be used with caution***

Calcium antagonists of the dihydropyridine type: Concomitant use may increase the risk of hypotension, and an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.

Concomitant use with other antihypertensive agents or with other medicinal products with blood pressure lowering potential may increase the risk of hypotension.

ACE inhibitors, Angiotensin II antagonists: Risk of significant fall in blood pressure and/or acute renal failure during initiation of ACE inhibitor therapy in patients with preexisting sodium depletion (particularly in patients with renal artery stenosis).

If prior diuretic therapy has produced sodium depletion, either stop the diuretic 3 days before starting ACE inhibitor therapy, or initiate ACE inhibitor therapy at a low dose.

Class-I antiarrhythmic agents: Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

Class-III antiarrhythmic agents: Effect on atrio-ventricular conduction time may be potentiated.

Antiarrhythmic agents that may induce torsade de pointes: Hypokalaemia may facilitate the occurrence of torsades de pointes.

Nonantiarrhythmic agents that may induce torsade de pointes: Hypokalaemia may facilitate the occurrence of torsades de pointes.

Parasympathomimetic agents: Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.

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

Insulin and oral antidiabetic agents: Increase of blood sugar lowering effect. Blockade of beta-adrenoceptors may mask symptoms of hypoglycaemia.

Anaesthetic agents: Attenuation of the reflex tachycardia and increase of the risk of hypotension.

Digitalis glycosides: Increase of atrio-ventricular conduction time, reduction in heart rate. If hypokalaemia and/or hypomagnesaemia develop during treatment with Lodoz the myocardium may show increased sensitivity to cardiac glycosides, leading to an enhanced effect and adverse effects of the glycosides.

Non-steroidal anti-inflammatory drugs (NSAIDs): NSAIDs may reduce the hypotensive effect.
In patients developing hypovolaemia the concomitant administration of NSAIDs can trigger acute renal failure.

Beta-sympathomimetics: Combination with bisoprolol may reduce the effect of both agents.

Sympathomimetics that activate both beta- and alpha-adrenoceptors: Combination with bisoprolol may lead to blood pressure increase. Such interactions are considered to be more likely with nonselective beta-blockers.

Potassium-wasting medicinal products may result in increased potassium losses.

Methyldopa: haemolysis due to the formation of antibodies to hydrochlorothiazide has been described in isolated cases.

The effect of uric-acid-lowering agents may be attenuated in concomitant administration of Lodoz.

Cholestyramine, colestipol: reduces the absorption of the hydrochlorothiazide component of Lodoz.

***Combinations to be considered***

Mefloquine: increased risk of bradycardia.

Corticosteroids: Reduced antihypertensive effect.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

Lodoz is not recommended during pregnancy.

*Bisoprolol*

Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/newborn. In general, beta-adrenoceptor blockers reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse effects (e.g. hypoglycaemia and bradycardia) may occur in the foetus and newborn infant. If treatment with beta-adrenoceptor blockers is necessary, beta1-selective adrenoceptor blockers are preferable.

*Hydrochlorothiazide*

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient.

Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Breast-feeding

Lodoz is not recommended in breastfeeding women. Hydrochlorothiazide can inhibit the milk production.

Fertility

No human data on fertility are known for Lodoz 2.5/5/10 mg/6.25 mg.

## 4.7 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 conjuction with alcohol.

## 4.8 Undesirable effects

List of adverse reactions
Adverse reactions are listed below by MedDRA system organ class and by frequency. The following definitions apply to the frequency terminology used hereafter: common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), frequency not known (cannot be estimated from the available data).

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Not known: non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma)

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: 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
Not known: interstitial lung disease

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, 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.

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 4.4 and 5.1).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## 4.9 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, vasodilatating agents.
Bronchospasm: Administer bronchodilatator therapy such as isoprenaline, beta$_2$-sympatthomimetic 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.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combination of an adrenoceptor blocking agent (ß$_1$-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 $\beta_1$-selective adrenoceptor blocking agent with no intrinsic sympathomimetic activity and without significant membrane-stabilizing activity.

As with other $\beta_1$-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 4.4).

## 5.2 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 metaboltes 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 $t_{1/2}$ 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 Cmax.

- Hydrochlorothiazide crosses the placental barrier and is excreted in human milk.

## 5.3 Preclinical safety data

Bisoprolol or hydrochlorothiazide 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 weigth gain) and to the embryo/fetus (increased late resorptions, reduced birth weigth 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.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 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

*Tablet coating*
Polysorbate 80, Yellow Iron Oxide (E172), Macrogol 400, Titanium Dioxide (E171), Hypromellose

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

*Tablet coating*
Iron oxide yellow (E 172), Iron oxide red (E 172), Polysorbate 80, Macrogol 400, Titanium Dioxide (E171), Hypromellose.

Lodoz 10 mg/6.25 mg, film-coated tablet.
*Tablet core*
Silica, colloidal anhydrous
Magnesium Stearate
Microcrystalline Cellulose
Maize Starch
Calcium-hydrogen phosphate, anhydrous

*Tablet coating*
Polysorbate 80, Macrogol 400, Hypromellose, Titanium Dioxide (E171)

**6.3 Incompatibilities**

Not applicable

**6.3 Shelf-life**

*Shelf life for PP/Alu and PVC/Alu blister*

Lodoz 2.5 mg/6.25 mg, 5 mg/6.25 mg and 10 mg/6.25 mg, film-coated tablet
5 years

*Shelf life for Alu/Alu blister*

Lodoz 2.5 mg/6.25 mg, film-coated tablet
2 years

Lodoz 5 mg/6.25 mg and 10 mg/6.25 mg, film-coated tablet
5 years

**6.4 Special precautions for storage**

*Storage conditions for PP/Alu and PVC/Alu blister*

Do not store above 30°C.

*Storage conditions for Alu/Alu blister*

This medicinal product does not require any special storage conditions.

### 6.5 Nature and contents of container

Polypropylene/aluminium blister or Polyvinylchloride/aluminium blister or Aluminium/aluminium blister.
Packs containing 30, 50, 60, 90, or 100 tablets.

Not all pack sizes may be marketed

### 6.6 Special precautions for disposal

No special requirements

## 7. MARKETING AUTHORIZATION HOLDER

[To be completed nationally]

## 8. MARKETING AUTORISATION NUMBER(S)

[To be completed nationally]

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

[To be completed nationally]

## 10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

# LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON FOR BLISTERPACK**

**1. NAME OF THE MEDICINAL PRODUCT**

Lodoz 2.5 mg/6.25 mg, film-coated tablets

Bisoprolol fumarate
Hydrochlorothiazide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

30 tablets
50 tablets
60 tablets
90 tablets
100 tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.
Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

*Storage conditions for PP/Alu and PVC/Alu blister*
Do not store above 30°C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

## 12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

## 13. BATCH NUMBER

Batch

## 14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

[To be completed nationally]

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS**

**BLISTER**

## 1. NAME OF THE MEDICINAL PRODUCT

Lodoz 2.5 mg/6.25 mg, film-coated tablets

Bisoprolol fumarate
Hydrochlorothiazide

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Batch

## 5. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON FOR BLISTERPACK**

**1. NAME OF THE MEDICINAL PRODUCT**

Lodoz 5 mg/6.25 mg, film-coated tablets

Bisoprolol fumarate
Hydrochlorothiazide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

30 tablets
50 tablets
60 tablets
90 tablets
100 tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.
Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

*Storage conditions for PP/Alu and PVC/Alu blister*
Do not store above 30°C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

## 12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

## 13. BATCH NUMBER

Batch

## 14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

[To be completed nationally]

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS**

**BLISTER**

## 1. NAME OF THE MEDICINAL PRODUCT

Lodoz 5 mg/6.25 mg, film-coated tablets

Bisoprolol fumarate
Hydrochlorothiazide

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Batch

## 5. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON FOR BLISTERPACK**

**1. NAME OF THE MEDICINAL PRODUCT**

Lodoz 10 mg/6.25 mg, film-coated tablets

Bisoprolol fumarate
Hydrochlorothiazide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

30 tablets
50 tablets
60 tablets
90 tablets
100 tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.
Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

*Storage conditions for PP/Alu and PVC/Alu blister*
Do not store above 30°C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

**12. MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

[To be completed nationally]

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

[To be completed nationally]

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER – HUMAN READABLE DATA**

PC:
SN:
NN:

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS**

**BLISTER**

## 1. NAME OF THE MEDICINAL PRODUCT

Lodoz 10 mg/6.25 mg, film-coated tablets

Bisoprolol fumarate
Hydrochlorothiazide

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Batch

## 5. OTHER

# PACKAGE LEAFLET

**Package leaflet: Information for the user**

**Lodoz 2.5 mg / 6.25 mg, film-coated tablet**
**Lodoz 5 mg / 6.25 mg, film-coated tablet**
**Lodoz 10 mg / 6.25 mg, film-coated tablet**

Bisoprolol fumarate and hydrochlorothiazide

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**:


## 1. What Lodoz is and what it is used for

Lodoz contains the active substances bisoprolol and hydrochlorothiazide:
- Bisoprolol belongs to a group of medicines called beta-blockers and is used to lower blood pressure.
- Hydrochlorothiazide belongs to a group of medicines called thiazide diuretic. It also helps to lower blood pressure by increasing urine output.

Lodoz is used to treat mild to moderate high blood pressure.

## 2. What you need to know before you take Lodoz

**Do not take Lodoz if one of the following conditions applies to you:**

- Allergy (hypersensitivity) to bisoprolol, hydrochlorothiazide, other thiazides, sulphonamides, or to any of the other ingredients (see section 6 'What Lodoz contains')
- Severe asthma
- Heart failure not controlled by therapy or cardigenic shock (an acute serious heart condition causing low blood pressure and circulatory failure)
- Certain cardiac rhythm disorders in particular slow heart rate causing problems, conduction disturbances and a disorder called sick sinus syndrome
- Untreated phaeochromocytoma (tumor of the adrenal gland secreting substances which induce severe high blood pressure)
- Severe blood circulation problems in your limbs (such as Raynaud's syndrome which may cause your fingers or toes to tingle or turn pale or blue)
- Increase in blood acidity (metabolic acidosis) as a result of severe illness
- Severe liver or kidney problems
- Low blood levels of potassium, not responding to treatment

**Warnings and precautions**

Never suddenly stop taking treatment, in particular if you suffer from certain heart disorders (ischaemic heart disease, for example angina pectoris)

Before taking Lodoz tell your doctor, if any of the following conditions applies to you;
- any heart disease such as heart failure, disturbances in heart rhythm, or Prinzmetal's angina
- less severe blood circulation problems in your limbs (in particular from Raynaud's syndrome)
- kidney or liver problems
- phaeochromocytoma (tumour of the adrenal gland)
- chronic lung disease or less severe asthma
- diabetes
- thyroid disorders
- psoriasis
- strict fasting
- history of penicillin allergy.

In addition, tell your doctor:
- If you have ever suffered from gout, as Lodoz may enhance the risk for gout attacks;
- If you are going to have anaesthesia (e.g. for surgery) because Lodoz may influence how your body reacts to this situation;
- If you plan to have desensitisation therapy, because Lodoz may make it more likely that you experience an allergic reaction, or such a reaction may be more severe;
- If you are breastfeeding or intend to do so;
- If you intend to expose yourself to the sun or to artificial UV light, as few patients have experienced skin rash after exposure to sunlight. In this case, you should protect your skin while you are treated with Lodoz;
- If you have had skin cancer or if you develop an unexpected skin lesion during the treatment. Treatment with hydrochlorothiazide, particularly long term use with high doses, may increase the risk of some types of skin and lip cancer (non-melanoma skin cancer). Protect your skin from sun exposure and UV rays while taking Lodoz;
- If you experience acute onset of decreased visual acuity or ocular pain within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma (a disorder affecting the eye) can lead to permanent vision loss, so inform your doctor about this immediately.

If you have chronic lung disease or less severe asthma please inform your doctor immediately if you start to experience new difficulties in breathing, cough, wheezing after exercise, etc. when using Lodoz.

Additional tests
Hydrochlorothiazide works by influencing the salt and water balance in your body. Your doctor may want to check this from time to time. This is especially important if you have additional conditions which may become worse if the electrolyte balance is disturbed. Your doctor will also check your levels of blood fats, uric acid, or blood glucose from time to time.

The concomitant use of this medicine is not recommended with lithium used to treat some psychiatric disorders, or medicines used to treat high blood pressure, angina pectoris or irregular heart beat (such as verapamil, diltiazem or bepridil) (see section "Taking other medicines").

Competitive athletes should be aware that this product contains medicines that may give a positive reaction in doping test.

**Other medicines and Lodoz**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Take Lodoz with any of the following medicines only if your doctor has advised you to do so as it is generally not recommended (see above, "Take special care with Lodoz"):

- Certain medicines used to treat high blood pressure, angina pectoris or irregular heart beat (such as verapamil or diltiazem or bepridil) which may increase the risk of heart rhythm disorders.
- Lithium used to treat some psychiatric disorders.

**Pregnancy, breast-feeding and fertility**

Use of this medicine is not recommended during pregnancy.
Use of this medicine is not recommendend during breastfeeding.

**Driving and using machines**

Normally Lodoz does not affect your ability to drive or use machines. However, your individual response may influence your ability to concentrate and react. If this happens, do not drive or use machines.

## 3. How to take Lodoz

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The usual starting dose is one tablet Lodoz 2.5 mg / 6.25 mg daily.
If the blood pressure lowering effect of this dose is inadequate, the dose will be increased to one tablet Lodoz 5 mg / 6.25 mg daily and, if response is still inadequate, to one tablet Lodoz 10 mg / 6.25 mg daily.

Take Lodoz in the morning, with or without food. Swallow the tablet with some liquid. Do not chew.

Never suddenly stop taking treatment (see section "If you stop taking Lodoz").

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

**Lodoz with food and drink**

Lodoz may be taken with or without food, but must be taken in the morning.

**If you take more Lodoz than you should**

If you have taken more Lodoz tablets than you should, inform your doctor immediately. Depending on the degree of overdose, your doctor can decide what measures are necessary.
Symptoms of an overdose may include low blood pressure, slow heartbeat, sudden heart problems, dizziness, nausea, sleepiness, sudden breathing problems, low blood sugar.

**If you forget to take Lodoz**

If you forget to take this medicine, take it as soon as you remember. Then take your next dose at its usual time. However, if it is almost time for your next dose skip the dose you missed. Do not take a double dose to make up for a forgotten tablet.

**If you stop taking Lodoz**

Never stop taking this medicine unless on your doctor's advice. Otherwise your condition could become much worse. If you have to stop treatment, your doctor will usually advise you to reduce the dose gradually.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. These side effects are listed below according to how frequently they may occur:

**Common side effects** (affect less than 1 person in 10):
- feeling of coldness or numbness in hands and feet
- tiredness, dizziness, headache. These symptoms occur mainly at the beginning of the treatment. They are generally mild, and usually disappear within 1 to 2 weeks after starting the treatment
- stomach or intestine problems such as nausea, vomiting, diarrhoea, or constipation.

**Uncommon side effects** (affect less than 1 person in 100):
- muscular weakness, muscular cramps, feeling weak
- slow heart beat, impaired heart rate, worsening of heart failure, drop in blood pressure after standing or sitting up
- sleep disorders, depression, loss of appetite
- breathing problems in patients with asthma or chronic bronchial disease
- increase of blood-levels for creatinine or urea
- abdominal complaints
- increased amylase levels (enzymes involved in digestion),
- disturbed balance of fluids and electrolytes
- increased blood levels for fat, cholesterol, uric acid or sugar; increased urine levels for sugar

**Rare side effects** (affect less than 1 person in 1,000):
- nightmares, hallucinations.
- allergy-type reactions, such as itching, sudden flushing of the face or skin rash, also after exposure to sunlight, hives, small purple-red marks on the skin caused by bleeding under the skin (purpura),
- increase in certain liver enzymes, inflammation of the liver, yellow colouring of skin and eyes (jaundice),
- erection disorders,
- hearing problems,
- allergic runny nose, reduced tear secretion, visual disturbance,
- decrease in number of white blood cells (leukocytopenia), or blood platelets (thrombocytopenia)
- syncope

**Very rare side effects** (affect less than 1 person in 10,000):
- irritation and redness of the eye (conjunctivitis), hair loss
- onset or worsening of pre-existing scaly skin rash (psoriasis); onset of thick scaly patches (cutaneous lupus erythematosus)
- chest pain
- severe reduction in the number of white blood cells (agranulocytosis)
- inflammation of the pancreas
- condition of too little acid in your blood (metabolic alkalosis)
- allergic (anaphylactic) reactions, severe bullous reactions (Lyell syndrome)

**Side effects with unknown frequency** (cannot be estimated from the available data):
- skin and lip cancer (non-melanoma skin cancer)
- interstitial lung disease

- short-sightedness
- eye pain (possible signs of acute angle-closure glaucoma)

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Lodoz

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton after EXP.

*Storage conditions for PP/Alu and PVC/Alu blister*
- Do not store above 30°C.

*Storage conditions for Alu/Alu blister*
- This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment

## 6. Contents of the pack and other information

**What Lodoz contains**

Lodoz 2.5 mg / 6.25 mg:
- The active substances are bisoprolol fumarate and hydrochlorothiazide. Each film-coated tablet contains 2.5 mg bisoprolol fumarate and 6.25 mg hydrochlorothiazide
- The other ingredients are
  *Tablet core*: magnesium stearate; crospovidone; maize starch; pregelatinized maize starch; microcrystalline cellulose; calcium hydrogen phosphate, anhydrous;
  *Tablet coating*: polysorbate 80; yellow iron oxide (E 172); macrogol 400; titanium dioxide (E171); hypromellose.

Lodoz 5 mg / 6.25 mg:
- The active substances are bisoprolol fumarate and hydrochlorothiazide. Each film-coated tablet contains 5 mg bisoprolol fumarate and 6.25 mg hydrochlorothiazide
- The other ingredients are
  *Tablet core*: silica, colloidal anhydrous; magnesium stearate; microcrystalline cellulose; maize starch; calcium hydrogen phosphate, anhydrous;
  *Tablet coating*: iron oxide yellow (E 172); iron oxide red (E 172); polysorbate 80; macrogol 400; titanium dioxide (E171); hypromellose.

Lodoz 10 mg / 6.25 mg:
- The active substances are bisoprolol fumarate and hydrochlorothiazide. Each film-coated tablet contains 10 mg bisoprolol fumarate and 6.25 mg hydrochlorothiazide
- The other ingredients are
  *Tablet core*: silica, colloidal anhydrous; magnesium stearate; microcrystalline cellulose; maize starch; calcium hydrogen phosphate, anhydrous;
  *Tablet coating*: polysorbate 80; macrogol 400; hypromellose; titanium dioxide (E171);

**What Lodoz looks like and contents of the pack**

**Lodoz 2.5 mg / 6.25 mg:** yellow, round, biconvex film-coated tablet; upper side embossed heart, downside embossed with the number “2.5”.

**Lodoz 5 mg / 6.25 mg:** pastel-pink, round, biconvex film-coated tablet; upper side embossed heart, downside embossed with the number “5”.

**Lodoz 10 mg / 6.25 mg:** white, round, biconvex film-coated tablet; upper side embossed heart, downside embossed with the number “10”.

Each pack contains: 30, 50, 60, 90, or 100 tablets.
Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

[To be completed nationally]

**This leaflet was last revised in .**

[To be completed nationally]