LODOZ
Bisoprolol fumarate/Hydrochlorothiazide
Selective beta$_1$ adrenoceptor blocker + Diuretic

1. 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

2. PHARMACEUTICAL FORM
Film-coated tablet

3. CLINICAL PARTICULARS
3.1 Indications
Treatment of hypertension.

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

Patient 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.

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 taken in the morning with or without food. The film-coated tablets should be swallowed with some liquid and not be chewed.

3.3 Contraindications
Lodoz must not be used in patients with:

- hypersensitive to Bisoprolol, Hydrochlorothiazide, other Thiazides, Sulfonamides, or any of the excipients listed in section 5.1 List of excipients.
- severe bronchial asthma
- acute heart failure or during episodes of heart failure decompensation requiring intravenous therapy with substances increasing the contractility of the heart
- cardiogenic shock (acute serious heart condition causing low blood pressure and circulatory failure)
- second- or third-degree AV block (severe disturbances of atrioventricular conduction) without a pacemaker
- sick sinus syndrome
- sinoatrial block
- symptomatic bradycardia (slowed heartbeat, causing problems)
- untreated tumours of the adrenal gland (phaeochromocytoma)
- severe forms of peripheral arterial occlusive disease or Raynaud's syndrome
- metabolic acidosis (increase of blood acidity as a result of severe illness)
- severe kidney impairment (creatinine clearance ≤ 30 mL/min)
- severe liver impairment
- refractory hypokalaemia (low blood levels of potassium, not responding to treatment)

3.4 Special warnings and precautions for use

Treatment with Bisoprolol must not be stopped suddenly unless clearly indicated, since abrupt withdrawal of Bisoprolol may lead to an acute worsening of the patient's condition in particular in patients with ischaemic heart disease (*see section 3.2 Posology and method of administration*).

The following section describes when Lodoz must be used with special caution (e.g. additional treatment or more frequent checks):

- there is no therapeutic experience of Bisoprolol treatment in patients with myocardial infarction within 3 months
- diabetes mellitus with extremely fluctuating blood glucose levels: symptoms of markedly reduced blood glucose (hypoglycaemia) such as tachycardia, palpitations or sweating can be masked
- strict fasting
- any heart disease such as heart failure, mild disturbances in heart rhythm (first degree AV block)
- 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.
- hypovolaemia
- impaired liver function
- peripheral arterial occlusive disease (intensification of complaints may occur especially when starting therapy)
- patients with psoriasis or with a personal history of psoriasis
- hyperuricaemia, as hydrochlorothiazide may enhance the risk for gout attacks

Respiratory system

Although cardioselective ($beta_1$) 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 disease, unless there are compelling clinical reason for their use. Where such reasons exist, Lodoz may be used with caution. In bronchial asthma or other symptomatic chronic obstructive pulmonary diseases concomitant bronchodilator therapy is indicated. An increase in airway resistance may occasionally occur in patients with asthma, requiring a higher dose of $beta_2$–sympathomimetics.

Allergic reactions

As with other beta-blockers, Bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. This also applies to desensitisation therapy. Epinephrine treatment may not always yield the expected therapeutic effect.

General anaesthesia
In patients undergoing general anaesthesia the anaesthetist must be aware of beta-blockade. It is currently recommended that maintenance beta-blockade be continued peri-operatively. If it is thought necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours prior to anaesthesia.

Phaeochromocytoma
In patients with a tumour of the adrenal gland (phaeochromocytoma) Bisoprolol may only be administered after previous alpha-receptor blockade.

Thyrotoxicosis
Under treatment with Bisoprolol the symptoms of a thyroid hyperfunction (thyrotoxicosis) may be masked.

Photosensitivity reactions
Photosensitivity reactions may occur with thiazide diuretics. If photosensitivity reactions occur, it is recommended to protect exposed areas to the sun or to artificial UVA light. In severe cases it may be necessary to stop the treatment.

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 section 3.8 Undesirable effects and 4.1 Pharmacodynamic properties*).

Fluid & Electrolyte Balance
During long term-therapy with Hydrochlorothiazide, 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. Hypokalaemia facilitates the development of severe arrhythmias, particularly torsade de pointes, which may be fatal.

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 can cause an idiosyncratic reaction, resulting in choroidal 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 alergy.

3.5 Interactions with other medicinal products and other form of interaction
The effect and tolerability of medicines can be influenced by simultaneous intake of other medication. Such interactions can also occur if a short time has elapsed since the use of the other medication.

Combinations not recommended
Lithium has a cardiotoxic and neurotoxic effect. This effect may be intensified through Hydrochlorothiazide because it may lead to a reduction of Lithium excretion.

Calcium antagonists of the Verapamil or Diltiazem type, or Bepridil may lead to reduced contractility of the heart muscle and delayed atrio-ventricular impulse conduction when used concomitantly with Bisoprolol.

Centrally-acting blood pressure-lowering medicines (such as Clonidine, Methyldopa, Moxonodine, Rilmenidine) may lead to a reduction of heart rate and cardiac output, as well as to vasodilation due to a decrease in the central sympathetic tonus. Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of “rebound hypertension”.

Combinations to be used with caution
Calcium antagonists of the Dihydropyridine type (e.g. Nifedipine, Amlodipine) may increase the risk of hypotension when used concomitantly with Bisoprolol. An increased risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.

Antihypertensive agents as well as other medicines with blood pressure lowering potential (e.g. Tricyclic antidepressants, Barbiturates, Phenothiazines, Baclofene, Amifostine) may increase the blood pressure lowering effect of Lodoz.

ACE inhibitors (e.g. Captopril, Enalapril) or angiotensin II antagonists bear the risk of significant fall in blood pressure and/or acute renal failure during initiation of ACE inhibitor therapy in patients with pre-existing 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 medicines (e.g. Quinidine, Disopyramide, Lidocaine, Phenytoin, Flecainide, Propafenone, Cibenzoline) may increase the depressant effect of bisoprolol on atrio-ventricular impulse conduction and the contractility of the heart.

Class-III antiarrhythmic medicines (e.g. Amiodarone) may increase the inhibitory effect of Bisoprolol on atrio-ventricular impulse conduction.

Antiarrhythmic agents that may induce torsades de pointes (Class IA e.g. Quinidine, Hydroquinidine, Disopyramide, and Class III e.g. Amiodarone, Sotalol, Dofetilide, Ibutilide): Hypokalaemia may facilitate the occurrence of torsades de pointes.

Nonantiarrhythmic agents that may induce torsades de pointes (e.g. Astemizole, Bepridil, Cisapride, Diphemanil, i.v. Erythromycin, Halofantrine, Lumefantrine, Methadone, Moxifloxacin, Pentamidine, Sotalol, i.v. Spiramycin, Sparfloxacin, Terfenadine, Vincamine, Pimozide, Haloperidol, Benzamides): Hypokalaemia may facilitate the occurrence of torsades de pointes.

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

The blood sugar lowering effect of Insulin or oral antidiabetic medicines may be intensified. Warning signs of reduced blood glucose (hypoglycaemia) - especially accelerated heart rate (tachycardia) - may be masked or suppressed.

Anaesthetic agents may increase the risk of cardiodepressive actions of Bisoprolol, leading to hypotension (for further information on general anaesthesia see also section special warnings and precautions)

Cardiac glycosides (digitalis) may increase the inhibitory effect on atrio-ventricular impulse conduction and the risk of bradycardia when used concomitantly with Bisoprolol. Toxic effects of cardiac glycosides (digitalis) may be facilitated if Hydrochlorothiazide leads to hypokalaemia.

Non-steroidal anti-inflammatory medicines (NSAIDs) may reduce the blood pressure-lowering effect of Lodoz. NSAIDs can trigger acute renal failure in patients developing hypovolaemia.

Beta-sympathomimetics (e.g. Isoprenaline, Dobutamine) used in combination with Bisoprolol may lead to a reduced effect of both agents.

A combination of Bisoprolol with sympathomimetics that activate both beta- and alpha-adrenoceptors (e.g. Noradrenaline, Adrenaline) may lead to blood pressure increase.

Hypokalaemic drugs (e.g. Amphotericin, Corticosteroids, ACTH, Carbenoxolone, Furosemide, or laxatives) may result in increased potassium losses when used concomitantly with Hydrochlorothiazide.

Methyldopa has been described in isolated cases to lead to haemolysis due to the formation of antibodies to Hydrochlorothiazide.

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

Resins such as Cholestyramine and Colestipol reduce the absorption of the Hydrochlorothiazide. A time-interval of at least two hours should separate the resin intake from Lodoz administration.

Combinations to be considered
Mefloquine: increased risk of bradycardia.

Corticosteroids may reduce the antihypertensive effect due to corticosteroid-induced water and sodium retention.

3.6 Fertility, pregnancy, and lactation
Pregnancy
Lodoz is not recommended during pregnancy because it contains a thiazide diuretic. Diuretics may give rise to foetoplacental ischaemia with the attendant risk of foetal hypotrophy. Hydrochlorothiazide is suspected to cause thrombocytopenia in the neonate.

Breast-feeding
Lodoz is not recommended in breastfeeding women, because Bisoprolol may be and Hydrochlorothiazide is excreted in breast milk. Hydrochlorothiazide can inhibit the milk production.

3.7 Effects on the ability to drive and use machines
Effects on the ability to drive and use machines
In general, Lodoz has no or negligible influence on the ability to drive and use machines. However, depending on the individual patient's response to treatment the ability to drive a vehicle or to use machines may be impaired. This needs to be considered particularly at start of treatment, upon change of medication, or in conjunction with alcohol.

3.8 Undesirable effects

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

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

Hpatobiliary 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 : erectyle 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 section 3.4 Special warning and precaution for use and 4.1 Pharmacodynamic properties*).

3.9 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.

4. PHARMACOLOGICAL PROPERTIES

4.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combination of an adrenoceptor blocking agent (beta$_1$-selective) and a Thiazide diuretic.

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) (s*ee section 3.4 Special warnings and precautions for use and 3.8 Undesirable effects*).

4.2 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 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 $t_{1/2}$ 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. PHARMACEUTICAL PARTICULARS

5.1 List of excipients

Lodoz 2.5 mg/6.25 mg

Tablet core

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

Tablet coating

Opadry Yellow YS16339G: Polysorbate 80, Yellow Iron Oxide, Macrogol, Titanium Dioxide, 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

Opadry Pink YS11252: Yellow Iron Oxide, Red Iron Oxide, Polysorbate 80, Macrogol, Titanium Dioxide, Hypromellose.

5.2 Shelf-life

The expiry date is indicated on the packaging.

5.3. Special precautions for storage

Store below 25^0C

5.4 Package Quantities and Registration Numbers

Lodoz 2.5 mg/6.25 mg : Box, 3 blisters @ 10 film-coated tablets in blister
Reg No. DKL9915807317A1
Lodoz 5 mg/6.25 mg : Box, 3 blisters @ 10 film-coated tablets in blister
Reg No. DKL0415807317B1

On medical prescription only
HARUS DENGAN RESEP DOKTER

Manufactured by
PT Merck Tbk

Jakarta, Indonesia

Under licence from
Merck Healthcare KGaA
Darmstadt, Germany

PI based on CCDS ver 13.0

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