

# Betaloc ZOK 25 mg, 50 mg, 100 mg and 200 mg

metoprolol succinate

## tablet

### Composition

Each tablet of Betaloc ZOK contains metoprolol succinate 23.75 mg, 47.5 mg, 95 mg and 190 mg corresponding to 25 mg, 50 mg, 100 mg and 200 mg of metoprolol tartrate.

### Pharmaceutical form

Tablets with controlled release of metoprolol.

Betaloc ZOK 25 mg tablet is white to off-white, oval, scored on both sides and marked A/β on one side.

Betaloc ZOK 50 mg tablet is white to off-white, circular, scored on one side and marked  $\frac{A}{mO}$  on the other side.

Betaloc ZOK 100 mg tablet is white to off-white, circular, scored on the one side and marked  $\frac{A}{mS}$  on the other side.

Betaloc ZOK 200 mg tablet is white to off-white, oval, scored and marked  $\frac{A}{mY}$  on one side.

### Indications

Hypertension: to reduce blood pressure and to reduce the risk of cardiovascular and coronary mortality (including sudden death), and morbidity.

Angina pectoris.

Stable symptomatic chronic heart failure with impaired systolic left ventricular function as an adjunct to existing heart failure therapy.

Prevention of cardiac death and reinfarction after the acute phase of myocardial infarction.

Cardiac arrhythmias especially including supraventricular tachycardia, reduction of ventricular rate in atrial fibrillation and in ventricular extrasystoles.

Functional heart disorders with palpitations.

Migraine prophylaxis.

### Posology and method of administration

Betaloc ZOK is intended for once daily treatment and is preferably taken in the morning. The Betaloc ZOK tablet should be swallowed with liquid. The tablets and the divided halves should not be chewed or crushed. Concomitant intake of food does not influence the bioavailability.

Dosage should be adjusted to avoid bradycardia.

#### Hypertension

The recommended dosage in patients with mild to moderate hypertension is 50 mg Betaloc ZOK given once daily. In patients not responding to 50 mg the dose could be increased to 100-200 mg once daily and/or combined with other antihypertensive agents.

#### Angina pectoris

The recommended dosage is 100-200 mg Betaloc ZOK given once daily. If needed, Betaloc ZOK can be combined with other antianginal agents.

#### Stable symptomatic chronic heart failure with impaired systolic left ventricular function as an adjunct to existing heart failure therapy

The patients should have a stable chronic heart failure, without acute failure for the latest 6 weeks and an essentially unchanged basal therapy for the latest 2 weeks.

Treatment of heart failure with  $\beta$ -blockers may sometimes cause a temporary exacerbation of the symptoms picture. In some cases, it is possible to continue the therapy or reduce the dose, and in other cases it may be necessary to discontinue the treatment. Initiation of Betaloc ZOK therapy in patients with severe heart failure (NYHA IV) should only be made by physicians especially trained in treatment of heart failure (see *Special Warnings and Precautions for Use*).

#### Dosage in patients with stable heart failure, function class II:

A recommended initial dosage for the first two weeks is 25 mg once daily. After two weeks, the dose can be increased to 50 mg once daily, and thereafter it can be doubled every second week. The target dose for long-term treatment is 200 mg once daily.

#### Dosage in patients with stable heart failure, function classes III-IV:

Recommended initial dose is 12.5 mg (half a 25 mg tablet) given once daily. The dose should be individually adjusted, and the patient should be closely monitored during the increase of the dosage as heart failure symptoms may be aggravated in some patients. After 1-2 weeks, the dose can be raised to 25 mg given once daily. Then, after further two weeks, the dosage can be increased to 50 mg given once daily. In those patients who tolerate a higher dose, the dosage can be doubled every second week up to a maximal dose of 200 mg daily.

In case of hypotension and/or bradycardia, decrease in concomitant medication or lowering of the Betaloc ZOK dose may be necessary. Initial hypotension does not necessarily mean that the dose of Betaloc ZOK cannot be tolerated in chronic treatment, but the dose must not be raised until the condition has been stabilised, and increased control of renal function, among other things, may be required.

#### Cardiac arrhythmias

The recommended dosage is 100-200 mg Betaloc ZOK given once daily.

#### Prophylactic treatment after myocardial infarction

Long-term oral treatment with metoprolol in doses of 200 mg given once daily has been shown to reduce the risk of death (including sudden death), and to reduce the risk of reinfarction (also in patients with diabetes mellitus).

#### Functional heart disorders with palpitations

The recommended dosage is 100 mg once daily. If needed, the dose can be increased to 200 mg.

#### Migraine prophylaxis

The recommended dosage is 100-200 mg once daily.

### **Impaired renal function**

Dose adjustment is not needed in patients with impaired renal function.

### **Impaired hepatic function**

Dose adjustment is normally not needed in patients suffering from liver cirrhosis because metoprolol has a low protein binding (5-10%). When there are signs of serious impairment of liver function (e.g. shunt-operated patients) a dose reduction should be considered.

### **Elderly**

Dose adjustment is not needed in the elderly.

### **Children**

There is limited experience with Betaloc ZOK treatment in children.

### **Contraindications**

Atrioventricular block of second or third degree, patients with unstable decompensated cardiac heart failure (pulmonary oedema, hypoperfusion or hypotension), and patients with continuous or intermittent inotropic therapy acting through  $\beta$ -receptor agonism; marked clinically relevant sinus bradycardia, sick sinus syndrome, cardiogenic shock, severe peripheral arterial circulatory disorder.

Metoprolol should not be given to patients with suspected acute myocardial infarction as long as the heart rate is <45 beats/min, the P-Q interval is > 0.24 sec or the systolic blood pressure is <100 mm Hg.

Betaloc ZOK is contra-indicated in patients who have shown hypersensitivity to any component of the product or to other  $\beta$ -blockers.

### **Special warnings and precautions for use**

Intravenous administration of calcium antagonists of the verapamil-type should not be given to patients treated with  $\beta$ -blockers.

Generally when treating patients with asthma, concomitant therapy with a  $\beta_2$ -agonist (tablet and/or inhalation) should be administered. The dosage of  $\beta_2$ -agonists may require adjustment (increase) when treatment with Betaloc ZOK is started. The risk of Betaloc ZOK interfering with  $\beta_2$ -receptors is however less than with conventional tablet formulations of  $\beta_1$ -selective blockers.

During treatment with Betaloc ZOK, the risk of interfering with carbohydrate metabolism or masking hypoglycaemia is likely to be less than during treatment with conventional tablet formulations of  $\beta_1$ -selective blockers and much less than with non selective  $\beta$ -blockers.

Patients suffering from heart failure should have their decompensation treated both before and during treatment with Betaloc ZOK.

Very rarely, a pre-existing A-V conduction disorder of moderate degree may become aggravated (possibly leading to A-V block).

If the patients develop increasing bradycardia, Betaloc ZOK should be given in lower doses or gradually withdrawn.

Betaloc ZOK may aggravate the symptoms of peripheral arterial circulatory disorders, mainly due to its blood pressure lowering effect.

Where Betaloc ZOK is prescribed for a patient known to be suffering from a phaeochromocytoma, an alpha blocker should be given concomitantly.

Prior to surgery the anaesthetist should be informed that the patient is receiving Betaloc ZOK. It is not recommended to stop  $\beta$ -blocker treatment in patients undergoing surgery.

Efficacy/safety data from controlled clinical studies in severe stable symptomatic heart failure (NYHA class IV) are limited. Treatment of heart failure in these patients should therefore only be initiated by physicians with especial experience and training in this area (see Posology and method of Administration).

Patients with symptomatic heart failure in association with acute myocardial infarction and unstable angina pectoris were excluded from the study on which the indication of heart failure is founded. Efficacy/safety conditions have therefore not been documented. Use in unstable, decompensated heart failure is contraindicated (see Contraindications).

Abrupt interruption of the medication is to be avoided. Sudden withdrawal of  $\beta$ -blockade is hazardous, especially in high-risk patients, and may aggravate chronic heart failure as well as increase the risk of myocardial infarction and sudden death. Any withdrawal of Betaloc ZOK should therefore, if possible, be made gradually over at least two weeks when the dose is reduced by half in each step, down to the final dose when a 25 mg tablet is reduced to half a tablet. The final dose should be given for at least four days before discontinuation. If symptoms occur, a slower withdrawal rate is recommended.

In patients taking  $\beta$ -blockers anaphylactic shock assumes a more severe form.

### **Interactions**

Metoprolol is a metabolic substrate for the cytochrome P450 isoenzyme CYP2D6. Drugs that act as enzyme-inducing and enzyme-inhibiting substances may exert an influence on the plasma level of metoprolol. Plasma levels of metoprolol may be raised by co-administration of compounds metabolised by CYP2D6, e.g. antiarrhythmics, antihistamines, histamine-2-receptor antagonists, antidepressants, antipsychotics, and COX-2-inhibitors. The plasma concentration of metoprolol is lowered by rifampicin and may be raised by alcohol and hydralazine.

Patients receiving concomitant treatment with sympathetic ganglion blocking agents, other  $\beta$ -blockers (i.e. eye drops), or Mono Amine Oxidase (MAO) inhibitors should be kept under close surveillance.

If concomitant treatment with clonidine is to be discontinued, the  $\beta$ -blocker medication should be withdrawn several days before clonidine.

A watch should be kept for possible negative inotropic and chronotropic effects when metoprolol is given together with calcium antagonists of the verapamil and diltiazem type and/or antiarrhythmic agents. In patients treated with  $\beta$ -blockers intravenous administration of calcium antagonists of the verapamil type should not be given.

$\beta$ -blockers may enhance the negative inotropic and negative dromotropic effect of antiarrhythmic agents (of the quinidine type and amiodarone).

Digitalis glycosides, in association with  $\beta$ -blockers, may increase atrioventricular conduction time and may induce bradycardia.

In patients receiving  $\beta$ -blocker therapy, inhalation anaesthetics enhance the cardiodepressant effect.

Concomitant treatment with indomethacin or other prostaglandin synthetase inhibiting drugs may decrease the antihypertensive effect of  $\beta$ -blockers.

Under certain conditions, when adrenaline is administered to patients treated with  $\beta$ -blockers, cardioselective  $\beta$ -blockers interfere much less with blood pressure control than non selective  $\beta$ -blockers.

The dosages of oral antidiabetics may have to be readjusted in patients receiving  $\beta$ -blockers.

### **Pregnancy and lactation**

As with most drugs, Betaloc ZOK should not be given during pregnancy and lactation unless its use is considered essential. As with all antihypertensive agents,  $\beta$ -blockers may cause side-effects, e.g. bradycardia, in the foetus and in the newborn and breast-fed infant.

The amount of metoprolol ingested via breast-milk, however, seems to be negligible as regards  $\beta$ -blocking effect in the infant if the mother is treated with metoprolol in doses within the normal therapeutic range.

### **Effects on ability to drive and use machines**

Patients should know how they react to Betaloc ZOK before they drive or use machines because occasionally dizziness or fatigue may occur.

### **Undesirable effects**

Betaloc ZOK is well tolerated and adverse reactions have generally been mild and reversible. The following events have been reported as adverse events in clinical trials or reported from routine use, mostly with conventional Betaloc (metoprolol tartrate). In many cases a relationship to treatment with Betaloc has not been established. The following definitions of frequencies are used: Very common ( $\geq 10\%$ ), common (1-9.9%), uncommon (0.1-0.9%), rare (0.01-0.09%) and very rare ( $< 0.01\%$ ).

#### *Cardiovascular system*

Common: Bradycardia, postural disorders (very rarely with syncope), cold hands and feet, palpitations.

Uncommon: Transient deterioration of heart failure symptoms, cardiogenic shock in patients with acute myocardial infarction, AV-block I, oedema, precordial pain.

Rare: Disturbances of cardiac conduction, cardiac arrhythmias.

Very rare: Gangrene in patients with pre-existing severe peripheral circulatory disorders.

#### *Central nervous system*

Very common: Fatigue.

Common: Dizziness, headache.

Uncommon: Paraesthesiae, muscle cramps.

#### *Gastrointestinal*

Common: Nausea, abdominal pain, diarrhoea, constipation.

Uncommon: Vomiting.

Rare: Dry mouth.

#### *Haematologic*

Very rare: Thrombocytopenia.

#### *Hepatic*

Rare: Liver function test abnormalities.

Very Rare: Hepatitis.

#### *Musculoskeletal*

Very rare: Arthralgia.

#### *Metabolism*

Uncommon: Weight gain.

#### *Psychiatric*

Uncommon: Depression, concentration impaired, somnolence or insomnia, nightmares.

Rare: Nervousness, anxiety, impotence/sexual dysfunction.

Very rare: Amnesia/memory impairment, confusion, hallucinations.

#### *Respiratory*

Common: Dyspnoea on exertion.

Uncommon: Bronchospasm.

Rare: Rhinitis.

#### *Sense organs*

Rare: Disturbances of vision, dry and/or irritated eyes, conjunctivitis.

Very rare: Tinnitus, taste disturbances.

#### *Skin*

Uncommon: Rash (in the form of urticaria psoriasiform and dystrophic skin lesions), increased sweating.

Rare: Loss of hair.

Very rare: Photosensitivity reactions, aggravated psoriasis.

### **Overdose**

#### *Symptoms*

Overdosage of Betaloc ZOK may lead to severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness/coma, nausea, vomiting, and cyanosis.

Concomitant ingestion of alcohol, antihypertensives, quinidine or barbiturates may aggravate the patient's condition.

The first manifestations of overdosage may be observed 20 minutes to 2 hours after the drug's ingestion.

#### *Management*

Activated charcoal, if necessary gastric lavage. In the presence of severe hypotension, bradycardia, and impending heart failure, administer a  $\beta_1$ -agonist (e.g. prenalterol) intravenously at 2-5 minutes intervals or as continuous infusion until the desired effect is achieved. Where a selective  $\beta_1$ -agonist is not available, dopamine may be used; or atropine sulphate i.v. may be used in order to block the vagus nerve.

If a satisfactory effect is not achieved, other sympathomimetic agents, such as dobutamine may be used, or noradrenaline may be given.

Glucagon in a dose of 1-10 mg can also be administered. Pacemaker may be necessary. To combat bronchospasm, a  $\beta_2$ -agonist can be given i.v.

Observe that the dosages of drugs (antidotes) needed to treat overdose of  $\beta$ -blockade are much higher than normally recommended therapeutic dosages. This is because  $\beta$ -receptors are occupied by the  $\beta$ -blocker.

## Pharmacodynamic properties

Metoprolol is a  $\beta_1$ -selective  $\beta$ -blocker, i.e. it blocks  $\beta_1$ -receptors at doses much lower than those needed to block  $\beta_2$ -receptors.

Metoprolol has an insignificant membrane stabilising effect and does not display partial agonistic activity.

Metoprolol reduces or inhibits the agonistic effect on the heart of catecholamines (which are released during physical and mental stress). This means that the usual increase in heart rate, cardiac output, cardiac contractility and blood pressure, produced by the acute increase in catecholamines, is reduced by metoprolol. During high endogenous adrenaline levels metoprolol interferes much less with blood pressure control than non-selective  $\beta$ -blockers.

When mandatory, Betaloc ZOK, in combination with a  $\beta_2$ -agonist, may be given to patients with symptoms of obstructive pulmonary disease. When given together with a  $\beta_2$ -agonist, Betaloc ZOK in therapeutic doses interferes less than non-selective  $\beta$ -blockers with the  $\beta_2$ -mediated broncho-dilation caused by the  $\beta_2$ -agonist.

Betaloc ZOK gives an even plasma concentration time profile and effect ( $\beta_1$ -blockade) over 24 hours in contrast to conventional tablet formulations of  $\beta_1$ -selective blockers.

Due to the lack of pronounced peaks in plasma concentration, the clinical  $\beta_1$ -selectivity is improved with the Betaloc ZOK formulation when compared to conventional tablet formulations of  $\beta_1$ -selective blockers. Furthermore the potential risk for peak plasma concentration related side effects, such as bradycardia and leg fatigue is reduced.

Betaloc ZOK interferes less with insulin release and carbohydrate metabolism than do non selective  $\beta$ -blockers.

Betaloc ZOK interferes much less with the cardiovascular response to hypoglycaemia than do non-selective  $\beta$ -blockers.

Short term studies have shown that Betaloc ZOK may cause a slight increase in triglycerides and a decrease in free fatty acids in the blood. In some cases, a small decrease in the high density lipoproteins (HDL) fraction has been observed, although to a lesser extent than that following non selective  $\beta$ -blockers. However, a significant reduction in total serum cholesterol levels has been demonstrated after metoprolol treatment in one study conducted over several years.

Quality of life is maintained, uncompromised or improved during treatment with Betaloc ZOK.

An improvement in quality of life has been observed after metoprolol treatment in patients after myocardial infarction.

In MERIT-HF, a survival study comprising 3991 patients with chronic heart failure (NYHA II-IV) and decreased ejection fraction ( $\leq 0.40$ ), Betaloc ZOK has been shown to increase survival and to reduce the number of hospitalisations. In long-term treatment the patients experience a general improvement of symptoms (NYHA class and Overall Treatment Evaluation score).

In addition, it has been shown that Betaloc ZOK therapy increases the ejection fraction and reduces the left ventricular end systolic and end diastolic volumes.

## Pharmacokinetic properties

### Absorption and distribution

Betaloc ZOK is completely absorbed after oral administration. Owing to an extensive first-pass effect, the systemic bioavailability of metoprolol from a single oral dose is approximately 50%. The bioavailability is reduced by about 20-30% for the controlled release preparation compared with a conventional tablet, but this has been demonstrated to be of no significance for clinical efficacy, since the area under the effect curve (AUEC) for heart rate is the same as with conventional tablets. The plasma protein binding of metoprolol is low, approximately 5-10%.

### Metabolism and elimination

Metoprolol undergoes oxidative metabolism in the liver primarily by the CYP2D6 isoenzyme. Three main metabolites have been identified, though none of them have a  $\beta$ -blocking effect of clinical importance.

As a rule, over 95% of an oral dose can be recovered in the urine. About 5% of the given dose is excreted in the urine in unchanged form, this figure rising up to 30% in isolated cases. The elimination half-life of metoprolol in plasma averages 3.5 hours (extremes: 1 and 9 hours). The total clearance rate is approximately 1 litre/minute.

Elderly show no significant changes in the pharmacokinetics of metoprolol as compared with young persons. The systemic bioavailability and elimination of metoprolol is unchanged in patients with reduced renal function. The excretion of metabolites, however, is reduced. Significant accumulation of metabolites was observed in patients with a glomerulus filtration rate (GFR) of less than 5 ml/min. This accumulation of metabolites, however, does not increase the  $\beta$ -blockade.

Due to its low protein binding the pharmacokinetics of metoprolol is little affected by decreased liver function. However, in patients with severe liver cirrhosis and a portacava shunt the bioavailability of metoprolol may increase and the total clearance may be reduced. Patients with a portacaval anastomosis had a total clearance of approximately 0.3 litres/min and area under the plasma concentration-time curve (AUC) values up to 6 times higher than in healthy subjects.

## List of excipients

Ethylcellulose, hydroxypropyl cellulose, hypromellose, microcrystalline cellulose, paraffin, macrogol, silicon dioxide, sodium stearyl fumarate, titanium dioxide (E 171).

## Shelf-life

Please see outer pack.

## Special precautions for storage

Do not store above 30°C

## Pack size

Please see outer pack.

## Date of revision of the text

February 2007

CV.000-158-440.4.0

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