

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Betalok Zok 25 mg controlled release
tablet Betalok Zok 50 mg controlled
release tablet Betalok Zok 100 mg
controlled release tablet Betalok Zok 200
mg controlled release tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

*1 controlled release tablet contains: 23.75 mg, 47.5 mg, 95 mg
or 190 mg metoprolol succinate corresponding to 25 mg, 50
mg, 100 mg or
200 mg metoprolol tartarate respectively.*
For a complete list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Controlled release tablet

Controlled release tablets 25 mg: White, oval with a size of 5.5 mm × 10.5 mm, bisected, marked A/ß. *Controlled release tablets 50 mg:* White, round with a diameter of 9 mm, bisected, marked A/mO. The score mark is not intended to divide the tablet into two equal doses. It is only intended to facilitate swallowing.

Controlled release tablets 100 mg: White, round with a diameter of 10 mm, bisected, marked A/mS. The score mark is not intended to divide the tablet into two equal doses. It is only intended to facilitate swallowing.

Controlled release tablets 200 mg: White, oval with a size of 8.5 mm × 17 mm, bisected, marked A/mY. The score mark is not intended to divide the tablet into two equal doses. It is only intended to facilitate swallowing.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

Hypertension. Angina pectoris. Stable symptomatic chronic heart failure with impaired systolic left ventricular function. 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.

4.2 Posology and method of administration

Betalok Zok controlled release tablets are given once daily, preferably in the morning. The controlled release tablets can be divided. They must not be chewed or crushed. The tablets should be swallowed together with at least half a glass of liquid. Concomitant intake of food does not influence the bioavailability.

Dosage should be adjusted individually to avoid bradycardia. The following is valid as

guidelines:

Hypertension

50-100 mg once daily. In patients not responding to 100 mg, the dose could be combined with other antihypertensive agents, preferably diuretics and calcium antagonists of the dihydropyridine type, or increased.

Angina pectoris

100-200 mg once daily. If needed, the dose can be combined with nitrates or increased.

Therapy supplementary to ACE-inhibitors, diuretics and possibly digitalis in stable symptomatic heart failure.

The patients should have a stable chronic heart failure, without acute failure for the last 6 weeks and an essentially unchanged basal therapy for the last 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 Betalok Zok therapy in patients with severe heart failure (NYHA IV) should only be made by physicians especially trained in treatment of heart failure (see section 4.4).

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, and 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 Betalok Zok dose may be necessary. Initial hypotension does not necessarily mean that the dose of Betalok 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

100-200 mg once daily. If needed, the dose can be increased.

Prophylactic therapy after myocardial infarction

As maintenance dosage, 200 mg is given once daily.

Functional heart disorders with palpitations

100 mg once daily. If needed, the dose can be increased.

Migraine prophylaxis

100-200 mg once daily.

Impaired renal function

The elimination rate is insignificantly affected by renal function, and dose adjustment is therefore not needed in impaired renal function.

Impaired hepatic function

Usually Betalok Zok is given in the same dose to patients suffering from liver cirrhosis as to patients with normal liver function. Only when there are signs of very severe impairment of liver function (e.g. shunt-operated patients), a dose reduction should be considered.

Elderly

Dose adjustment is not needed.

Paediatric population

There is limited experience with Betaloc ZOK treatment in children.

4.3 Contraindications

- Cardiogenic shock.
- Sick-sinus syndrome (provided there is no permanent pacemaker).
- AV-block of second and third degree.
- Patients with unstable, not compensated heart failure (pulmonary oedema, hypoperfusion or hypotension), and patients with continuous or intermittent inotropic therapy acting through beta-receptor agonism.
- Symptomatic bradycardia or hypotension. 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.
- In the indication heart failure, patients with repeated supine blood pressure below 100 mmHg should be re-evaluated before treatment is initiated.
- Serious peripheral vascular disease with gangrene threat.
- Hypersensitivity to the active substance, to other beta-blockers or to any of the excipients specified in section 6.1.

4.4 Special warnings and special precautions for use

Intravenous administration of verapamil should not be given to patients treated with beta-blockers.

Metoprolol may aggravate the symptoms of peripheral arterial circulatory disorders e.g. intermittent claudication. Severely impaired renal function. Serious acute conditions with metabolic acidosis.

Concomitant treatment with digitalis.

In patients with Prinzmetal's angina the frequency and the extent of angina attacks may increase due to alpha-receptor mediated contraction of the coronary vessels. For this reason non-selective beta-blockers must not be used in these patients. Beta1-selective receptor blockers should be used with caution.

In bronchial asthma or other chronic obstructive lung diseases, adequate bronchodilating therapy should be given concomitantly. The dose of beta2-stimulants may need to be increased.

During treatment with metoprolol the risk for interfering with carbohydrate metabolism or masking hypoglycaemia is less than with non-selective beta-blockers.

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

Treatment with beta-blockers may aggravate the treatment of an anaphylactic reaction. Adrenaline treatment in normal dose does not always give the expected therapeutic effect. If Betalok Zok is given to a patient with phaeochromocytoma, treatment with an alpha-blocker should be considered.

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 4.2).

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 for treatment of acute myocardial infarction in association with these conditions has therefore not been documented. Use in unstable, not compensated heart failure is contraindicated (see 4.3).

Sudden withdrawal of beta-blockade is hazardous, especially in high-risk patients, may be hazardous and may aggravate chronic heart failure as well as increase the risk of myocardial infarction and sudden death. Any withdrawal of Betalok 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.

Prior to surgery the anaesthetist should be informed that the patient is receiving Betalok Zok. It is not recommended to stop beta-blocker treatment in patients undergoing surgery. Acute initiation of high-dose metoprolol to patients undergoing non-cardiac surgery should be avoided, since it has been associated with bradycardia, hypotension and stroke including fatal outcome in patients with cardiovascular risk factors.

This medicine contains less than 1 mmol sodium (23 mg) per controlled release tablet, that is to say essentially 'sodium-free'.

4.5 Interactions with other medicinal products and other forms of interaction

Metoprolol is a CYP2D6-substrate. Drugs that inhibit CYP2D6 can have an effect on the plasma concentration of metoprolol. Examples of drugs that inhibit CYP2D6 are quinidine, terbinafine, paroxetine, fluoxetine, sertraline, celecoxib, propafenone and difenhydramine. When treatment with these drugs is initiated the dose of Betalok Zok might have to be reduced for patients treated with Betalok Zok.

The following combinations with Betalok Zok should be avoided:

Barbituric acid derivatives: Barbiturates (investigated for pentobarbital) induce the metabolism of metoprolol by enzyme induction.

Propafenone: Upon administration of propafenone to four patients on metoprolol therapy, the plasma concentrations of metoprolol increased 2-5 fold and two patients experienced

side-effects typical of metoprolol. The interaction was confirmed in eight healthy volunteers. The interaction is probably explained by the fact that propafenone, similarly to quinidine, inhibits the metabolism of metoprolol via cytochrome

P450 2D6. The combination is probably difficult to handle since propafenone also has beta-receptor blocking properties.

Verapamil: In combination with beta-receptor blocking drugs (described for atenolol, propranolol and pindolol) verapamil may cause bradycardia and fall in blood pressure. Verapamil and beta-blockers have additive inhibitory effects on AV-conduction and sinusnode function.

The following combinations with Betalok Zok may require modified drug dosage:

Amiodarone: A case report suggests that patients treated with amiodarone may develop pronounced sinus bradycardia when treated simultaneously with metoprolol. Amiodarone has extremely long half-life (around 50 days), which implies that interactions can occur for a long time after withdrawal of the drug.

Antiarrhythmics, class I: Class I-antiarrhythmics and beta-receptor blocking drugs have additive negative inotropic effects which may result in serious haemodynamic side effects in patients with impaired left ventricular function. The combination should also be avoided in “sick sinus syndrome” and pathological AV-conduction. The interaction is best documented for disopyramide.

Non-steroidal anti-inflammatory/antirheumatic drugs: NSAID-antiphlogistics have been shown to counteract the antihypertensive effect of beta-receptor blocking drugs. Primarily, indomethacin has been studied. This interaction probably does not occur with sulindac. A negative interaction study on diclofenac has been performed.

Digitalis glycosides: digitalis glycosides in association with β -blockers, may increase atrioventricular conduction time and may induce bradycardia.

Diphenhydramin: Diphenhydramin decreases (2.5 times) clearance of metoprolol to alpha-hydroximetoprolol via CYP 2D6 in fast hydroxylating persons. The effects of metoprolol are enhanced.

Diltiazem: Diltiazem and beta-receptor blockers have additive inhibitory effects on the AV-conduction and sinusnode function. Pronounced bradycardia has been observed (case reports) during combination treatment with diltiazem.

Epinephrine: There are about ten reports on patients treated with non-selective beta-receptor blockers (including pindolol and propranolol) that developed pronounced hypertension and bradycardia after administration of epinephrine (adrenaline). These clinical observations have been confirmed in studies in healthy volunteers. It has also been suggested that epinephrine in local anesthetics may provoke these reactions upon intravascular administration. The risk is probably less with cardioselective beta-receptor blockers.

Phenylpropanolamine: Phenylpropanolamine (norephedrine) in single doses of 50 mg may increase the diastolic blood pressure to pathological values in healthy volunteers. Propranolol generally counteracts the rise in blood pressure induced by phenylpropanolamine. However, beta-receptor blockers may provoke paradoxical hypertensive reactions in patients who take high doses of phenylpropanolamine.

Hypertensive crises during treatment with only phenylpropanolamine have been described in a couple of cases.

Quinidine: Quinidine inhibits the metabolism of metoprolol in so-called rapid hydroxylators (more than 90% in Sweden) with markedly elevated plasma levels and enhanced beta-blockade as a result. A corresponding interaction might occur with other beta-blockers metabolised by the same enzyme (cytochrome P450 2D6).

Clonidine: The hypertensive reaction when clonidine is suddenly withdrawn may be potentiated by beta-blockers. If concomitant treatment with clonidine is to be discontinued, the beta-blocker medication should be withdrawn several days before clonidine.

Rifampicin: Rifampicin may induce the metabolism of metoprolol resulting in decreased plasma levels.

Patients receiving concomitant treatment with other beta-blockers (i.e. eye drops) or MAO-inhibitors should be kept under close surveillance. In patients receiving beta-receptor blocker therapy, inhalation anaesthetics enhance the cardio-depressant effect. The dosages of oral antidiabetics may have to be readjusted in patients receiving beta-blockers. The plasma concentration of metoprolol can increase when cimetidine or hydralazine are administered simultaneously.

4.6 Fertility, pregnancy and lactation

Pregnancy

Betalok Zok should only be given during pregnancy and lactation when use is considered essential. In general, β -blockers reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion and early labour. It is therefore suggested that appropriate maternofetal monitoring be performed in pregnant women treated with metoprolol. Beta-receptor blockers may cause bradycardia in the foetus and in the new-born infant. This should be considered if these drugs are prescribed in the last trimester and in association with delivery. Betalok Zok should gradually be withdrawn 48-72 hours before planned childbirth. If this is not possible the newborn infant should be supervised during 48-72 hours postpartum for signs and symptoms of beta-blockade (e.g. heart- and lung complications).

Lactation

Metoprolol is concentrated in human breast milk in a quantity that corresponds to approximately three times the quantity found in the plasma of the mother. The risk for harmful reactions with respect to the breast-feeding child seems to be low at therapeutic doses of the medicine. The breast-feeding child should however be observed regarding signs of beta-blockade.

4.7 Effect on ability to drive and use machines

As dizziness and fatigue may occur in Betalok Zok treatment, this should be considered when strict attention is required, e.g. when driving or operating machines.

4.8 Undesirable effects

Adverse reactions occur in approximately 10% of the patients and they are usually dose-related. Adverse reactions, related to metoprolol are presented below according to organ class and frequency. The frequencies are defined as following: very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), less common ($\geq 1/1000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1000$), very rare ($< 1/10,000$) and frequency unknown (cannot be calculated from available data)

Blood and lymphatic system

Rare Thrombocytopenia

Psychiatric disorders

Less common Depression, nightmares, sleeping disturbance

Rare Memory impairment, confusion,
hallucinations, nervousness, anxiety

Frequency unknown Impaired concentration ability

Central and peripheral nervous system

Very common Fatigue

Common Dizziness, headache

Less common Paraesthesiae

Rare Taste disturbances

Frequency unknown Muscular cramps

Eyes

Rare Visual disturbances, dry and/or irritated eyes

Unknown frequency Conjunctivitis-like symptoms

Ears and balance organ

Rare Tinnitus

Heart

Common Peripheral coldness in extremities, bradycardia,
palpitations

Less common Transient aggravation of heart failure,
cardiogenic shock in patients with acute
myocardial infarction

Rare Prolonged AV-conduction time, cardiac arrhythmias

Frequency unknown Gangrene in patients with severe peripheral vascular disorders

Respiratory

Common Shortness of breath when physically active

Less common Bronchospasm in patients with bronchial
asthma or asthmatic problems

Frequency unknown

Rhinitis

Gastrointestinal

Common Abdominal pain, nausea, vomiting, diarrhoea, constipation

Frequency unknown

Dry mouth

Liver and biliary tracts

Rare Elevated transaminases

Frequency unknown Hepatitis

Skin and subcutaneous tissue

Less common Hypersensitivity reactions in the skin

Rare Aggravated psoriasis, photosensitivity reactions, hyperhidrosis, hair loss

Musculoskeletal system and connective tissue *Frequency unknown*
Arthralgia

Reproductive organs and mammary glands

Rare Reversible libido dysfunction

General

Less common Chest pain, oedema, weight gain

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 pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>

4.9 Overdose

Toxicity

7.5 g to an adult caused lethal intoxication. 100 mg to a 5-year old gave no symptoms after gastric lavage. 450 mg to a 12-year old and 1.4 g to an adult gave moderate intoxication, 2.5 g to an adult caused serious intoxication, and 7.5 g to an adult gave very serious intoxication.

Symptom

Cardiovascular symptoms are most important, but in some cases, especially in children and young individuals, CNS symptoms and respiratory depression may dominate. Bradycardia, AV-block I-III, QT-prolongation (exceptional cases), asystole, fall in blood pressure, poor peripheral perfusion, cardiac insufficiency, cardiogenic shock. Respiratory depression, apnoea. Others: Fatigue, confusion, unconsciousness, fine tremor, cramps, perspiration, paraesthesiae, bronchospasm, nausea, vomiting, possibly oesophageal spasm, hypoglycaemia (especially in children) or hyperglycaemia, hyperkalaemia. Effect on the kidneys. Transient myasthenic syndrome. Concomitant ingestion of alcohol antihypertensives, quinidine or barbiturates may aggravate the patient's condition. The first signs of overdosing may be seen 20 minutes to 2 hours after ingestion.

Management

Care should be provided at a unit that can offer suitable support measures, monitoring and supervision. If justified, gastric lavage and/or activated charcoal can be used.

Atropine, adrenoceptor stimulant or pacemaker for treatment of bradycardia and conduction disorders.

Intubation and mechanical ventilation should be done with very broad indication. Pacemaker is option. With circulatory arrest in connection with overdose, resuscitation measures for several hours may be warranted.

Hypotension, acute myocardial infarction and shock should be treated with appropriate volume expansion, administration of glucagon (followed by intravenous infusion of glucagon if necessary), intravenous administration of an adrenoceptor stimulant, such as dobutamine, with the addition of α_1 receptor agonists upon vasodilation. Intravenous use of Ca^{2+} may also be considered.

Bronchospasm can usually be reversed through bronchodilators.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta-receptor blocker,
selective ATC code: C07A B02

Metoprolol is a beta1-selective receptor blocker, i.e. metoprolol affects the beta1-receptors of the heart in lower doses than needed to affect beta2-receptors in peripheral vessels and bronchi. The selectivity for Betalok Zok is dose dependent, but, as the peak plasma concentration for this dosage form is significantly lower compared to the same dose given as ordinary tablets, a higher degree of beta1-selectivity is obtained with the ZOC-dosage form.

Metoprolol has no beta-stimulating effect and has little membrane-stimulating effect. Beta-receptor blockers have negative inotropic and chronotropic effect.

Metoprolol therapy reduces the effect of catecholamines in association with physical and psychic strain and gives lower heart rate, cardiac output and blood pressure. In stress situations with an increased release

of adrenaline from the adrenal glands, metoprolol does not prevent the normal physiological vascular dilation. In therapeutic doses, metoprolol has less contractile effect on the bronchial muscles than non-selective beta-blockers. This property enables treatment of patients with bronchial asthma or other pronounced obstructive lung diseases with metoprolol in combination with beta2-receptor stimulants. Metoprolol influences insulin release and carbohydrate metabolism to less extent than non-selective beta-blockers and therefore it can also be given to patients with diabetes mellitus. The cardiovascular reaction in hypoglycaemia, e.g. tachycardia, is less influenced by metoprolol and the return of blood sugar level to normal is faster than for non-selective beta-receptor blockers.

In hypertension, Betalok Zok lowers the blood pressure significantly for more than 24 hours both in lying and standing position as well as during exercise. In treatment with metoprolol an increase in the peripheral vascular resistance is observed initially. In long-

term treatment, however, the obtained lowering in blood pressure may be due to reduced peripheral vascular resistance and unchanged cardiac output.

Metoprolol reduces the risk of cardiovascular-related deaths in men with moderate/serious hypertension. There is no disturbance in the electrolyte balance.

Effect in chronic heart failure: In MERIT-HF, a survival study comprising 3,991 patients with heart failure (NYHA II-IV) and decreased ejection fraction (≤ 0.40), Betalok 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 (New York Heart Association class and Overall Treatment Evaluation score).

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

In tachyarrhythmias the effect of increased sympatholytic activity is blocked and this gives a lower heart rate primarily by reduced automatism in the pacemaker cells, but also through a prolonged supraventricular conduction time. Metoprolol reduces the risk of reinfarction and cardiac death, especially sudden death after myocardial infarction.

5.2 Pharmacokinetic properties

The Betalok Zok controlled release tablet consists of micro-encapsulated beads of metoprolol succinate, and each bead is a separate depot unit. Each bead is coated with a polymeric membrane, which controls the rate of drug release. The tablet disintegrates rapidly in contact with fluid whereby the beads are dispersed over a large surface in the gastrointestinal tract. The release is independent of the pH of the surrounding fluid and goes on with an almost constant rate for about 20 hours. The dosage form gives an even plasma concentration and effect duration over 24 hours.

The absorption is complete after oral administration and the substance is absorbed along the whole gastrointestinal tract, also in colon. The bioavailability of Betalok Zok is 30-40%. Metoprolol is metabolised in the liver mainly by CYP2D6. Three main metabolites have been identified, though none has a beta-blocking effect of clinical importance. Metoprolol is excreted to approximately 5% in unchanged form via the kidneys, the remaining dose as metabolites.

The pharmacokinetics of metoprolol in children and young adults, 6 – 17 years, resembles that of adults. Clearance of orally given metoprolol (CL/F) increased with linear relation to the bodyweight.

5.3 Preclinical safety data

Metoprolol has been tested clinically to a very large extent. Relevant information for the prescriber can be found in other parts of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

Blister (PVC film and Aluminium foil): Controlled release tablets 25 mg (14's)

HDPE bottles with polypropylene cap: Controlled release tablets 50 mg and 100mg (30's)

6.6 Special precautions for disposal

Not applicable.

7. MARKETING AUTHORIZATION HOLDER

AstraZeneca UK Limited
1 Francis Crick Avenue, Cambridge Biomedical Campus
Cambridge, CB2 0AA, United Kingdom

8. MARKETING AUTHORIZATION NUMBERS

Betalok Zok tablets 25 mg: 14598/R1

Betalok Zok tablets 50 mg: 12435/R1

Betalok Zok tablets 100 mg: 12437/R2

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Betalok Zok tablets 25 mg:

2/24/2003 Betalok Zok tablets

50 mg: 6/30/1999 Betalok Zok

tablets 100 mg: 6/3/1999

10. DATE OF REVISION OF THE TEXT

2020-11-16