

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Metoprolol Medical Valley 25 mg prolonged-release tablets
Metoprolol Medical Valley 50 mg prolonged-release tablets
Metoprolol Medical Valley 100 mg prolonged-release tablets
Metoprolol Medical Valley 200 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablets contains 23.75 mg of metoprolol succinate corresponding to 25 mg metoprolol tartrate.

Each prolonged-release tablets contains 47.5 mg of metoprolol succinate, corresponding to 50 mg of metoprolol tartrate.

Each prolonged-release tablets contains 95 mg of metoprolol succinate, corresponding to 100 mg of metoprolol tartrate.

Each prolonged-release tablets contains 190 mg of metoprolol succinate corresponding to 200 mg of metoprolol tartrate.

Excipient(s) with known effect

25 mg: Each prolonged-release tablet contains 12.8 mg as lactose anhydrous

50 mg: Each prolonged-release tablet contains 24.3 mg lactose anhydrous

100 mg: Each prolonged-release tablet contains 49.5 mg lactose anhydrous

200 mg: Each prolonged-release tablet contains 97.1 mg lactose anhydrous

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet.

<Invented name> 25 mg prolonged-release tablets: White to off white, oval, approx 8.5 mm x 4.5 mm, biconvex prolonged-release tablets, debossed with C on one side and 69 on other side of break line and break line on other side.

<Invented name> 50 mg prolonged-release tablets: White to off white, oval, approx 12.0 mm x 6.0 mm, biconvex prolonged-release tablets, debossed with C on one side and 68 on other side of break line and break line on other side.

<Invented name> 100 mg prolonged-release tablets: White to off white, oval, approx 14.0 mm x 8.0 mm, biconvex prolonged-release tablets, debossed with C on one side and 67 on other side of break line and break line on other side.

<Invented name> 200 mg prolonged-release tablets: White to off white, oval, approx 18.5 mm x 9.5 mm, biconvex prolonged-release tablets, debossed with C on one side and 66 on other side of break line and break line on other side.

The tablets can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults:

- Hypertension
- Angina pectoris
- Cardiac arrhythmias, especially including supraventricular tachycardia, reduction of ventricular rate in atrial fibrillation and in ventricular extrasystoles
- Functional heart disorders with palpitations
- Prevention of cardiac death and reinfarction after the acute phase of myocardial infarction
- Prophylaxis of migraine
- Stable chronic symptomatic heart failure with impaired systolic left ventricular function

Children and adolescents 6-18 years of age:

- Treatment of hypertension.

4.2 Posology and method of administration

Posology

<Invented name> prolonged-release tablets are taken once a day, preferably in the morning.

<Invented name> can be divided into equal doses..

<Invented name> tablets (or the divided halves) should not be chewed or crushed. They 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

47.5-95 mg metoprolol succinate (50 mg-100 mg metoprolol tartrate) once daily.

In patients not responding to 95 mg metoprolol succinate (100 mg metoprolol tartrate), the dose could be combined with other antihypertensive agent, preferably diuretics and calcium antagonists of the dihydropyridine type, or increased to 190 mg metoprolol succinate (200 mg metoprolol tartrate) once daily.

Angina pectoris

95-190 mg metoprolol succinate (100 mg- 200 mg metoprolol tartrate) once daily.

If necessary, the dose can be combined with nitrates.

Cardiac arrhythmias

95-190 mg metoprolol succinate (100-200 mg metoprolol tartrate) once daily.

Functional heart disorders with palpitations

95 mg metoprolol succinate (100 mg metoprolol tartrate) once daily. If needed, the dose may be increased to 190 mg metoprolol succinate (200 mg metoprolol tartrate) once daily.

Preventive treatment after myocardial infarction

As maintenance dosage, 190 mg metoprolol succinate (200 mg metoprolol tartrate) is given once daily.

Prophylaxis of migraine

95-190 mg metoprolol succinate (100-200 mg metoprolol tartrate) once daily.

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 <Invented name> 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 23.75 mg metoprolol succinate (25 mg metoprolol tartrate) once daily.

After two weeks, the dose can be increased to 47.5 mg metoprolol succinate (50 mg metoprolol tartrate) once daily, and thereafter it can be doubled every second week, and the target dose for longterm treatment is 190 mg metoprolol succinate (200 mg metoprolol tartrate) once daily.

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

Recommended initial dose is 11.88 mg metoprolol succinate (12.5 mg metoprolol tartrate) (half a 23.75 mg metoprolol succinate/25 mg metoprolol tartrate 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 23.75 mg metoprolol succinate (25 mg metoprolol tartrate) given once daily. Then, after further two weeks, the dosage can be increased to 47.5 mg metoprolol succinate (50 mg metoprolol tartrate) 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 190 mg metoprolol succinate (200 mg metoprolol tartrate) daily.

In case of hypotension and/or bradycardia, decrease in concomitant medication or lowering of the <Invented name> dose may be necessary. Initial hypotension does not necessarily mean that the dose of <Invented name> 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.

Renal impairment

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

Hepatic impairment

Usually <Invented name> 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

The safety and efficacy of <Invented name> in treating children and adolescents for indications other than hypertension has not yet been determined. There is no data available.

The recommended initial dosage in hypertensive patients ≥ 6 years is 0.48 mg/kg metoprolol succinate (0.5 mg/kg metoprolol tartrate) once daily. The final dose administered in milligrams should be the closest approximation of the calculated dose in mg/kg. In patients not responding to 0.48 mg/kg metoprolol succinate, the dose can be increased to 0.95 mg/kg metoprolol succinate (1.0 mg/kg metoprolol tartrate), not exceeding 47.5 mg metoprolol succinate (50 mg metoprolol tartrate). In patients not responding to 0.95 mg/kg metoprolol succinate, the dose can be increased to a maximum daily dose of 1.9 mg/kg metoprolol succinate (2.0 mg/kg metoprolol tartrate). Doses above 190 mg metoprolol succinate (200 mg metoprolol tartrate) once daily have not been studied in children and adolescents.

Efficacy and safety of use in children < 6 years have not been studied. Therefore, metoprolol succinate is not recommended in this age group.

Method of administration

Oral use

4.3 Contraindications

- Hypersensitivity to the active substance, other beta blockers or to any of the excipients listed in section 6.1.
- Patients with unstable not compensated heart failure (pulmonary oedema, hypoperfusion or hypotension) and patients with continuous or intermittent treatment with positive inotropic therapy acting through beta-receptor agonism.
- Symptomatic bradycardia or hypotension. Metoprolol should not be administered to patients with suspected acute myocardial infarction and a heart rate of < 45 beats/min, PQ interval > 0.24 seconds or systolic blood pressure < 100 mmHg.
- In the indication heart failure, patients with repeated supine blood pressure below 100 mmHg should be re-evaluated before treatment is initiated.
- Cardiogenic shock.
- AV-block of second and third degree.
- Sick sinus syndrome (provided there is no permanent pacemaker).
- Serious peripheral arterial disease with gangrene threat.

4.4 Special warnings and 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, the symptoms of severely impaired renal function, serious acute conditions with metabolic acidosis and 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 betablockers 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 <Invented name> the risk for interfering with carbohydrate metabolism or masking hypoglycaemia is less than with non-selective beta-blockers. **Beta-blockers could further increase the risk of severe hypoglycaemia when used concurrently with sulfonylureas. Diabetic patients should be advised to carefully monitor blood glucose levels (see Section 4.5).**

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 <Invented name> 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 special experience and training in this area (see section 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, 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 <Invented name> 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 23.75 mg metoprolol succinate (25 mg metoprolol tartrate) 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 <Invented name>. 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.

Warnings about excipients

<Invented name> contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction 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 <Invented name> might have to be reduced for patients treated with <Invented name>.

The following combinations with <Invented name> 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 <Invented name> 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 (adrenaline) 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 concomitant use of beta-blockers with sulfonylureas could increase the risk of severe hypoglycaemia (see Section 4.4).** The plasma concentration of metoprolol can increase when cimetidine or hydralazine are administered simultaneously.

4.6 Fertility, pregnancy and lactation

Pregnancy

<Invented name> should only be given during pregnancy and lactation when its use is considered essential. In general, beta-blockers reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion and early labour. It is therefore suggested that appropriate maternofoetal monitoring to 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.

<Invented name> 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 betablockade (e.g. heart- and lung complications).

Breast-feeding

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.

Fertility

There are no fertility data available.

4.7 Effects on ability to drive and use machines

As dizziness and fatigue may occur in <Invented name> 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 frequency of the undesirable effects has been ranked according to the MedDRA frequency convention.

- Very common ($\geq 1/10$)
- Common ($\geq 1/100$ to $< 1/10$)
- Uncommon ($\geq 1/1,000$ to $< 1/100$)
- Rare ($\geq 1/10,000$ to $< 1/1,000$)
- Very rare ($< 1/10,000$)
- Not known (cannot be estimated from the available data).

	Very common	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders				thrombocytopenia		
Psychiatric disorders			depression, nightmares, sleep disturbances	memory impairment, confusion, hallucinations, nervousness, anxiety		impaired concentration ability
Nervous system disorders	fatigue	dizziness, headache	paresthesia	taste disturbances		muscle cramps
Eye disorders				visual disturbances, dry and/or irritated eyes		conjunctivitis-like symptoms
Ear and labyrinth disorders				tinnitus		
Cardiac disorders		peripheral coldness in	transient aggravation of	prolonged AV - conduction time,		gangrene in patients

		extremities, bradycardia, palpitations	heart failure, cardiogenic shock in patients with acute myocardial infarction	cardiac arrhythmias		with severe peripheral vascular disorders
Respiratory, thoracic and mediastinal disorders		shortness of breath when physically active	bronchospasm in patients with bronchial asthma or asthmatic problems			rhinitis
Gastrointestinal disorders		nausea, abdominal pain, vomiting, diarrhoea, constipation				dry mouth
Hepatobiliary disorders				elevated transaminases		hepatitis
Skin and subcutaneous tissue disorders			hypersensitivity reactions in the skin	aggravated psoriasis, photosensitivity reactions, hyperhidrosis, hair loss		
Musculoskeletal and connective tissue disorders						arthralgia
Reproductive system and breast disorders				reversible libido dysfunction		
General disorders and administration site conditions			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 **the national reporting system** listed in [Appendix V](#).

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.

Symptoms

Cardiovascular symptoms are most important, but in some cases, especially in children and adolescents, CNS symptoms and respiratory depression may dominate: Bradycardia, AV-block I-III, QT-prolongation (exceptional cases), asystole, hypotension, 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 and 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 facility that can provide appropriate supporting measures, monitoring and supervision.

If justified, gastric lavage and/or activated charcoal can be used.

Atropine, adrenostimulating drugs or pacemaker to treat bradycardia and conduction disorders.

Hypotension, acute myocardial failure and shock should be treated with appropriate volume expansion, administration of glucagon (if necessary followed by an intravenous infusion of glucagon), intravenous administration of α -adrenoceptor stimulating drugs such as dobutamine, with the addition of α -1-receptor agonist in vasodilation. Intravenous use of Ca^{2+} can also be considered. Intubation and mechanical ventilation should be done with very broad indication. Pacemaker is option. In circulatory arrest in connection with overdose, resuscitation actions for several hours could be required.

Bronchospasm can usually be reserved by bronchodilators.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, selective

ATC code: C07AB02

Metoprolol is a beta-1-selective receptor blocker, i.e. metoprolol affects the beta-1 receptors of the heart in lower doses than needed to affect beta-2 receptors in peripheral vessels and bronchi. The selectivity for metoprolol 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 prolonged release 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, metoprolol 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.

Paediatric population

In 144 paediatric patients (6 to 16 years of age) with primarily essential hypertension, metoprolol has been shown in a 4-week study to reduce systolic blood pressure by 5.2 mmHg with 0.2 mg/kg ($p=0.145$), 7.7 mmHg for 1.0 mg/kg ($p=0.027$) and by 6.3 mmHg for 2.0 mg/kg doses ($p=0.049$) with a maximum of 200 mg/day compared to 1.9 mmHg on placebo. For diastolic blood pressure, this reduction was 3.1 mmHg ($p=0.655$), 4.9 mmHg ($p=0.280$), 7.5 mmHg ($p=0.017$), and 2.1 mmHg, respectively. No apparent differences in blood pressure reduction were observed based on age, Tanner stage or race. 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 3991 patients with heart failure (NYHA II-IV) and decreased ejection fraction (≤ 0.40), metoprolol 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 metoprolol 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 prolonged-release tablets consist 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 <Invented name> 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.

Paediatric population

The pharmacokinetic profile of metoprolol in paediatric hypertensive patients aged 6-17 years is similar to the pharmacokinetics described previously in adults. Metoprolol apparent oral clearance (CL/F) increased linearly with body weight.

5.3 Preclinical safety data

-

There are no other relevant preclinical data than those already mentioned in other sections of this summary of product characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The tablets also contain:

Tablet core:

Microcrystalline cellulose (E 460 (i))
Ethylcellulose
Dibutyl Sebacate
Tributyl Acetylcitrate
Poly(vinyl acetate)
Macrogol (E 1521)
Povidone (E 1201)
Silicified Microcrystalline Cellulose
Lactose Monohydrate
Silica, colloidal anhydrous
Magnesium stearate
Hypromellose
Talc (E 553b)

Tablet coating:

Hypromellose
Titanium Dioxide (E 171)
Macrogol (E 1521)
Talc (E 553b)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

<Invented name> 25 mg prolonged-release tablets:

HDPE bottle with aluminium induction seal liner with child resistant cap containing viscose. Pack sizes: 30, 50, 100, 105, 112 prolonged-release tablets

HDPE bottle with aluminium induction seal liner with screw cap containing viscose. Pack sizes: 250 prolonged release tablets

<Invented name> 50 mg prolonged-release tablets:

HDPE bottle with with aluminium induction seal liner child resistant cap containing viscose. Pack sizes: 30, 32, 50, 100, 105, 112 prolonged-release tablets

HDPE bottle with aluminium induction seal liner with screw cap containing viscose. Pack sizes: 250 prolonged release tablets

<Invented name> 100 mg prolonged-release tablets:

HDPE bottle with aluminium induction seal liner with child resistant cap containing viscose. Pack sizes: 30, 50, 100, 105, 112 prolonged-release tablets

HDPE bottle with aluminium induction seal liner with screw cap containing viscose. Pack sizes: 250 prolonged release tablets

<Invented name> 200 mg prolonged-release tablets:

HDPE bottle with aluminium induction seal liner with child resistant cap containing viscose. Pack sizes: 30, 50, 100, 105 prolonged-release tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

2026-02-23