

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Metoprolol Teva 25 mg prolonged-release tablet
Metoprolol Teva 50 mg prolonged-release tablet
Metoprolol Teva 100 mg prolonged-release tablet
Metoprolol Teva 200 mg prolonged-release tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 23.75 mg metoprolol succinate, corresponding to 25 mg metoprolol tartrate. Each prolonged-release tablet contains 47.5 mg metoprolol succinate, corresponding to 50 mg metoprolol tartrate. Each prolonged-release tablet contains 95 mg metoprolol succinate, corresponding to 100 mg metoprolol tartrate. Each prolonged-release tablet contains 190 mg metoprolol succinate, corresponding to 200 mg metoprolol tartrate.

Excipient with known effect: sucrose.

One 23.75 mg prolonged-release tablet contains the maximum of 1.84 mg sucrose.
One 47.5 mg prolonged-release tablet contains the maximum of 3.68 mg sucrose.
One 95 mg prolonged-release tablet contains the maximum of 7.36 mg sucrose.
One 190 mg prolonged-release tablet contains the maximum of 14.72 mg sucrose.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Prolonged-release tablet

Metoprolol Teva 25 mg prolonged-release tablet

White, oblong, biconvex tablet with a break line on both sides (dimension: approx. 9.2 x 4.2 mm).

Metoprolol Teva 50 mg prolonged-release tablet

White, oblong, biconvex tablet with a break line on both sides (dimension: approx. 12.2 x 5.7 mm).

Metoprolol Teva 100 mg prolonged-release tablet

White, oblong, biconvex tablet with a break line on both sides (dimension: approx. 15.2 x 7.2 mm).

Metoprolol Teva 200 mg prolonged-release tablet

White, oblong, biconvex tablet with a break line on both sides (dimension: approx. 19.2 x 9.2 mm).

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults:

- Stable, chronic symptomatic heart failure with reduced systolic left ventricular function.
- Hypertension
- Angina pectoris
- Prevention of cardiac death and re-infarction after the acute phase of myocardial infarction.
- Cardiac arrhythmias, particularly in supraventricular tachycardia, reduction of ventricular rate in atrial fibrillation and in ventricular ectopi.
- Palpitations in the absence of organic heart disease.
- Prophylactic treatment of migraine.

Children and adolescents 6-18 years of age

Treatment of hypertension

4.2 Posology and method of administration

Posology

The dosage should be tailored to the individual and adjusted so that bradycardia is avoided. The following guidelines apply:

Adults

Add-on therapy to ACE-inhibitors, diuretics and possibly digitalis in symptomatic, stable heart failure.

The patients should have stable, chronic heart failure, without acute failure during the past 6 weeks and an essentially unchanged primary therapy over the past two weeks.

Treatment of heart failure with beta-blockers may sometimes cause a **temporary** worsening of the symptoms. In a number of cases it is possible to continue the treatment or reduce the dose, and in other cases it may be necessary to discontinue the treatment. Initial treatment with Metoprolol Teva in patients with severe heart failure (NYHA IV) should only be initiated by a doctor with specific expertise in the treatment of heart failure (see section 4.4).

Dosage in patients with stable heart failure in function class II

The recommended starting dose for the first two weeks is 25 mg once daily. After two weeks the dose may be increased to 50 mg once daily and thereafter may be doubled on alternate weeks. The target dose for long-term treatment is 200 mg once daily.

Dosage in patients with stable heart failure in function class III-IV

The recommended starting dose is 12.5 mg (half a 25 mg tablet) given once daily. The dose should be tailored to the individual and the patient followed-up carefully during upward dose titration as increasing symptoms of heart failure may occur in some patients. After 1-2 weeks the dose may be increased to 25 mg given once daily. After a further two weeks the dose may

then be increased to 50 mg given once daily. For those patients that tolerate a higher dose, a doubling of the dose may occur on alternate weeks up to a maximum dose of 200 mg daily.

In the event of hypotension and/or bradycardia it may be necessary to reduce the dose of other medication or the dose of Metoprolol Teva. Initial hypotension need not mean that the dose of Metoprolol Teva cannot be tolerated in chronic treatment, but upward titration of the dose should not take place until the condition has stabilized, and strict monitoring of renal function may be indicated.

Hypertension

50-100 mg once daily. If the desired effect is not achieved with 100 mg, the dose may be combined with other antihypertensive agents, primarily diuretics and dihydropyridine type calcium antagonists, or the dose increased.

Angina pectoris

100-200 mg once daily. If required the dose may be combined with nitrates or increased.

Arrhythmias

100-200 mg once daily. The dose may be increased as indicated.

Preventive treatment following myocardial infarction

Start therapy only in hemodynamically stabilized patients. After the treatment of the acute phase of the myocardial infarction, the patient is given the maintenance therapy of 200 mg once daily.

Palpitations with no organic cause

100 mg once daily. The dose may be increased as indicated.

Migraine prophylactic

100-200 mg once daily.

Renal impairment

The elimination rate is only slightly influenced by renal function and dose adjustment is therefore not indicated in renal impairment.

Hepatic impairment

Metoprolol may normally be given in the same dose to patients with liver cirrhosis as to patients with normal liver function. A reduction in dose should only be considered in the presence of signs of severely impaired hepatic function (e.g. shunt-operated patients).

The elderly

No dose adjustment required.

Paediatric population

Hypertension

The recommended initial dosage in hypertensive patients ≥ 6 years is 0.5 mg/kg Metoprolol Teva (0,48 mg/kg metoprolol succinate) 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 0.5 mg/kg, the dose can be increased to 1.0 mg/kg (0,95 mg/kg metoprolol succinate), not exceeding 50 mg (47,5 metoprolol succinate). In patients not responding to 1.0 mg/kg, the dose can be increased to a maximum daily dose of 2.0 mg/kg (1.9 mg/kg

metoprolol succinate). Doses above 200 mg (190 mg metoprolol succinate) 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 Teva is not recommended in this age group.

Method of administration

Metoprolol Teva prolonged-release tablets should be given once daily, preferably in the morning.

The prolonged-release tablets are divisible. The tablets should not be chewed or crushed. The tablets should be swallowed with at least half a glass of liquid. Concomitant intake of food does not affect bioavailability.

4.3 Contraindications

- Hypersensitivity to the active substance(s), other beta-receptor blockers or to any of the excipients listed in section 6.1
- Cardiogenic shock.
- Sick sinus syndrome (provided there is no permanent pacemaker).
- Second- and third degree AV-block.
- Patients with unstable, uncompensated heart failure (pulmonary oedema, hypoperfusion or hypotension), and patients undergoing continuous or intermittent inotrope therapy with beta-receptor agonism.
- Symptomatic bradycardia or hypotension.
- Patients with suspected acute myocardial infarction, with a heart rate <45 beats/minute, P-Q interval >0.24 seconds or systolic blood pressure <100 mmHg.
- In patients with heart failure, patients with a repeated lying systolic blood pressure below 100 mmHg should be reassessed before treatment is initiated.
- Severe peripheral vascular disease with gangrene.

4.4 Special warnings and precautions for use

Verapamil should not be administered to patients undergoing treatment with beta blockers.

Metoprolol can exacerbate symptoms of peripheral vascular disease, e.g. intermittent claudication. Severe renal impairment. Severe, acute illness involving metabolic acidosis. Combination treatment with digitalis.

In patients with Prinzmetal's angina, the number and duration of angina attacks may increase due to alpha-receptor mediated vasoconstriction. Consequently, non-selective beta-blockers should not be used for these patients. Beta 1-selective receptor blockers should be used with caution.

Adequate bronchodilator therapy should be administered concomitantly in the presence of bronchial asthma or other chronic obstructive airways disease. If necessary the dose of beta-2-stimulator may need to be increased.

Treatment with Metoprolol Teva may affect carbohydrate metabolism or mask hypoglycaemia, but the risk is less than with non-selective beta-receptor 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).

In rare cases an existing, moderate disturbance in AV-conduction time may be exacerbated (possibly resulting in AV-block).

Treatment with beta-blockers may render treatment of an anaphylactic reaction more difficult. Treatment with adrenaline at the normal dose not always produce the anticipated therapeutic effect. Where Metoprolol Teva is administered to a patient with phaeochromocytoma, treatment with alpha-blockers should be considered. Efficacy/safety data from controlled clinical trials in patients with severe, stable, symptomatic heart failure (NYHA class IV) is limited. Initiation of treatment of heart failure in these patients should, therefore, only be managed by a physician with special experience and expertise within this field (see 4.2).

Patients with symptomatic heart failure associated with acute myocardial infarction and unstable angina pectoris are excluded from the study, which forms the basis of the indication myocardial infarction.

Consequently, efficacy/safety in respect of treatment of acute heart failure in connection with these conditions has not been documented. Use in unstable uncompensated heart failure is contraindicated (see 4.3).

Rapid withdrawal of beta blockade, especially in high risk patients, can be hazardous, and can worsen chronic heart failure and increase the risk of myocardial infarction and sudden death. Therefore, any discontinuation of Metoprolol Teva should, where possible, occur gradually over at least two weeks, whereby the dose is halved step-by-step, until the end dose, where one 25 mg tablet is reduced to half a tablet.

The end dose should be administered for at least four days before discontinuing entirely. If symptoms arise a slower withdrawal is recommended.

Prior to any surgical procedure the anaesthetist should be informed that the patient is receiving Metoprolol Teva. Discontinuation of beta-blocker therapy is not recommended in patients undergoing surgery. Acute high-dose metoprolol administration in patients undergoing non-cardiac surgery should be avoided as it has been associated with bradycardia, hypotension and stroke including death in patients with cardiovascular risk factors.

Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

Metoprolol is a CYP2D6-substrate. Drugs which inhibit CYP2D6 can affect the plasma concentration of metoprolol. Examples of inhibitors of CYP2D6 are quinidine, terbinafine, paroxetine, fluoxetine, sertraline, celecoxib, propafenon and diphenhydramine. On commencement of treatment with these medicinal products in patients being treated with Metoprolol Teva the dose of Metoprolol Teva may need to be reduced.

The following combinations with Metoprolol Teva should be avoided:

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

Propafenon: When propafenon was commenced in four patients, who were then treated with

metoprolol, the plasma concentrations of metoprolol increased 2-5-fold and two patients suffered typical metoprolol side effects. The interaction was confirmed in a study involving eight healthy research subjects. The interaction is probably due to the fact that propafenone, like quinidine, inhibits the metabolism of metoprolol via cytochrome P450 2D6. The combination is probably difficult to manage due to the fact that propafenone also has beta-receptor blocking properties.

Verapamil: In combination with beta-receptor blockers (here described for atenolol, propranolol and pindolol), verapamil may give rise to bradycardia and hypotension. Verapamil and beta-receptor blockers have additive inhibiting effects on AV-conduction and sinus node function.

The following combinations with Metoprolol Teva may require dose adjustment:

Amiodarone: One case history indicates that patients treated with amiodarone can develop severe sinus bradycardia during concomitant treatment with metoprolol. Amiodarone has an extremely long half-life (approximately 50 days), which means that interactions can occur a long time after discontinuation of the preparation.

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

Non-steroidal anti-inflammatory drugs/antirheumatic agents (NSAID): NSAID-type antiphlogistics counteract the antihypertensive effect of beta-receptor blocking agents. Studies have primarily been performed on indomethacin. This interaction is not believed to occur with sulindac. It has not been possible to demonstrate such an interaction in a study relating to diclofenac.

Diphenhydramine: Diphenhydramine reduces (2.5 times) clearance of metoprolol to alpha-hydroxymetoprolol in fast hydroxylators via CYP 2D6, at the same time as the effects of metoprolol are increased.

Digitalis glycosides: Digitalis glycosides in connection with beta-receptor blockers, can increase the atrioventricular conduction time and induce bradycardia.

Diltiazem: Diltiazem and beta-receptor blockers have additive inhibiting effects on AV-conduction and sinus node function. Severe bradycardia has been observed (case reports) in combination therapy with diltiazem.

Epinephrine: A dozen reports exist in respect of severe hypertension and bradycardia in patients treated with non-selective beta-receptor blockers (including pindolol and propranolol), who were administered epinephrine (adrenaline). These clinical observations have been confirmed in studies on healthy research subjects. It has also been suggested that epinephrine, administered as local anaesthesia, may give rise to these reactions on intravascular administration. The risk should be considerably less with cardioselective beta-receptor blockers.

Phenylpropanolamine: Phenylpropanolamine (norephedrine) in single doses of 50 mg may

increase the diastolic blood pressure to pathological levels in healthy research subjects. Generally speaking, propranolol counteracts the rise in blood pressure triggered by phenylpropanolamine. Beta-receptor blockers may, however, trigger paradoxical hypertensive reactions in patients taking high doses of phenylpropanolamine. Hypertensive crises during treatment solely with phenylpropanolamine have been described in a couple of cases.

Quinidine: Quinidine inhibits the metabolism of metoprolol in so-called “fast hydroxylators” (just over 90% in Sweden), with significantly increased plasma values and resultant increase in beta blockade. Similar reaction might be expected to occur with other beta-blockers which are metabolized by the same enzyme (cytochrome P450 2 D6).

Clonidine: The hypertensive reaction on abrupt withdrawal of clonidine may be enhanced by beta-blockers. If combination treatment with clonidine is to be discontinued, the beta-blocker should be withdrawn several days prior to clonidine.

Rifampicin: Rifampicin can induce metabolism of metoprolol, resulting in reduced plasma levels.

Patients concomitantly treated with metoprolol and other beta-receptor blockers (e.g. eye drops) or MAO-inhibitors, should be observed carefully. Inhalation anaesthetics increase the cardiodepressive effects in patients being treated with beta-receptor blockers. The dose of oral antidiabetics may require adjustment in patients receiving treatment with 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 may increase with concomitant administration of cimetidine or hydralazine.

4.6 Fertility, pregnancy and lactation

Pregnancy

Metoprolol Teva should only be administered during pregnancy where absolutely necessary. In general, beta-receptor blockers reduce placental perfusion, which is associated with growth retardation, intrauterine death, miscarriage, and premature birth. Therefore, appropriate monitoring of pregnant women treated with metoprolol and their fetuses is recommended. Beta-receptor blockers may give rise to bradycardia in the foetus and the newborn. Consequently these preparations should be prescribed with consideration of the above during the third trimester of pregnancy and in connection with labour. Metoprolol Teva should be discontinued gradually, 48-72 hours before anticipated labour. If this is not possible, the newborn infant should be monitored for 48-72 hours post partum for signs and symptoms of beta blockade (e.g. heart and lung complications).

Breastfeeding

Metoprolol is concentrated in breast milk in a quantity which approximately corresponds to three times the amount found in the mother's plasma. The risk of harmful reactions to the nursing infant appears to be low with ingestion of therapeutic doses of the drug. The nursing infant should, however, be observed for signs of beta blockade.

4.7 Effects on ability to drive and use machines

As dizziness and tiredness can occur during treatment with Metoprolol Teva, this should be taken into consideration during tasks requiring close concentration, e.g. when driving or

using machines.

4.8 Undesirable effects

Adverse reactions occur in approximately 10% of patients and are most commonly dose related.

The assessment of the side effects is based on the following frequencies:

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 ($\geq 1/10$)	Common $\geq 1/100$ and $< 1/10$	Uncommon $\geq 1/1,000$ and $< 1/100$	Rare $\geq 1/10,000$ and $< 1/1,000$	Not known
Blood and lymphatic system disorders				Thrombocytopenia.	
Metabolism and nutrition disorders			Weight gain.		
Psychiatric disorders			Sleep disturbances, nightmares, depression,	Memory disturbances, confusion, nervousness, anxiety, hallucinations.	Impaired ability to concentrate
Nervous system disorders	Tiredness	Headache, dizziness.	Paresthesia.	Taste disorder	
Eye disorders				Visual disturbances, dry and/or irritated eyes.	Conjunctivitis-like symptoms
Ear and labyrinth disorders				Tinnitus.	
Cardiac disorders		Bradycardia, palpitations.	Chest pain, transient worsening of heart failure, cardiogenic shock in patients with acute myocardial infarction.	Prolonged AV-conduction time, cardiac arrhythmias.	

Vascular disorders		Peripherally cold extremities.			Gangrene in patients with severe peripheral vascular disease
Respiratory, thoracic and mediastinal disorders		Dyspnoea upon exertion	Bronchospasm in patients with bronchial asthma or persistent asthma.		Rhinitis
Gastrointestinal disorders		Abdominal pain, nausea, vomiting, diarrhoea, constipation.			Dry mouth
Hepatobiliary disorders.				Increase in transaminase.	Hepatitis
Skin and subcutaneous tissue disorders			Hypersensitivity reactions affecting the skin	Hyperhidrosis, hair loss, exacerbation of psoriasis, photosensitivity.	
Musculoskeletal and connective tissue disorders					Muscle cramps, arthralgia
Reproductive system and breast disorders				Reversible disturbance in libido.	
General disorders and administration site conditions			Oedema		
Investigations			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

[To be completed nationally]

4.9 Overdose

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

Symptoms: Cardiovascular symptoms are most important, but in certain cases, especially in children, CNS-symptoms and respiratory depression can dominate. Bradycardia, AV-block I-III, QT-prolongation (isolated cases), asystole, hypotension, poor peripheral perfusion, cardiac decompensation, cardiogenic shock. Respiratory depression, apnoea. Other: Tiredness, confusion, unconsciousness, fine tremor, seizures, sweating, paraesthesias, bronchospasm, nausea, vomiting, possible oesophageal spasm, hypoglycaemia (especially in children) or hyperglycaemia, hyperkalaemia. Renal effects. Transient symptoms of myasthenia. Concomitant intake of alcohol, antihypertensives, quinidine or barbiturates, can exacerbate the patient's condition. The first signs of overdose can be observed 20 minutes to 2 hours after ingestion.

Treatment:

The patient must be treated in an institution where the required support treatment, observation and monitoring can be carried out.

If justified, gastric lavage and/or charcoal may be given.

Atropine an adrenoceptor-stimulating drug or pacemaker for the treatment of bradycardia and conduction disorders..

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

Intubation and assisted ventilation should occur based on a very wide indication. Consider pacemaker. In cardiac standstill in connection with overdose, resuscitation measures lasting several hours may be indicated.

Bronchospasm can usually be treated with bronchodilators.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta-receptor blockers, selective

ATC code: C07AB02

Metoprolol is a beta 1-selective receptor blocker, which means that metoprolol affects beta 1-receptors in the heart at lower doses than are required to affect beta 2-receptors in

peripheral vessels and bronchi. The selectivity of Metoprolol Teva is dose-dependent, but since the peak plasma concentration for this preparation is significantly lower than for the same dose of normal tablets, a higher degree of beta 1-selectivity is achieved with the ZOC-preparation.

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

Treatment with metoprolol reduces the effects of catecholamines in connection with physical and psychological stress and causes lower heart rate, cardiac minute volume and blood pressure. In stress conditions, with elevated release of adrenaline from the adrenal glands, metoprolol does not inhibit normal physiological vasodilation. At therapeutic doses metoprolol has less constricting effects on the bronchial musculature than non-selective beta blockers. This property facilitates treatment of patients with bronchial asthma or other significant obstructive pulmonary disease with metoprolol in combination with beta 2-receptor stimulators. Metoprolol affects release of insulin and carbohydrate metabolism to a lesser extent than non-selective beta blockers and, consequently, can also be administered to patients with diabetes mellitus. The cardiovascular reaction in hypoglycaemia, e.g. tachycardia, is influenced to a lesser extent with metoprolol, and normalization of blood sugar levels occurs more rapidly than for non-selective beta receptor blockers.

In the presence of hypertension, Metoprolol Teva causes a significant reduction in blood pressure for more than 24 hours in both supine and standing positions as well as during physical exertion. Initially, treatment with metoprolol causes an elevation in peripheral vascular resistance. With long term treatment, however, the reduction in blood pressure achieved can be attributed to a reduced peripheral vascular resistance and an unchanged cardiac minute volume. Metoprolol reduces the risk of cardiovascular death in individuals with moderate/severe hypertension. Disturbances in electrolyte balance do not occur.

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 with 5.2 mmHg with 0.2 mg/kg ($p=0.145$), 7.7 mmHg for 1.0 mg/kg ($p=0.027$) and 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 ($p=0.655$), 4.9 ($p=0.280$), 7.5 ($p=0.017$) and 2.1 mmHg, respectively. No apparent differences in blood pressure reduction were observed based on age, Tanner stage, or race.

Effects in chronic heart failure: In IMERIT-HF, a survival study involving 3991 patients with heart failure (NYHAI-IV) and reduced ejection fraction (<0.40), Metoprolol Teva has been shown to result in increased survival and reduced need for hospital care. During long-term treatment, the patients experience an overall symptomatic improvement (New York Heart Association class and Overall Treatment Evaluation score).

Treatment with Metoprolol Teva has also been shown to increase the ejection fraction and reduce left-ventricular end-systolic and end-diastolic volume.

In the presence of tachyarrhythmias, Metoprolol Teva blocks the effects of increased sympathetic activity and thereby achieves a lower heart rate, primarily via reduced automaticity in the pacemaker cells, but also via prolonged supraventricular conduction time. Metoprolol reduces the risk of reinfarction and cardiac death, especially sudden death

following myocardial infarction.

5.2 Pharmacokinetic properties

In Metoprolol Teva, metoprolol succinate takes the form of microencapsulated granules, each of which constitutes a prolonged release unit. Each individual granule is coated with a polymer film, which governs release of the drug. The tablets dissolve rapidly in contact with liquid, whereby the coated granules are distributed over a large area of the gastrointestinal tract. Release is independent on pH of the surrounding liquid and occurs at a relatively constant rate over approximately 20 hours. This form of preparation results in even plasma concentrations and duration of action over 24 hours.

Absorption following oral administration is complete and the substance is absorbed throughout the entire gastrointestinal tract, including the colon. The bioavailability of Metoprolol Teva is 30-40%. Metoprolol is chiefly metabolised in the liver by CYP2D6. Three main metabolites have, however, been identified as having no clinical significance in terms of beta-blocking effect. Approximately 5% of metoprolol is eliminated unchanged via the kidneys, the remainder of the dose in the form of metabolites.

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

Non-clinical data revealed no special hazard for humans based on conventional studies of genotoxicity and carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Sugar spheres (containing sucrose and maize starch)

Macrogol

Ethyl acrylate-methyl methacrylate copolymer

Talc

Povidone

Microcrystalline cellulose

Magnesium stearate

Silica, colloidal anhydrous.

Tablet coating:

Hypromellose

Talc

Macrogol

Titanium dioxide (E 171).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25° C.

6.5 Nature and contents of container

Blisterpack (Al/Al)

Metoprolol Teva 25 mg prolonged-release tablet

14, 28, 30, 50x1, 50, 56, 60, 90, 98, 100 prolonged-release tablets.

Metoprolol Teva 50 mg prolonged-release tablet

28, 30, 50x1, 50, 56, 60, 90, 98, 100 prolonged-release tablets.

Metoprolol Teva 100 mg prolonged-release tablet

28, 30, 50x1, 50, 56, 60, 90, 98, 100 prolonged-release tablets.

Metoprolol Teva 200 mg prolonged-release tablet

28, 30, 50, 56, 60, 90, 98, 100 prolonged-release tablets.

Bottle (HDPE) with screw cap (PP)

30, 60, 100, 250, 500 prolonged-release tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special 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 AUTHORISATION

2009-01-30/2014-01-30

10 DATE OF REVISION OF THE TEXT

2026-02-19