1.3.1	Metoprolol
SPC, Labeling and Package Leaflet	Common

SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

1.3.1	Metoprolol
SPC, Labeling and Package Leaflet	Common

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<Invented name> 25 mg prolonged-release tablets
<Invented name> 50 mg prolonged-release tablets
<Invented name> 100 mg prolonged-release tablets
<Invented name> 200 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet

25 mg: white to almost white, oval, biconvex, film coated tablets with score line on one side of the tablet (dimension 8.5 mm x 4.5 mm). On one side of the score line mark C is engraved on the other side of the score line mark 1 is engraved.
The tablet can be divided into equal doses.

50 mg: white to almost white, oval, slightly biconvex, film coated tablets with score line on one side of the tablet (dimension 10.5 mm x 5.5 mm). On one side of the score line mark C is engraved on the other side of the score line mark 2 is engraved.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

100 mg: white to almost white, oval, biconvex, film coated tablets with score line on one side of the tablet (dimension 13 mm x 8 mm). On one side of the score line mark C is engraved on the other side of the score line mark 3 is engraved.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

200 mg: white to almost white, biconvex, capsule shaped film coated tablets with score line on both sides of the tablet (dimension 19 mm x 8 mm). On one side of the tablet on one side of the score line mark C is engraved on the other side of the score line mark 4 is engraved.
The score line is only to facilitate breaking for ease of swallowing and not to divide 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> 25 mg tablet can be divided into equal doses. <Invented name> 50 mg, 100 mg, 200 mg tablet can be halved for ease of swallowing and not to divide 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 (50-100 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 (100-200 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 long-term 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.

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 beta-blockers must not be used in these patients. $Beta_1$-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 $beta_2$-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.

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.

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

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, propafenon 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.

Antiarrythmics, class I: Class I-antiarrythmics 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 additative 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 anestethics may provoke these reactions upon intravasal 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-receptorblocker 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
<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 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).

Breastfeeding
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 (≥ 1/10)
- Common (≥ 1/100 to < 1/10)
- Uncommon (≥ 1/1,000 to < 1/100)
- Rare (≥ 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 imparement, confusion, hallucinations, nervousness,		impaired concentration ability

				anxiety		
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 extremities, bradycardia, palpitations	transient aggravation of heart failure, cardiogenic shock in patients with acute myocardial infarction	prolonged AV - conduction time, cardiac arrythmias		gangrene in patients 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			chest pain, oedema,			

administration site conditions			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 heart 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 -adrenoceptor stimulating drugs such as dobutamine, with the addition of α1-receptor agonists 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 reversed 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 $beta_1$-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 beta$_2$-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 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.

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 ($\leq$ 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 automatisation 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

<Invented name> prolonged-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 <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

Tablet core
Silica, colloidal anhydrous
Cellulose, microcrystalline
Hypromellose
Sodium laurilsulfate
Polysorbate 80
Glycerol
Hydroxypropylcellulose
Ethylcellulose
Sodium stearyl fumarate

Film coating
Hypromellose
Titanium dioxide (E171)
Talc
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

1.3.1	Metoprolol
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6.5 Nature and contents of container

Blister (PVC/PE/PVDC foil - Alu foil): 10, 14, 28, 30, 50, 56, 60, 84, 90, 98 and 100 tablets, in a box.
Polyethylene (HDPE) tablet container with a tamper-evident polypropylene (PP) closure, in a box:

- 250 tablets (25 mg, 50 mg and 100 mg).
- 100 tablets (200 mg).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.
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

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

Detailed information on this medicinal product is available on the website of {name of Member State Agency (link)}

1.3.1	Metoprolol
SPC, Labeling and Package Leaflet	Common

LABELLING

1.3.1	Metoprolol
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PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX for blisters
CARTON BOX for HDPE container

1. NAME OF THE MEDICINAL PRODUCT

<Invented name> 25 mg prolonged-release tablets
<Invented name> 50 mg prolonged-release tablets
<Invented name> 100 mg prolonged-release tablets
<Invented name> 200 mg prolonged-release tablets

metoprolol succinate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release tablet

Blister:
10 prolonged-release tablets
14 prolonged-release tablets
28 prolonged-release tablets
30 prolonged-release tablets
50 prolonged-release tablets
56 prolonged-release tablets
60 prolonged-release tablets
84 prolonged-release tablets
90 prolonged-release tablets
98 prolonged-release tablets
100 prolonged-release tablets

HDPE tablet container for 25 mg, 50 mg, 100 mg:
250 prolonged-release tablets

1.3.1	Metoprolol
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HDPE tablet container for 200 mg:
100 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

1.3.1	Metoprolol
SPC, Labeling and Package Leaflet	Common

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

<Invented name> 25 mg
<Invented name> 50 mg
<Invented name> 100 mg
<Invented name> 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

<Invented name> 25 mg prolonged-release tablets
<Invented name> 50 mg prolonged-release tablets
<Invented name> 100 mg prolonged-release tablets
<Invented name> 200 mg prolonged-release tablets

metoprolol succinate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

1.3.1	Metoprolol
SPC, Labeling and Package Leaflet	Common

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL for HDPE container

1. NAME OF THE MEDICINAL PRODUCT

<Invented name> 25 mg prolonged-release tablets
<Invented name> 50 mg prolonged-release tablets
<Invented name> 100 mg prolonged-release tablets
<Invented name> 200 mg prolonged-release tablets

metoprolol succinate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release tablet

HDPE tablet container for 25 mg, 50 mg, 100 mg:
250 prolonged-release tablets

HDPE tablet container for 200 mg:
100 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

1.3.1	Metoprolol
SPC, Labeling and Package Leaflet	Common

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

1.3.1	Metoprolol
SPC, Labeling and Package Leaflet	Common

1.3.1	Metoprolol
SPC, Labeling and Package Leaflet	Common

PACKAGE LEAFLET

Package leaflet: Information for the user

<Invented name> 25 mg prolonged-release tablets
<Invented name> 50 mg prolonged-release tablets
<Invented name> 100 mg prolonged-release tablets
<Invented name> 200 mg prolonged-release tablets
metoprolol succinate

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What <Invented name> is and what it is used for

Metoprolol succinate belongs to a group of medicines called beta-blockers. Metoprolol reduces the effect of stress hormones on the heart during physical and mental effort. It leads to the heart to beat more slowly (heart rate decreases) in these situations.

<Invented name> is used to **treat**:
- high blood pressure (hypertension),
- a tight pain in the chest caused by insufficient oxygen to the heart (angina pectoris),
- irregular heart rhythm (arrhythmia),
- palpitations (feeling your heart beat) due to non-organic (functional) heart disorders,
- stable heart failure with symptoms (such as shortness of breath or swollen ankles), when taken together with other medicines for heart failure.

<Invented name> is used to **prevent:**
- further heart attacks or damage to the heart after a heart attack,
- migraine.

<Invented name> is used to treat high blood pressure in children and adolescents aged 6 - 18 years.

2. What you need to know before you take <Invented name>

Do not take <Invented name>
- if you are allergic to active substance, other beta-blockers or any of the other ingredients of this medicine (listed in section 6),

- if you have unstable heart failure, are receiving treatment to increase heart contractions,
- if you have heart failure and your blood pressure keeps falling below 100 mmHg,
- if you have a slow heart rate (less than 45 beats/min) or low blood pressure (hypotension),
- if you are in shock caused by heart problems,
- if you have heart conduction problems (2nd or 3rd degree atrioventricular block) or heart rhythm problems (sick sinus syndrome),
- if you suffer from severe blood circulation problems (severe peripheral arterial disease).

Warnings and precautions
Talk to your doctor or pharmacist before taking <Invented name>.
- if you recieve verapamil intravenously
- if you suffer from blood circulation problems which may cause your fingers and toes to tingle or turn pale or blue
- if you have tight chest pain usually occurring during the night (Prinzmetal's angina)
- if you have asthma or other chronic obstructive lung diseases
- low blood sugar levels may be hidden by this medicine (diabetes mellitus)
- if you suffer from a heart conduction disorder (heart block)
- if you are having treatment to reduce allergic reactions. <Invented name> may increase your hypersensitivity to the substances you are allergic to and increase the severity of allergic reactions
- if you have high blood pressure due to a rare tumour in one of your adrenal glands (phaeochromocytoma)
- if you have heart failure
- if you are going to have an anaesthetic please tell your doctor or dentist that you are taking metoprolol tablets
- if you suffer from increased acidity of the blood (metabolic acidosis),
- if you have severely impaired renal function
- if you are being treated with digitalis.

Other medicines and <Invented name>
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
In particular, tell your doctor or pharmacist if you are taking any of the following medicines:
- propafenone, amiodarone, quinidine, verapamil, diltiazem, clonidine, disopyramide and hydralazine, digitalis / digoxin (a medicine for cardiovascular disease),
- barbituric acid derivatives (antiepileptic drug),
- medicines for inflammation (e.g., indomethacin and celecoxib),
- adrenalin (drug in acute shock and severe allergic reaction),
- phenylpropanolamine (medicines to mucous membranes in the nose),
- diphenhydramine (medicines for allergic conditions),
- terbinafine (for fungal infection),
- rifampicin (an antibiotic),
- other beta-blockers (e.g. eye drops),
- MAO inhibitors (used to treat depression and Parkinson's disease),
- inhalation anesthetics (drugs for anesthesia),
- medicines used to treat diabetes, the symptoms of low blood sugar may be hidden,
- cimetidine (a medicine for heartburn and acid regurgitation),
- paroxetine, fluoxetine, and sertraline (medicines for depression).

<Invented name> with food, drink and alcohol
<Invented name> can be taken with or without food.

Pregnancy and breast-feeding

1.3.1	Metoprolol
SPC, Labeling and Package Leaflet	Common

Beta-receptor blockers (including metoprolol) may decrease heart rate in the foetus and in the new-born infant. <Invented name> is not recommended during pregnancy or breastfeeding. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
<Invented name> may make you feel tired and dizzy. Make sure you are not affected before you drive or operate machinery, particularly after changing to another medicine or if taken with alcohol.

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

3. How to take <Invented name>

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

<Invented name> prolonged-release tablet is a dosage form that provides a uniform effect through the day and is to be taken once daily with a glass of water in the morning.
<Invented name> 25 mg prolonged-release tablet can be divided into equal doses.
<Invented name> 50 mg, 100 mg, 200 mg prolonged-release tablet can be halved: for ease of swallowing and not to divide into equal doses.
<Invented name> tablets (or the divided halves) should not be chewed or crushed. They should be swallowed with liquid.

Usual doses:
High blood pressure (hypertension):
47.5-95 mg metoprolol succinate (50-100 mg metoprolol tartrate) once daily.

Tight chest pain (angina pectoris):
95-190 mg metoprolol succinate (100-200 mg metoprolol tartrate) once daily.

Irregular heart beats (arrhythmia):
95-190 mg metoprolol succinate (100-200 mg metoprolol tartrate) once daily.

Preventive therapy following a heart attack.
190 mg metoprolol succinate (200 mg metoprolol tartrate) once daily.

Palpitations due to heart disease:
95 mg metoprolol succinate (100 mg metoprolol tartrate) once daily.

Prevention of migraine:
95-190 mg metoprolol succinate (100-200 mg metoprolol tartrate) once daily.

Patients with stable heart failure in combination with other medications:
The starting dose is 11.88-23.75 mg metoprolol succinate (12.5-25 mg metoprolol tartrate) once daily. The dose can be increased gradually as needed to a maximum 190 mg metoprolol succinate (200 mg metoprolol tartrate) once daily.

Patients with impaired liver function:
If you have **severely** impaired liver function your doctor may adjust the dose. Always follow your

doctor's advice.

Use in children and adolescents
<Invented name> is not recommended for children under 6 years. Always use <Invented name> for children and adolescents exactly as your doctor has told you.
The doctor will calculate the dose that is right for your child. The dosage depends on the weight of the child.
The recommended starting dose for high blood pressure is 0.48 mg/kg metoprolol succinate (0.5 mg/kg metoprolol tartrate) once daily (half a tablet of <Invented name> 25 mg for a child weighing 25 kg). The dose will be adjusted to the nearest tablet strength. In patients not responding to 0.5 mg/kg metoprolol tartrate, the dose can be increased to 0.95 mg/kg metoprolol succinate (1.0 mg/kg metoprolol tartrate), not exceeding 50 mg metoprolol tartrate. In patients not responding to 1.0 mg/kg metoprolol tartrate, the dose may be increased to 1.9 mg/kg metoprolol succinate (2 mg/kg metoprolol tartrate) once daily (1 tablet of <Invented name> 50 mg for a child weighing 25 kg). Doses above 190 mg metoprolol succinate (200 mg metoprolol tartrate) once daily have not been studied in children and adolescents.

If you take more <Invented name> than you should
If you have accidentally taken more than the prescribed dose, contact your nearest casualty department or tell your doctor or pharmacist at once.

If you forget to take <Invented name>
If you forget to take a dose, take it as soon as you remember, then go on as before.
Do not take a double dose to make up for a forgotten tablet.

If you stop taking <Invented name>
Do not suddenly stop taking <Invented name> as this may cause worsening of heart failure and increase the risk of heart attack. Only change the dose or stop the treatment in consultation with your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common (may affect more than 1 in 10 people):
- tiredness.

Common (may affect up to 1 in 10 people):
- headache, dizziness,
- cold hands and feet, slow heartbeat, palpitations,
- shortness of breath with strenuous physical activity,
- feeling sick, abdominal pain, vomiting, diarrhoea, constipation.

Uncommon (may affect up to 1 in 100 people):
- depression, nightmares, difficulty in sleeping,
- pins and needles,
- transient worsening of symptoms of heart failure,
- during a heart attack, blood pressure may be greatly reduced, cardiogenic shock in patients with acute myocardial infarction
- shortness of breath worsening of bronchial problems,

- hypersensitivity reactions of the skin,
- chest pain, fluid retention (swelling), weight gain.

Rare (may affect up to 1 in 1,000 people):
- a reduction in the number of platelets in the blood (thrombocytopenia),
- forgetfulness, confusion, hallucinations, nervousness, anxiety,
- taste changes,
- visual disturbances, dry or irritated eyes,
- heart conduction disturbances, heart rhythm disturbances,
- changes in liver function tests,
- worsening or new psoriasis (a type of skin disease), sensitivity to light, increased sweating, hair loss,
- impotence (inability to obtain an erection),
- ringing in the ears.

Not known (frequency cannot be estimated from the available data):
- impaired concentration,
- muscle cramps,
- eye inflammation,
- tissue death in patients with severe blood circulation problems,
- runny nose,
- dry mouth,
- inflammation of the liver (hepatitis),
- joint pain.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store <Invented name>

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the packaging after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What <Invented name> contains
- The active substance is metoprolol succinate.
  - Each prolonged-release tablet contains 23.75 mg metoprolol succinate equivalent to 25 mg metoprolol tartrate.
  - Each prolonged-release tablet contains 47.5 mg metoprolol succinate equivalent to 50 mg metoprolol tartrate.

- Each prolonged-release tablet contains 95 mg metoprolol succinate equivalent to 100 mg metoprolol tartrate.
- Each prolonged-release tablet contains 190 mg metoprolol succinate equivalent to 200 mg metoprolol tartrate.

- The other ingredients are silica, colloidal anhydrous; cellulose, microcrystalline; hypromellose; sodium laurilsulfate; polysorbate 80; glycerol; hydroxypropylcellulose; ethylcellulose; and sodium stearyl fumarate in the tablet core and hypromellose; titanium dioxide (E171); talc and propylene glycol in the film coating.
  See section 2 "<Invented name> contains sodium".

What <Invented name> looks like and contents of the pack

25 mg: white to almost white, oval, biconvex, film coated tablets with score line on one side of the tablet (dimension 8.5 mm x 4.5 mm). On one side of the score line mark C is engraved on the other side of the score line mark 1 is engraved.

50 mg: White to almost white, oval, slightly biconvex, film coated tablets with score line on one side of the tablet (dimension 10.5 mm x 5.5 mm). On one side of the score line mark C is engraved on the other side of the score line mark 2 is engraved.

100 mg: White to almost white, oval, biconvex, film coated tablets with score line on one side of the tablet (dimension 13 mm x 8 mm). On one side of the score line mark C is engraved on the other side of the score line mark 3 is engraved.

200 mg: White to almost white, biconvex, capsule shaped film coated tablets with score line on both sides of the tablet (dimension 19 mm x 8 mm). On one side of the tablet on one side of the score line mark C is engraved on the other side of the score line mark 4 is engraved.

<Invented name> is available in boxes containing:
- 10, 14, 28, 30, 50, 56, 60, 84, 90, 98 and 100 tablets in blisters.
- 250 tablets in a plastic tablet container with a tamper-evident closure (for 25 mg, 50 mg and 100 mg tablets).
- 100 tablets in a plastic tablet container with a tamper-evident closure (for 200 mg tablets).

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
[To be completed nationally]

This medicine is authorised in the Member States of the European Economic Area under the following names:
[To be completed nationally]

This leaflet was last revised in
[To be completed nationally]

Detailed information on this medicine is available on the website of {name of Member State Agency (link)}