Summary of Products Characteristics

WARNING: ISCHEMIC HEART DISEASE:

Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered metoprolol succinate extended-release tablets, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1 - 2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, metoprolol succinate extended-release tablet administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Warn patients against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue metoprolol succinate extended-release tablet therapy abruptly even in patients treated only for hypertension.

1. NAME OF THE MEDICINAL PRODUCT

Carelio™ 25/50/100/200 mg Retard Tablets

2. QUALITATIVE AND QUANTATIVE COMPOSITION

Active substance: Metoprolol succinate.
Excipients: Excipients for coated tablets.

3. PHARMACEUTICAL FORM

One prolonged-release tablet contains 23.75 mg, 47.5 mg, 95 mg or 190 mg of metoprolol succinate, equivalent to 25 mg, 50 mg, 100 mg or 200 mg of metoprolol tartrate respectively.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension;
Angina pectoris (long-term prophylaxis);
Treatment of NYHA class II and III chronic heart failure, in addition to the standard treatment;
Cardiac arrhythmias, especially supraventricular tachyarrhythmias;
Functional cardiovascular disorders with palpitations;
Prophylaxis of migraine.

4.2 Posology and Method of Administration

Carelio prolonged-release tablets are taken once daily with a glass of water. They can be taken with or without meals. The Carelio prolonged-release tablets have a score line and can be easily divided to allow dosage adjustment. They must not be chewed or crushed.
The following dosage guidelines apply:

Hypertension
Patients with mild or moderate hypertension: M 50 once daily in the morning.
For patients not responding to the Carelio 50 dose, Carelio 100 or Carelio 200 can be administered once daily. If necessary, a further antihypertensive can additionally be prescribed.
Hypertensive patients receiving long-term antihypertensive treatment with 100–200 mg of Carelio once daily have shown a reduced mortality rate including sudden cardiac death as well as a diminished rate of stroke and coronary events (see "Properties/Effects").
Angina pectoris
Carelio 100 or Carelio 200 once daily.
In severe cases, the dose, given once daily, may be further increased.

Chronic heart failure
The dosage of Carelio should be adjusted individually for patients with chronic heart failure who receive the standard therapy.
Starting dose: one 25 mg tablet once daily for 2 weeks.
The recommended starting dose for patients with NYHA class III heart failure is 12.5 mg (half a 25 mg tablet) once daily during the first week of treatment. Thereafter, the dose can be doubled every two weeks of treatment up to a maximum dose of 200 mg once daily. During long-term therapy a maximum dose of 200 mg once daily (or the highest dose tolerated by the individual patient) is recommended.
After each increase in the dose the tolerability of the treatment must be reviewed carefully. In the event of hypotension a reduction in the dose(s) of the concomitant medication(s) will be necessary. Incipient hypotension at the start of therapy does not necessarily mean that long-term therapy will not be tolerated. In this case, however, the patient must take a lower dose until his/her condition is stable.

Heart rhythm disorders
Carelio 100 or Carelio 200 once daily.
If necessary, the dose, given once daily, may be further increased.
Functional cardiovascular disorders with palpitations
Carelio 100 once daily.
If necessary, the dose, given once daily, may be further increased.

Prophylaxis of migraine
Carelio 100 or Carelio 200 once daily.
The treatment should not be stopped abruptly but tapered off, especially in patients with coronary heart disease or after long-term use (See "Warnings and precautions").

Special dosage instructions
Renal insufficiency
An adjustment of the dose is not necessary in patients with renal impairment.
Hepatic impairment
Because of low binding of metoprolol to plasma proteins (5-10%), a dose adjustment is usually not necessary in patients with mild hepatic impairment. However, in patients with

severe hepatic impairment (e.g. patients who have undergone shunt surgery) the dose should be adjusted accordingly.

Elderly patients

An adjustment of the dose is not necessary in elderly patients.

Paediatric population

The recommended starting dose for hypertensive patients > 6 years old is 1.0 mg/kg metoprolol, with a maximum of 50 mg/day. This dose is administered once daily and must be approximated to the Carelio tablets dose strengths. In patients who are not responsive to 1.0 mg/kg, the dose can be increased to a maximum of 2.0 mg/kg. Doses higher than 200 mg once daily have not been studied in children and adolescents.

Efficacy and safety of use in children < 6 years old have not been studied.

4.3 Contraindications

Known hypersensitivity to the active substance metoprolol, other beta-receptor blockers and related derivatives or to any of the excipients.

Second- or third-degree atrioventricular block, congestive heart failure (pulmonary oedema, impaired blood flow or hypotension), concomitant continuous or intermittent inotropic treatment with beta-agonists, clinically manifest sinus bradycardia, sick sinus syndrome (except in patients with a permanent pacemaker), severe peripheral arterial circulatory disturbances, cardiogenic shock, hypotension, bradycardia (pulse rate < 50 beats/min), untreated phaeochromocytoma (see "Warnings and precautions").

In cases of suspected acute myocardial infarction, patients should not take Carelio when the heart rate is < 45 beats/min, the PQ interval is > 0.24 sec or systolic blood pressure is < 100 mmHg. Carelio must also not be taken in the presence of severe heart failure (NYHA class IV).

A history of severe bronchial asthma or severe bronchospasm.

4.4 Special warnings and precautions for use

Patients being treated with beta-receptor blockers should not receive intravenous administrations of verapamil-type calcium antagonists.

In general, patients being treated for hypertension with concomitant obstructive pulmonary disease should not receive beta-receptor blockers. Because of its cardioselectivity, Carelio can still be administered in cases where relevant other medicines such as diuretics are not tolerated or are ineffective. In such circumstances, the lowest effective dose must be chosen and the dosage of the beta-2 stimulant must be re-adjusted.

Carelio may lead to an increased plasma concentration in the presence of genetically induced debrisoquine polymorphism in poor metabolisers.

Metoprolol influences insulin release and carbohydrate metabolism to a lesser extent than non-selective beta-receptor blockers. Unlike non-selective beta-receptor blockers, metoprolol only partially masks hypoglycaemic symptoms in diabetic patients. Caution is nevertheless advised. Diabetic patients should be warned that beta-receptor blockers can attenuate tachycardia associated with hypoglycaemia; other signs of hypoglycaemia such as light-headedness or sweating may not be significantly suppressed. Sweating may even be increased.

Patients with pre-existing cardiac decompensation should be treated for this before and during metoprolol therapy.
A moderate AV conduction abnormality may worsen (to the point of AV block).
Metoprolol may exacerbate peripheral arterial circulatory disorders, mainly due to its antihypertensive effect.
If metoprolol is given to patients with known phaeochromocytoma, an alpha-receptor blocker should be administered concomitantly (see “Contraindications”).
In the case of liver cirrhosis, the bioavailability of beta-receptor blockers may be enhanced, leading to an increase in plasma concentrations.
Abrupt discontinuation of therapy is dangerous, particularly in high-risk patients, and must therefore be avoided.
Beta-receptor blocker medication should not be discontinued during surgery. Before surgery the anaesthetist should be informed that the patient is being treated with metoprolol.
Patients undergoing surgery that does not involve the heart should not receive initial acute treatment with high doses of metoprolol as this has been shown to be associated with bradycardia, hypotension and stroke (including with a fatal outcome) in patients with cardiovascular risk factors.
Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered metoprolol succinate extended-release tablets, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1 - 2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, metoprolol succinate extended-release tablet administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Warn patients against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue metoprolol succinate extended-release tablet therapy abruptly even in patients treated only for hypertension.
If treatment with Carelio is to be stopped, the metoprolol dose must be reduced gradually, if possible, over a minimum of 2 weeks. It is recommended that half the dose (a tablet with a lower active substance content) be taken each time until the final step, when half a 25 mg tablet should be taken. The final dose level of 12.5 mg should be taken for at least 4 days before treatment is stopped. If any symptoms appear during this cessation phase, dose reduction must be slower. Abrupt cessation of the treatment may exacerbate chronic heart failure and increase the risk of myocardial infarction and sudden cardiac death.
Patients with ischaemic heart disease in particular should be closely monitored during this phase. The risk of coronary events including sudden cardiac death may be increased in the beta-receptor blocker cessation phase.
Patients taking beta-receptor blockers who experience anaphylactic shock tend to show a more severe form.

4.5 Interactions with other medicinal products and other forms of interaction
Metoprolol enhances the effect of other antihypertensive medicinal products. Special caution is advised when a beta-receptor blocker is used concomitantly with prazosin for the first time.

Patients concomitantly receiving sympatholytic medicinal products, other beta-receptor blockers (including in the form of eye drops) or MAO inhibitors should be monitored.
Nitroglycerine may enhance the antihypertensive effect of beta-receptor blockers.
If concomitant therapy with clonidine is to be terminated, therapy with the beta-receptor blocker must be ended several days prior to clonidine.
When administered concomitantly with calcium channel blockers (of the verapamil/diltiazem type) and/or anti-arrhythmic agents, attention should be paid to the possible occurrence of a negative inotropic and chronotropic effect. Patients being treated with beta-receptor blockers should not receive calcium channel blockers of the verapamil type intravenously.
Beta-receptor blockers may enhance the negative inotropic and negative dromotropic effects of anti-arrhythmic agents (of the quinidine type and amiodarone).
Inhalation anaesthetics enhance the cardiodepressant effect in the presence of beta-receptor blockade. Digitalis glycosides in association with beta-receptor blockers may increase atrioventricular conduction time and induce bradycardia.
Metoprolol is a substrate of the cytochrome P450 isoenzyme CYP2D6. Substances that act as enzyme inducers and enzyme inhibitors may therefore alter plasma concentrations of metoprolol.
Co-administration with substances that are metabolised by CYP2D6, such as anti-arrhythmic agents (e.g. amiodarone, quinidine), anti-histamine agents (e.g. diphenhydramine), H_2 receptor antagonists (e.g. cimetidine), antidepressants (e.g. clomipramine, selective serotonin reuptake inhibitors [SSRIs]), antipsychotics (e.g. haloperidol) and COX-2 inhibitors (e.g. celecoxib) as well as ritonavir, may increase plasma metoprolol concentrations. This may potentiate the hypotensive effect of Carelio.
This must be taken into consideration when titrating the Carelio dose and attention must be paid to the possibility of adverse effects, e.g. bradycardia.
Rifampicin may reduce the plasma metoprolol level. This may attenuate the hypotensive effect of Carelio.
Alcohol may increase the plasma metoprolol concentration.
Concomitant treatment with indomethacin and some other inhibitors of prostaglandin synthesis may reduce the antihypertensive effect of metoprolol.
When co-administered with adrenaline or other sympathomimetic substances (e.g. as contained in cough remedies, nasal drops and eye drops), cardioselective beta-receptor blockers in therapeutic doses lead to less pronounced hypertensive reactions than non-selective beta-receptor blockers.
Caution is advised when treating diabetic patients with beta-receptor blockers. The diabetic treatment should be adjusted.
Metoprolol may reduce the clearance of other medicinal products (e.g. lidocaine).

4.6 Fertility, Pregnancy and lactation

Pregnancy

Metoprolol should not be taken during pregnancy unless absolutely necessary.
There are no controlled studies in pregnant women.
In general, beta-receptor blockers reduce placental perfusion. Human studies have shown indications of impaired placental perfusion due to metoprolol. This was associated with growth retardation, intrauterine foetal death, abortion and premature labour. It is therefore

recommended that appropriate foetomaternal monitoring be performed in pregnant women treated with metoprolol. Beta-receptor blockers may induce bradycardia in the foetus, neonates or infants when breast feeding.
Animal studies have shown no direct or indirect toxicity affecting pregnancy, embryonic development, foetal health and/or post-natal development.
Due to the possible development of adverse reactions, e.g. bradycardia, hypotension and hypoglycaemia, in the neonate, therapy with metoprolol should be discontinued 48–72 hours before the estimated time of delivery. If this is not possible, newborns must be carefully monitored by a physician for 48–72 hours after delivery.

Lactation
Metoprolol should not be taken while breastfeeding unless absolutely necessary. Metoprolol is excreted in human milk. At the time of delivery, serum concentrations in mother and child are comparable. In breast milk, metoprolol reaches approximately three-fold the serum concentration measured in the mother. With daily oral dosing of 200 mg metoprolol, approximately 225 micrograms are excreted per litre of milk. Although the amount of active substance ingested with breast milk is unlikely to pose any risk to the child, infants should be monitored for signs of beta-blockade.

4.7 Effects on ability to drive and use machines
Carelio may impair patients' reaction time when driving vehicles or using machines, as dizziness is common and fatigue very common.

4.8 Undesirable effects
The following adverse effects have been mainly observed in clinical trials and during daily use of conventional metoprolol tablets (metoprolol tartrate).

Blood and lymphatic system disorders
Very rare: Thrombocytopenia.
Psychiatric disorders
Uncommon: Depression, reduced concentration, somnolence or insomnia, nightmares.
Rare: Nervousness, anxiety.
Very rare: Personality changes (e.g. mood swings), amnesia/impaired memory, confusion, hallucinations.

Nervous system disorders
Very common: Fatigue.
Common: Dizziness, headache.
Uncommon: Paraesthesia, asthenia.
Rare: Muscle weakness.

Eye disorders
Rare: Visual disturbances, dry and irritated eyes, conjunctivitis, reduced lachrymal secretion.

Ear and labyrinth disorders
Very rare: Tinnitus

Cardiac disorders
In common with all anti-arrhythmic agents, the treatment of rhythm disorders with beta-receptor blockers may cause arrhythmogenic effects.
Common: Bradycardia, palpitations.
Uncommon: Transient deterioration of the symptoms of heart failure, cardiogenic shock in patients with acute myocardial infarction, 1st degree AV block, oedema, precordial pain.
Rare: Cardiac conduction disorders, heart failure, cardiac arrhythmias, Raynaud's syndrome.

Vascular disorders
Common: Orthostatic disorders (very rarely associated with syncope), cold hands and feet.
Very rare: Gangrene in patients with existing severe circulatory disturbances.

Respiratory, thoracic and mediastinal disorders
Common: Exertional dyspnoea.
Uncommon: Bronchospasm, even in patients with no known history of obstructive pulmonary disease.
Rare: Rhinitis.

Gastrointestinal disorders
Common: Nausea, abdominal pain, diarrhoea or constipation.
Uncommon: Vomiting.
Rare: Dry mouth.
Very rare: Taste alterations.

Hepatobiliary disorders
Rare: Liver function test abnormalities.
Very rare: Hepatitis.

Skin and subcutaneous tissue disorders
Uncommon: Erythema, rash (in the form of urticaria and psoriasiform and dystrophic skin changes), increased sweating.
Rare: Alopecia.
Very rare: Photosensitivity, exacerbation of psoriasis.

Musculoskeletal and connective tissue disorders
Very rare: Arthralgia.
Uncommon: Muscle cramps.

Reproductive system
Rare: Libido disorders and impotence.

General disorders
Uncommon: Weight gain.

To report any side effect(s):

The National Pharmacovigilance and Drug Safety Centre (NPC)

- Fax: +966-11-205-7662
- Call NPC at +966-11-2038222, Exts: 2317-2356-2353-2354-2334-2340.
- Toll free phone: 8002490000
- E-mail: npc.drug@sfda.gov.sa
- Website: www.sfda.gov.sa/npc

4.9 Overdose
Symptoms
Symptoms of overdose can include hypotension, heart failure, bradycardia/bradyarrhythmia, cardiac conduction abnormalities, atrioventricular block, cardiogenic shock, cardiac arrest, bronchospasm, disorders of consciousness (up to coma), nausea, vomiting and cyanosis.
Concomitant ingestion of alcohol, antihypertensives, quinidine or barbiturates potentiates the signs and symptoms.
Measures
In the event of an overdose, the clinically necessary measures should be taken to stabilise and monitor the patient's vital signs.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
ATC code: C07AB02
Carelio is a controlled-release formulation for once-daily oral administration.
The prolonged-release tablet contains the active substance metoprolol succinate in a large number of pellets. Each pellet is coated with a polymeric membrane. After ingestion, the tablet dissolves very rapidly and the pellets disperse in the gastrointestinal tract and release metoprolol there continuously for 20 hours. The release rate is independent of physiological factors such as pH or peristalsis.
Metoprolol, the active substance in Carelio, is a cardioselective beta-1-receptor blocker. It acts on beta-1 receptors, which are mainly located in the heart, at lower doses than required to influence beta-2 receptors, which are mainly located in the bronchi and peripheral vessels.
Metoprolol does not have a membrane-stabilising effect or a partial agonist effect (intrinsic sympathomimetic activity = ISA).
Metoprolol decreases or inhibits the agonist effects of catecholamines which cause an increase in heart rate, cardiac output, cardiac contractility and blood pressure.

At high endogenous adrenaline levels, metoprolol has less effect on the control of blood pressure than non-selective beta-receptor blockers.
The Carelio formulation leads to a balanced plasma concentration profile and an even effect (β1 blockade) over 24 hours, unlike conventional tablet formulations of beta-1 blockers, including metoprolol tartrate. Marked plasma concentration peaks do not occur on Carelio, which improves clinical beta-1 selectivity. Therefore, adverse effects due to high plasma concentration peaks, such as bradycardia and tired legs, are reduced.
In general, patients being treated for hypertension with concomitant obstructive pulmonary disease should not receive beta-receptor blockers. Metoprolol can be administered in combination with a beta-2 agonist to patients with obstructive pulmonary disease in cases where relevant other medicines such as diuretics are not tolerated or are ineffective. Within the therapeutic dose range, metoprolol counteracts the bronchodilation caused by beta-2 agonists less strongly than a non-selective beta-receptor blocker (see "Warnings and precautions").
Metoprolol influences insulin release and carbohydrate metabolism to a lesser extent than non-selective beta-receptor blockers. Metoprolol affects cardiovascular response to hypoglycaemia less than non-specific beta-receptor blockers. Caution is nevertheless advised. Sensitivity to insulin may decrease on long-term treatment with metoprolol.
Short-term studies show that metoprolol may cause a slight increase in triglyceride levels and a decrease in free fatty acids in the blood. In some cases, a slight decrease in the HDL fraction has been noted, albeit to a lesser extent than with non-selective beta-receptor blockers. A long-term study over several years showed a significant decrease in the cholesterol level.
Metoprolol treatment may enhance quality of life. Improved quality of life has been observed in patients following myocardial infarction. The treatment has also enhanced the quality of life of patients with chronic heart failure.

Effect on hypertension
Metoprolol has an antihypertensive effect in standing as well as lying patients.
At the beginning of treatment, metoprolol initially causes an increase in peripheral vascular resistance.
During long-term treatment, a decrease in total peripheral resistance can be obtained due to the regression of hypertrophy in the peripheral arterial vessels.
Long-term antihypertensive treatment with metoprolol has also achieved a reduction in left-ventricular hypertrophy and at the same time improved ventricular function/filling.
A 4-week study performed in 144 children and adolescents (from 6 to 16 years old) with essential hypertension showed that 1.0 and 2.0 mg/kg metoprolol can reduce placebo-corrected systolic blood pressure (4 to 6 mmHg). A greater decrease in diastolic blood pressure (5 mmHg) was observed with the dose of 2.0 mg/kg versus placebo. No evident differences were found as a function of age, Tanner stage or race.
It has been noted that metoprolol treatment reduces the risk of death from cardiovascular disease in cases of mild to moderate hypertension, especially due to a lowering of the risk factor of "sudden cardiovascular death". At the same time, these patients have a lower risk of non-fatal or fatal myocardial infarction or of stroke.

Effect on angina pectoris
In angina pectoris patients, metoprolol decreases the frequency, the length and the intensity of angina attacks. Moreover, metoprolol increases physical exercise tolerance.
Effect on chronic heart failure
In NYHA class II and III heart failure patients with an ejection fraction of ≤40%, the use of Carelio in addition to the standard treatment leads to an improvement in the survival rate and a reduction in the number of hospitalisations normally required due to a worsening of heart failure.
Carelio treatment has also allowed the following objectives to be achieved:
- improvement in functional NYHA class;
- improvement in quality of life.

Effect on cardiac rhythm
Metoprolol is used to regulate the heart rate in cases of supraventricular tachycardia, atrial fibrillation and ventricular extrasystole.

Effect on functional cardiac disorders with palpitations
Carelio is suitable for the treatment of functional cardiac disorders with palpitations.
Its effect on myocardial infarction has also been studied. In cases of suspected or confirmed myocardial infarction, metoprolol reduces mortality by reducing the risk of sudden cardiac death. This effect may be based on a preventive action against ventricular fibrillation. This inhibitory effect on ventricular fibrillation is probably based on a dual mechanism: on the one hand, a vagal effect, which has a positive influence on the electrophysiological stability of the heart, and, on the other hand, a sympathetically mediated anti-ischaemic effect, which improves contractility and heart rate and stabilises blood pressure.
After early or late intervention, a reduction in mortality has been demonstrated in high-risk patients with a history of cardiovascular disorders as well as in patients with diabetes mellitus and/or congestive heart failure. Metoprolol administration has also been shown to decrease the frequency of non-fatal reinfarctions.
Carelio can also be used as an additional treatment in cases of hyperthyroidism.

5.2 Pharmacokinetic properties
Absorption/Distribution
Metoprolol is almost completely absorbed after oral administration. Due to an extensive first-pass effect, systemic bioavailability following a single oral dose is approximately 50%. The bioavailability of the prolonged-release tablets (delayed active-substance release) is approximately 20-30% lower than that of conventional tablets. This reduction has, however, been shown not to be clinically significant because the “area under the effect curve” (AUEC) in terms of heart rate is identical for both formulations.
Only a small fraction of metoprolol, approximately 5-10%, is bound to plasma proteins.
Each prolonged-release tablet consists of several hundred pellets containing metoprolol succinate. Each pellet is surrounded by a polymeric membrane, which controls metoprolol succinate release.
After ingestion, the prolonged-release tablet disintegrates rapidly and the pellets are released in the gastrointestinal tract. Metoprolol is released continuously for 20 hours. The elimination

half-life of metoprolol is 3.5 hours (see “Metabolism / Elimination”). This is the reason why a balanced plasma level is achieved over a dosing interval of 24 hours. Metoprolol succinate release is independent of pH and peristalsis.

Metabolism
Metoprolol is metabolised by oxidation in the liver, mainly by CYP2D6. Three major metabolites without a pharmacological effect can be identified.
Carelio may lead to an increased plasma concentration in the presence of genetically induced debrisoquine polymorphism in poor metabolisers.

Elimination
As a rule, approximately 95% of an oral dose of metoprolol can be recovered in the urine. Approximately 5% of the dose is excreted unchanged in the urine. In isolated cases, this figure can rise to 30%. The plasma half-life of metoprolol amounts to an average of 3.5 hours (extremes: 1 and 9 hours). Total clearance is about 1 L/min.

Kinetics in special patient groups
Elderly patients
The pharmacokinetics of metoprolol is unchanged in elderly patients compared with younger patients.
Paediatric population
The pharmacokinetic profile of metoprolol in children and adolescents (6 to 16 years old) is similar to that in adults. Oral clearance (CL/F) seems to increase linearly with body weight.
Renal insufficiency
The systemic bioavailability and the elimination of metoprolol are unchanged in patients with impaired renal function. Elimination of the metabolites, however, is reduced. Significant metabolite accumulation has been observed in patients with a glomerular filtration rate (GFR) of about 5 mL/min. However, this does not lead to an increased beta-receptor blocking effect of metoprolol.
Hepatic impairment
Increased plasma levels of unchanged metoprolol must be expected in liver cirrhosis due to the reduced biotransformation rate.
In patients with severe liver cirrhosis and a portacaval shunt, the bioavailability of metoprolol may be increased and total clearance decreased. Patients with a portacaval shunt have a total elimination rate of approximately 0.3 L/min and the area under the plasma concentration/time curve (AUC) values are approximately six times higher than in healthy subjects.

5.3 Preclinical safety data
Mutagenic and tumorigenic potential
Metoprolol has not been subject to extensive mutagenicity testing; previous studies have shown no indications of a mutagenic potential.
Results from carcinogenicity studies in rats and mice are available, from which no tumorigenic potential can be inferred.
Reproductive toxicity

Studies on two animal species (rat, rabbit) have shown no indications of any teratogenic properties for metoprolol.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients:
Tablet core:
Sugar spheres, Macrogol 6000, Polyacrylate dispersion 30%, Talc, Povidone, Cellulose microcrystalline, Magnesium stearate, Colloidal Silica anhydrous.
Tablet coating:
Hypromellose, Talc, macrogol 6000, Titanium dioxide (E171).

6.2 Incompatibilities

None known to date.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 25°C.
Store out of the sight and reach of children.

6.5 Nature and contents of container

Aluminium/Aluminium blister and/or HDPE bottles with PP twist-off caps.
Packs:
Carelio 25: 30, 50, 100.
Carelio 50: 30, 50, 100.
Carelio 100: 30, 50, 100.
Carelio 200: 30, 50, 100.

Not all pack sizes may be marketed.

7. MARKETING AUTHORISATION HOLDER

Acino Pharma AG, Liesberg (Switzerland)

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

October 2018