# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Bisoprololfumaraat ratiopharm 5 mg, tabletten
Bisoprololfumaraat ratiopharm 10 mg, tabletten

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[Bisoprolol fumarate 5 mg tablets]
Each tablet contains 5 mg of bisoprolol fumarate

[Bisoprolol fumarate 10 mg tablets]
Each tablet contains 10 mg of bisoprolol fumarate

Excipient with known effect: Lactose monohydrate

For the full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

Tablet

[Bisoprolol fumarate 5 mg tablets]
The tablets are pale yellow mottled in colour, round and convex with the following identification markings: Break-score on one side with embossing 5 on the right.
The tablet can be divided into equal doses.

[Bisoprolol fumarate 10 mg tablets]
The tablets are mottled beige, round and convex with the following identification markings: Break-score on one side with embossing “1” on the left and embossing “0” on the right.
The tablet can be divided into equal doses.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Hypertension
Chronic stable angina pectoris

### 4.2 Posology and method of administration

Posology

The dosage should be individually adjusted. It is recommended to start with the lowest possible dose. In some patients, 5 mg per day may be adequate. The usual dose is 10 mg once daily with a maximum recommended dose of 20 mg per day.

Renal or liver impairment
In patients with severe renal impairment (creatinine clearance < 20ml/min) and in patients with severe liver function disorders it is recommended that a daily dose of 10 mg bisoprolol fumarate is not exceeded.
Experience with the use of bisoprolol in renal dialysis patients is limited; however there is no evidence that the dosage regimen needs to be altered.

Elderly:
No dosage adjustment is normally required. It is recommended to start with the lowest possible dose.

Paediatric population:
There is no paediatric experience with this medicine, therefore its use cannot be recommended.

Discontinuation of treatment
Treatment should not be stopped abruptly (see section 4.4). The dosage should be diminished slowly by a weekly halving of the dose**.**

Method of administration

Bisoprolol fumarate tablets are for oral administration.
The tablets should be swallowed with a glass of water and should not be chewed or crushed.
The tablets should be taken the same time each day, preferably in the morning, before, with or after breakfast.

## 4.3 Contraindications

Bisoprolol is contraindicated in patients with:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy
- cardiogenic shock
- second or third degree AV block (without a pacemaker)
- sick sinus syndrome
- sinoatrial block
- symptomatic bradycardia
- symptomatic hypotension
- severe bronchial asthma or severe chronic obstructive pulmonary disease
- severe forms of peripheral arterial occlusive disease or severe forms of Raynaud's syndrome
- metabolic acidosis
- untreated phaeochromocytoma (see section 4.4).

## 4.4 Special warnings and precautions for use

Other formulations of bisoprolol containing medicinal products are used in the treatment of chronic heart failure. The use of β-blocking agents in this indication needs a very cautious approach and should be started with a very strict titration phase. In this phase increments are necessary all of which are not possible with the current medicinal product. This product should therefore not be used in the treatment of chronic heart failure.

The initiation of treatment with bisoprolol necessitates regular monitoring, especially when treating elderly patients.
Especially in patients with ischaemic heart disease the cessation of therapy with bisoprolol must not be done abruptly unless clearly indicated, because this may lead to transitional worsening of heart condition. There is a risk of myocardial infarction and sudden death if the treatment is suddenly discontinued in patients with ischaemic heart disease. For more information please refer to section 4.2.

The combination with amiodarone is not recommended considering the risk of contractility automatism and conduction disorders (suppression of compensatory sympathetic reactions).

Combination of bisoprolol with calcium antagonists of the verapamil and diltiazem type, and with centrally-acting antihypertensive drugs is generally not recommended (see also section 4.5)

Bisoprolol must be used with caution in:

- diabetes mellitus showing large fluctuations in blood glucose values Symptoms of hypoglycaemia (e.g. tachycardia, palpitations or sweating).can be masked. Blood glucose levels should be monitored during treatment with bisoprolol
- strict fasting
- ongoing desensitisation therapy
  As with other beta-blockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Epinephrine treatment may not always yield the expected therapeutic effect.
- First degree AV block
- Prinzmetal's angina. Cases of coronary vasospasm have been observed. Despite its high $\beta_1$-selectivity, angina attacks cannot be completely excluded when bisoprolol is administered to patients with Prinzmetal’s angina
- peripheral arterial occlusive disease. Aggravation of symptoms may occur especially when starting therapy.

Patients with psoriasis or with a history of psoriasis should only be given beta-blockers (e.g. bisoprolol) after a careful balancing of benefits against risks.

The symptoms of thyrotoxicosis may be masked under treatment with bisoprolol.

In patients with phaeochromocytoma bisoprolol must not be administered until after alpha-receptor blockade.

In patients undergoing general anaesthesia beta-blockade reduces the incidence of arrhythmias and myocardial ischemia during induction and intubation, and the post-operative period. It is currently recommended that maintenance of beta-blockade be continued peri-operatively. The anaesthetist must be aware of beta-blockade because of the potential for interactions with other drugs, resulting in bradyarrhythmias, attenuation of the reflex tachycardia and the decreased reflex ability to compensate for blood loss. If it is thought necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.

Although cardioselective (beta1) beta-blockers may have less effect on lung function than non-selective beta-blockers, as with all beta-blockers, these should be avoided in patients with obstructive airways diseases, unless there are compelling clinical reasons for their use. Where such reasons exist, bisoprolol may be used with caution. In bronchial asthma or other chronic obstructive pulmonary diseases, which may cause symptoms, concomitant bronchodilating therapy is recommended. Occasionally an increase of the airway resistance may occur in patients with asthma, therefore the dose of beta2-stimulants may have to be increased.

Excipients
This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## 4.5 Interaction with other medicinal products and other forms of interaction

***Combinations not recommended***

Calcium antagonists of the verapamil type and to a lesser extent of the diltiazem type: Negative effect on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients on beta-blocker treatment may lead to profound hypotension and atrio-ventricular block.

Centrally-acting antihypertensive drugs (e.g. clonidine, methyldopa, moxonodine, rilmenidine and reserpine): Concomitant use of centrally-acting antihypertensive drugs may lead to reduction of heart rate and cardiac output and to vasodilatation. Abrupt withdrawal may increase the risk of 'rebound hypertension'.

Monoamine oxidase inhibitors (except MAO-B inhibitors): Enhanced hypotensive effect of the beta-blockers but also risk for hypertensive crisis.

***Combinations to be used with caution***

Class-I antiarrhythmic drugs (e.g. disopyramide, quinidine, lidocaine, phenytoin, flecainide, propafenone): Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased**.**

Class-III antiarrhythmic drugs (e.g. amiodarone): Effect on atrio-ventricular conduction time may be potentiated.

Calcium antagonists of the dihydropyridine type (e.g. nifedipine): Concomitant use may increase the risk of hypotension, and an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.

Parasympathomimetic drugs (e.g. tacrine): Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.

Other β-blocking agents, including topical beta-blockers (e.g. eye drops for glaucoma treatment) may add to the systemic effects of bisoprolol.

Insulin and oral anti-diabetic drugs: Increase of blood sugar lowering effect. Blockade of beta-adrenoceptors may mask symptoms of hypoglycaemia..

Digitalis glycosides: Increase of atrio-ventricular conduction time, reduction in heart rate.

Anaesthetic agents: Attenuation of the reflex tachycardia and increased risk of hypotension (for further information on anaesthesia see also section 4.4).

Non-steroidal anti-inflammatory drugs (NSAIDs): NSAIDs may reduce the hypotensive effect of bisoprolol.

Ergotamine derivatives: exacerbation of peripheral circulatory disturbances.

Beta-sympathomimetics (e.g. isoprenaline, dobutamine): combination with bisoprolol may reduce effects of both agents.

Sympathomimetics that activate both beta- and alpha-adrenoceptors (e.g. epinephrine, norepinephrine): Combination with bisoprolol may lead to blood pressure increase and exacerbated intermittent claudication. Such interactions are considered to be more likely with non-selective β- blockers.

Concomitant use with antihypertensive agents as well as with other drugs with blood pressure lowering potential may increase the risk of hypotension.

Tricyclic antidepressants, barbiturates, phenothiazines as well as other antihypertensive agent: increased blood pressure lowering effect.

Baclofene: increased antihypertensive activity

Amifostine: increased hypotensive activity

***Combinations to be considered***

Mefloquine: increased risk of bradycardia.

## 4.6 Fertility, pregnancy and lactation

***Pregnancy***
Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/newborn.
In general, β-blockers reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse effects (e.g. hypoglycaemia and bradycardia) may occur in the foetus and newborn infant. If treatment with β-adrenoceptor blockers is necessary, $\beta_1$-selective adrenoceptor blockers are preferable.
Bisoprolol is not recommended during pregnancy unless clearly necessary. If treatment is considered necessary, monitoring of the uteroplacental blood flow and foetal growth is recommended. In case of harmful effects on pregnancy or the foetus consideration of alternative treatment is recommended. The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 3 days.

***Breastfeeding***
It is not known whether this drug is excreted in human milk. Therefore, breastfeeding is not recommended during administration of bisoprolol.

## 4.7 Effects on ability to drive and use machines

In a study with coronary heart disease patients, bisoprolol did not impair driving performance. However, due to individual variations in reactions to the drug, the ability to drive a vehicle or to use machines may be impaired. This needs to be considered particularly at start of the treatment, upon change of medication or in conjunction with alcohol.

## 4.8 Undesirable effects

The frequencies of adverse events are ranked according to the following:
Very common (≥ 1/10),
common (≥ 1/100 and < 1/10),
uncommon (≥1/1,000 and < 1/100),
rare (≥ 1/10,000 and <1/1,000),
very rare (< 1/10,000)
not known (cannot be estimated from the available data)

Immune system disorders
Rare: The appearance of antinuclear antibodies with exceptional clinical symptoms such as lupus syndrome, which disappear upon cessation of treatment

Metabolism and nutrition disorders
Rare: Hypoglycaemia

Psychiatric disorders
Uncommon: Sleep disorders, depression
Rare: Nightmares, hallucinations

Nervous system disorders
Common: Tiredness, exhaustion, dizziness*, headache*
Rare: Syncope

Eye disorders
Rare: Reduced tear flow (to be considered if the patient uses lenses)
Very rare: Conjunctivitis

Ear and labyrinth disorders
Rare: Hearing disorders

Cardiac disorders
Uncommon: Bradycardia, AV-conduction disturbances, worsening of pre-existing heart failure

Vascular disorders
Common: Feeling of coldness or numbness of the extremities, Raynaud's disease, increase of existing intermittent claudication, hypotension (especially in patients with heart failure)
Uncommon: orthostatic hypotension

Respiratory, thoracic and mediastinal disorders
Uncommon: Bronchospasm in patients with bronchial asthma or a history of obstructive airway disease
*Rare:* Allergic rhinitis

Gastrointestinal disorders
Common: gastrointestinal complaints such as nausea, vomiting, diarrhoea, constipation, abdominal pain

Hepatobiliary disorders
Rare: Hepatitis

Skin and subcutaneous tissue disorders
Rare: Hypersensitivity reactions such as itching, flush, rash and angioedema
Very rare: β-blocking agents may provoke or worsen psoriasis or induce psoriasis-like rash, alopecia

Musculoskeletal and connective tissue disorders

Uncommon: Muscle weakness, muscle cramps, arthropathy

Reproductive system and breast disorders
Rare: erectile dysfunction

General disorders and administration site conditions
Common: Fatigue*
Uncommon: Asthenia

Investigations
Rare: increased triglycerides, increased liver enzymes (ALAT, ASAT)

*These symptoms especially occur at the beginning of the therapy. They are generally mild and usually disappear within 1 - 2 weeks.

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

***Symptoms***

The most common signs expected with overdose of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. To date, few cases of overdose (maximum: 2,000 mg) with bisoprolol have been reported. Bradycardia and/or hypotension were noted. All patients recovered. There is a wide inter-individual variation in sensitivity to one single high dose of bisoprolol and patients with heart failure are probably very sensitive.

***Management***

In general, if overdose occurs, discontinuation of bisoprolol treatment and supportive and symptomatic treatment is recommended. Resorption of bisoprolol in the gastrointestinal tract must be avoided; gastric lavage, or administration of adsorbents (i.e. activated charcoal), and a laxative agent (i.e. sodium sulphate) may be used. Respiration must be monitored and if necessary, artificial respiration should be initiated.
Based on the expected pharmacological actions and recommendations for other ß-blockers, the following general measures should be considered when clinically warranted:

- Bronchospasm should be counteracted with bronchodilator therapy such as isoprenaline, $\beta_2$- sympathicomimetic drugs and/or aminophylline.
- AV-block (second or third degree) needs careful monitoring and should be treated with isoprenaline infusion or transvenous cardiac pacemaker insertion.
- Acute worsening of heart failure should be treated with i.v. diuretics, positive inotropic agents, vasodilating agents.
- Bradycardia should be treated with intravenous atropine (or M-methyl atropine). If the response is inadequate, isoprenaline or another agent with positive chronotropic properties may be given cautiously. Under some circumstances, transvenous cardiac pacemaker insertion may be necessary.
- Fall in blood pressure or shock should be treated with plasma substituting agents and vasopressors. Intravenous glucagon may be useful.
- Hypoglycaemia can be treated with i.v. glucose.

Limited data suggest that bisoprolol is hardly dialysable.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: selective β1-blocking agents, ATC code: C07AB07

Bisoprolol is a potent, highly β1-selective-adrenoceptor blocking agent devoid of intrinsic sympathomimetic activity. As with other β1-blocking agents, the mode of action in hypertension is unclear. However, it is known that bisoprolol markedly depresses plasma renin activity.

In patients with angina, the blockade of β-receptors reduces heart action and thus reduces oxygen demand.

Bisoprolol possesses similar local anaesthetic properties to propranolol.

### 5.2 Pharmacokinetic properties

Bisoprolol is absorbed almost completely from the gastrointestinal tract. Together with the very small first pass effect in the liver, this results in a high bioavailability of approximately 90%. The plasma protein binding of bisoprolol is about 30 %. The distribution volume is 3.5 l/kg. The total clearance is approximately 15 l/h
The plasma elimination half-life (10-12 hours) provides 24 hours efficacy following a once daily dosage.
Bisoprolol is excreted from the body by two routes, 50 % is metabolised by the liver to inactive metabolites which are then excreted by the kidneys. The remaining 50 % is excreted by the kidneys in an unmetabolised form. Since elimination takes place in the kidneys and the liver to the same extent a dosage adjustment is not required for patients with impaired liver function or renal insufficiency.
The kinetics of bisoprolol are linear and independent of age.
In patients with chronic heart failure (NYHA stage III) the plasma levels of bisoprolol are higher and the half-life is prolonged compared to healthy volunteers. Maximum plasma concentration at steady state is 64±21 ng/ml at a daily dose of 10 mg and the half life is 17±5 hours

### 5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenicity. Like other β-blocking agents, bisoprolol caused maternal (decreased food intake and decreased body weight) and embryo/fetal toxicity (increased incidence of resorptions, reduced birth weight of the offspring, retarded physical development) at high doses was not teratogenic.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

[Bisoprolol fumarate 5 mg tablets]
Lactose monohydrate
Cellulose, microcrystalline
Magnesium stearate
Crospovidone
Yellow PB 22812 (lactose monohydrate and iron oxide yellow (E172))

[Bisoprolol fumarate 10 mg tablets]
Lactose monohydrate
Cellulose, microcrystalline

Magnesium stearate
Crospovidone
Beige PB 27215 (lactose monohydrate and iron oxides red and yellow (E172))

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

3 years

**6.4 Special precautions for storage**

Do not store above 25 °C. Store in the original package in order to protect from moisture.

**6.5 Nature and contents of container**

Bisoprolol fumarate 5mg tablets are presented in:
Blisters formed from rigid aluminium foil heat-sealed with varnish, printed on PVC/PVDC and contained within a printed box board carton. Each carton will contain either; 20, 28, 30, 50, 56, 60, 98, 100x1 (unit dose) or 100 tablets.

Bisoprolol fumarate 10mg tablets are presented in:
Blisters formed from rigid aluminium foil heat-sealed with varnish, printed on PVC/PVDC and contained within a printed box board carton. Each carton will contain either; 20, 28, 30, 50, 56, 60, 84, 90, 98, 100x1 (unit dose) or 100 tablets.

Not all pack size may be marketed.

**6.6 Special precautions for disposal <and other handling>**

No special requirements

## 7. MARKETING AUTHORISATION HOLDER

Ratiopharm GmbH
Graf-Arco-Str. 3
89079 Ulm
Duitsland

## 8. MARKETING AUTHORISATION NUMBER

RVG 24382: Bisoprololfumaraat ratiopharm 5 mg
RVG 24383: Bisoprololfumaraat ratiopharm 10 mg

## 9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 3 april 2000
Datum van laatste verlenging: 3 april 2010

## 10. DATE OF REVISION OF TEXT

Laatste gedeeltelijke wijziging betreft de rubrieken: 1 t/m 3, 4.2 t/m 4.9, 6.1, 6.5 en 8: 19 december 2024