Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bisoprolol Syri Pharma 0.5 mg/ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml oral solution contains 0.5 mg of bisoprolol fumarate.

Excipient(s) with known effect:
Each ml oral solution contains 1.5 mg methyl parahydroxybenzoate (E218), 0.125 mg propyl parahydroxybenzoate (E216) and 0.894 mg sodium.

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Oral solution

Clear, colourless solution

pH of solution: 5.5 - 6.5
Density of solution: 0.9812 - 1.0212 g/ml

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of hypertension.
Treatment of chronic stable angina pectoris.
Treatment of stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides (for additional information see section 5.1).

4.2 Posology and method of administration

Posology
Treatment of hypertension and chronic stable angina pectoris

Adults
The dosage should be individually adjusted. It is recommended to start with 5 mg (10 ml) per day. The usual dose is 10 mg (20 ml) once daily with a maximum recommended dose of 20 mg (40 ml) per day.

Patients with renal or hepatic impairment
In patients with severe renal impairment (creatinine clearance < 20 ml/min) and in patients with severe hepatic function disorders the dose should not exceed 10 mg (20 ml) once daily. This dosage may eventually be divided into halves.

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

Paediatric population
There is no experience with bisoprolol in children, therefore its use cannot be recommended for children.

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.

Treatment of stable chronic heart failure

Adults

Standard treatment of CHF consists of an ACE inhibitor (or an angiotensin receptor blocker in case of intolerance to ACE inhibitors), a beta-blocking agent, diuretics, and when appropriate cardiac glycosides. Patients should be stable (without acute failure) when bisoprolol treatment is initiated.

It is recommended that the treating physician should be experienced in the management of chronic heart failure.

Titration phase

The treatment of stable chronic heart failure with bisoprolol requires a titration phase.

The treatment with bisoprolol is to be started with a gradual uptitration according to the following steps:

- 1.25 mg (2.5 ml) once daily for 1 week, if well tolerated increase to
- 2.5 mg (5 ml) once daily for a further week, if well tolerated increase to
- 3.75 mg (7.5 ml) once daily for a further week, if well tolerated increase to
- 5 mg (10 ml) once daily for the 4 following weeks, if well tolerated increase to
- 7.5 mg (15 ml) once daily for the 4 following weeks, if well tolerated increase to
- 10 mg (20 ml) once daily for the maintenance therapy.

The maximum recommended dose is 10 mg (20 ml) once daily.

Close monitoring of vital signs (heart rate, blood pressure) and symptoms of worsening heart failure is recommended during the titration phase. Symptoms may already occur within the first day after initiating the therapy.

Treatment modification

If the maximum recommended dose is not well tolerated, gradual dose reduction may be considered.

In case of transient worsening of heart failure, hypotension, or bradycardia reconsideration of the dosage of the concomitant medication is recommended. It may also be necessary to temporarily lower the dose of bisoprolol or to consider discontinuation.

The reintroduction and/or uptitration of bisoprolol should always be considered when the patient becomes stable again.

If discontinuation is considered, gradual dose decrease is recommended, since abrupt withdrawal may lead to acute deterioration of the patients condition.

Treatment of stable chronic heart failure with bisoprolol is generally a long-term treatment.

Special populations

Hepatic or renal impairment:

There is no information regarding pharmacokinetics of bisoprolol in patients with chronic heart failure and with impaired hepatic or renal function. Titration of the dose in these populations should therefore be made with particular caution.

Elderly

No dosage adjustment is normally required.

Paediatric population

There is no paediatric experience with bisoprolol in children, therefore its use cannot be recommended for children.

Method of administration

For oral administration only.

Bisoprolol fumarate oral solution should be taken in the morning and can be taken with food.

4.3 Contraindications

Bisoprolol is contraindicated in chronic heart failure patients with:

- acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy

- cardiogenic shock
- second or third degree AV block
- sick sinus syndrome
- sinoatrial block
- symptomatic bradycardia
- symptomatic hypotension
- severe bronchial asthma
- severe forms of peripheral arterial occlusive disease or severe forms of Raynaud's syndrome
- untreated phaeochromocytoma (see section 4.4)
- metabolic acidosis
- hypersensitivity to bisoprolol or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

Special warnings

The treatment of stable chronic heart failure with bisoprolol has to be initiated with a special titration phase (see section 4.2).

Applies to all indications:
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 (see section 4.2).

Precautions
Applies only to hypertension or angina pectoris:
Bisoprolol must be used with caution in patients with hypertension or angina pectoris and accompanying heart failure.
Applies only to chronic heart failure
The initiation and cessation of treatment with bisoprolol necessitates regular monitoring. For the posology and method of administration please (see section 4.2).

There is no therapeutic experience of bisoprolol treatment of heart failure in patients with the following diseases and conditions:

- insulin dependent diabetes mellitus (type I)
- severely impaired renal function
- severely impaired hepatic function
- restrictive cardiomyopathy
- congenital heart disease
- haemodynamically significant organic valvular disease
- myocardial infarction within 3 months

Applies to all indications:
Bisoprolol must be used with caution in:

- bronchospasm (bronchial asthma, obstructive airways diseases)
- diabetes mellitus with large fluctuations in blood glucose values; Symptoms of hypoglycaemia can be masked. Beta-blockers could further increase the risk of severe hypoglycaemia when used concurrently with sulfonylureas. Diabetic patients should be advised to carefully monitor blood glucose levels (see section 4.5).
- 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 does not always yield the expected therapeutic effect.
- first degree AV block
- Prinzmetal's angina: Cases of coronary vasospasm have been observed. Despite its high beta1-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.

- general anaesthesia

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 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.

Combination of bisoprolol with calcium antagonists of the verapamil or diltiazem type, with Class I antiarrhythmic drugs and with centrally acting antihypertensive drugs is generally not recommended, for details please refer to section 4.5.

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, <Invented Name> may be used with caution. In patients with obstructive airways diseases, the treatment with bisoprolol should be started at the lowest possible dose and patients should be carefully monitored for new symptoms (e.g. dyspnea, exercise intolerance, cough). In bronchial asthma or other chronic obstructive lung diseases, which may cause symptoms, bronchodilating therapy should be given concomitantly. Occasionally an increase of the airway resistance may occur in patients with asthma, therefore the dose of beta2-stimulants may have to be increased.

Excipient warnings

Sodium: This medicine contains less than 1 mmol sodium (23 mg) per 20 ml, that is to say essentially 'sodium-free'.

Methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216): May cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

Combinations not recommended:

Applies only to chronic heart failure:

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

- Calcium antagonists of the verapamil type and to a lesser extent of the diltiazem type: Negative influence on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients on β-blocker treatment may lead to profound hypotension and atrioventricular block.
- Centrally acting antihypertensive drugs such as clonidine and others (e.g. methyldopa, moxonodine, rilmenidine): Concomitant use of centrally acting antihypertensive drugs may worsen heart failure by a decrease in the central sympathetic tonus (reduction of heart rate and cardiac output, vasodilation). Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of "rebound hypertension".

Combinations to be used with caution:

Applies only to hypertension or angina pectoris:

- 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.

Applies to all indications:

- Calcium antagonists of the dihydropyridine type (e.g. such as nifedipine, felodipine and amlodipine): 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.
- Class-III antiarrhythmic drugs (e.g. amiodarone): Effect on atrio-ventricular conduction time may be potentiated.
- Topical beta-blockers (e.g. eye drops for glaucoma treatment) may add to the systemic effects of bisoprolol.
- Parasympathomimetic drugs: Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.
- Insulin and oral antidiabetic drugs: Increase of blood sugar lowering effect. Blockade of beta-adrenoreceptors may mask symptoms of hypoglycaemia.The concomitant use of beta-blockers with sulfonylureas could increase the risk of severe hypoglycaemia (see section 4.4).
- Anaesthetic agents: Attenuation of the reflex tachycardia and increase of the risk of hypotension (for further information on general anaesthesia see also section 4.4.).
- Digitalis glycosides: Reduction of heart rate, increase of atrio-ventricular conduction time.
- Non-steroidal anti-inflammatory drugs (NSAIDs): NSAIDs may reduce the hypotensive effect of bisoprolol.
- Beta-sympathomimetic agents (e.g. isoprenaline, dobutamine): Combination with bisoprolol may reduce the effect of both agents.
- Sympathomimetics that activate both beta- and alpha-adrenoceptors (e.g. noradrenaline, adrenaline): Combination with bisoprolol may unmask the alpha-adrenoceptor-mediated vasoconstrictor effects of these agents leading to blood pressure increase and exacerbated intermittent claudication. Such interactions are considered to be more likely with nonselective beta-blockers.
- Sympathomimetic agents: Combination with bisoprolol may reduce the effect of both agents. Higher doses of epinephrine may be necessary for treatment of allergic reactions.
- Concomitant use with antihypertensive agents as well as with other drugs with blood pressure lowering potential (e.g. tricyclic antidepressants, barbiturates, phenothiazines) may increase the risk of hypotension.

Combinations to be considered

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

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/newborn. In general, beta-adrenoceptor 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 fetus and newborn infant. If treatment with beta-adrenoceptor blockers is necessary, beta1-selective adrenoceptor blockers are preferable.

Bisoprolol should not be used during pregnancy unless clearly necessary. If treatment with bisoprolol is considered necessary, the uteroplacental blood flow and the fetal growth should be monitored. In case of harmful effects on pregnancy or the fetus alternative treatment should be considered. The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 3 days.

Breast-feeding
There are no data on the excretion of bisoprolol in human breast milk or the safety of bisoprolol exposure in infants. 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 operate machinery may be impaired. This should be considered particularly at start of treatment and upon change of medication as well as in conjunction with alcohol.

4.8 Undesirable effects

The following definitions apply to the frequency terminology used hereafter:

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)
Frequency not known (cannot be estimated from available data)

Cardiac disorders:
Very common: bradycardia (in patients with chronic heart failure).
Common: worsening of heart failure (in patients with chronic heart failure).
Uncommon: AV-conduction disturbances (in patients with hypertension or angina pectoris); bradycardia (in patients with hypertension or angina pectoris).

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

Nervous system disorders:
Common: 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.

Respiratory, thoracic and mediastinal disorders:
Uncommon: bronchospasm in patients with bronchial asthma or a history of obstructive airways disease.
Rare: allergic rhinitis.

Gastrointestinal disorders:
Common: gastrointestinal complaints such as nausea, vomiting, diarrhoea and constipation.

Skin and subcutaneous tissue disorders:
Rare: hypersensitivity reactions (pruritus, flush, rash and angioedema).
Very rare: alopecia. Beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash

Musculoskeletal and connective tissue disorders:
Uncommon: muscular weakness and cramps.

Vascular disorders:
Common: feeling of coldness or numbness in the extremities, hypotension.
Uncommon: orthostatic hypotension.

General disorders:
Common: asthenia, (in patients with chronic heart failure), fatigue*.
Uncommon: asthenia (in patients with hypertension or angina pectoris).

Hepatobiliary disorders:
Rare: hepatitis.

Reproductive system and breast disorders:
Rare: erectile dysfunction.

Psychiatric disorders:
Uncommon: sleep disorder, depression.
Rare: nightmare, hallucination.

Applies only to hypertension or angina pectoris:
*These symptoms especially occur at the beginning of the therapy. They are generally mild and often disappear within 1 to 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 HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Symptoms
With overdose (e.g. daily dose of 15 mg instead of 7.5 mg) third degree AV-block, bradycardia, and dizziness have been reported**.** In general, the most common signs expected with overdosage of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. There is limited experience with overdose of bisoprolol, only a few cases of overdose with bisoprolol (maximum: 2000 mg) have been reported in patients suffering from hypertension and/or coronary heart disease showing 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. Therefore it is mandatory to initiate the treatment of these patients with a gradual uptitration according to the scheme given in section 4.2.

Management
In general, if overdose occurs, discontinuation of bisoprolol treatment and supportive and symptomatic treatment is recommended.
Based on the expected pharmacologic actions and recommendations for other beta-blockers, the following general measures should be considered when clinically warranted.

Bradycardia: Administer intravenous atropine. If the response is inadequate, isoprenaline or another agent with positive chronotropic properties may be given cautiously. Under some circumstances, transvenous pacemaker insertion may be necessary.

Hypotension: Intravenous fluids and vasopressors should be administered. Intravenous glucagon may be useful.

AV block (second or third degree): Patients should be carefully monitored and treated with isoprenaline infusion or transvenous cardiac pacemaker insertion.

Acute worsening of heart failure: Administer i.v. diuretics, inotropic agents, vasodilating agents.

Bronchospasm: Administer bronchodilator therapy such as isoprenaline, $beta_2$-sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose.

Limited data suggest that bisoprolol is hardly dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, selective
ATC Code: C07AB07

Mechanism of action
Bisoprolol is a highly beta$_1$-selective-adrenoceptor blocking agent, lacking intrinsic stimulating and relevant membrane stabilising activity. It only shows low affinity to the beta$_2$-receptor of the smooth muscles of bronchi and vessels as well as to the beta$_2$-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and beta2-mediated metabolic effects. Its beta1-selectivity extends beyond the therapeutic dose range.

Clinical efficacy and safety
In total 2647 patients were included in the CIBIS II trial. 83% (n = 2202) were in NYHA class III and 17% (n = 445) were in NYHA class IV. They had stable symptomatic systolic heart failure (ejection fraction <35%, based on echocardiography). Total mortality was reduced from 17.3% to 11.8% (relative reduction 34%). A decrease in sudden death (3.6% vs 6.3%, relative reduction 44%) and a reduced number of heart failure episodes requiring hospital admission (12% vs 17.6%, relative reduction 36%) was observed. Finally, a significant improvement of the functional status according to NYHA classification has been shown. During the initiation and titration of bisoprolol hospital admission due to bradycardia (0.53%), hypotension (0.23%), and acute decompensation (4.97%) were observed, but they were not more frequent than in the placebo-group (0%, 0.3% and 6.74%). The numbers of fatal and disabling strokes during the total study period were 20 in the bisoprolol group and 15 in the placebo group.

The CIBIS III trial investigated 1010 patients aged ≥65 years with mild to moderate chronic heart failure (CHF; NYHA class II or III) and left ventricular ejection fraction ≤35%, who had not been treated previously with ACE inhibitors, beta-blockers, or angiotensin receptor blockers. Patients were treated with a combination of bisoprolol and enalapril for 6 to 24 months after an initial 6 months treatment with either bisoprolol or enalapril.

There was a trend toward higher frequency of chronic heart failure worsening when bisoprolol was used as the initial 6 months treatment. Non inferiority of bisoprolol-first versus enalapril-first treatment was not proven in the per-protocol analysis, although the two strategies for initiation of CHF treatment showed a similar rate of the primary combined endpoint death and hospitalization at study end (32.4% in the bisoprolol-first group vs. 33.1 % in the enalapril-first group, per-protocol population). The study shows that bisoprolol can also be used in elderly chronic heart failure patients with mild to moderate disease.

Hypertension or angina pectoris:
Mechanism of action
Antianginal mechanism: Bisoprolol by inhibiting the cardiac beta receptors inhibits the response given to sympathetic activation. That results in the decrease of heart rate and contractility this way decreasing the oxygen demand of the cardiac muscle.

In acute administration in patients with coronary heart disease without chronic heart failure bisoprolol reduces the heart rate and stroke volume and thus the cardiac output and oxygen consumption. In chronic administration the initially elevated peripheral resistance decreases.

Pharmacodynamic effects
Bisoprolol is used for the treatment of hypertension and angina pectoris. As with other Beta-1- blocking agents, the method of acting in hypertension is unclear. However, it is known that Bisoprolol reduces plasma renin activity markedly.

5.2 Pharmacokinetic properties

Absorption
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%.

Distribution
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.

Biotransformation
50% is metabolised by the liver to inactive metabolites which are then excreted by the kidneys.

Elimination

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 the 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.

Linearity
The kinetics of bisoprolol are linear and independent of age.

Special population
Since the 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 pharmacokinetics in patients with stable chronic heart failure and with impaired liver or renal function has not been studied. 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 beta-blockers, 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 but was not teratogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl Parahydroxybenzoate (E218)
Propyl Parahydroxybenzoate (E216)
Sodium Dihydrogen Phosphate Monohydrate (E339)
Disodium Phosphate (anhydrous disodium hydrogen phosphate)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months
Discard 60 days after first opening.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Bottle: 150 ml Ph. Eur. Type III amber glass

Closure: Tamper evident, child-resistant white plastic (polyethylene/polypropylene) cap with (EPE) liner

Dosing Device: A 20 ml oral syringe with 5 ml graduation, 1 ml intermediate graduation and 0.5 ml sub graduation with an adaptor.

Pack size: 150 ml

6.6 Special precautions for disposal

No special requirements for disposal.

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

7 MARKETING AUTHORISATION HOLDER

Syri Pharma Limited t/a Thame Laboratories
Floor 0
1 WML
1 Windmill Lane
Dublin 2
D02 F206
Ireland

8 MARKETING AUTHORISATION NUMBER

PA22697/019/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6th June 2025

10 DATE OF REVISION OF THE TEXT

June 2026