VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Heart failure

Heart failure is a syndrome with symptoms and signs caused by cardiac dysfunction, resulting in reduced longevity. Heart failure patients in general practice are generally 64 to 79 years, more often women (58% to 22%), and more often have a history of hypertension. The prevalence of heart failure can be estimated at 1-2% in the western world and the incidence approaches 5-10 per 1000 person per year. The prevalence and incidence of heart failure, after 50 years old, increase progressively with age (being 1% in age group 55–64 years, 3% in age group 65– 74 years, 7% in age group 75–84 years, and over 10% in those aged >85 years). (4)
In a recent United States population-based study the prevalence of heart failure was 2.2%, increasing from 0.7% in persons aged 45 through 54 years to 8.4% for those aged 75 years or older. (4)

VI.2.2 Summary of treatment benefits

The choice of a hypertensive depends of numerous factors, including the patient's conditions, response and tolerance. In preventing cardiovascular death, heart attack or stroke, bisoprolol should be considered in hypertensive patients who have an indication (e.g., prior heart attack, ischemic heart disease - reduced blood supply to the heart-, heart failure) for their use or in add-on therapy and for those who do not respond adequately to the preferred drug classes. (5) (2)

Studies have shown that bisoprolol reduces mortality and hospitalization rate, while improving hemodynamic and cardiac performance in patients with cardiac heart failure. Bisoprolol may be given as adjunctive therapy with diuretics, angiotensin-converting-enzyme (ACE) inhibitors, and with or without digoxin in patients with cardiac heart failure. (6) Long-term therapy with Bisoprolol with ACE inhibitors, can reduce heart failure symptoms and improve clinical status in patients with chronic heart failure and decrease the risk of death as well as the combined risk of death and hospitalization. These beneficial effects were demonstrated in patients already receiving an ACE inhibitor, suggesting that combined inhibition of the renin-angiotensin system and sympathetic nervous system can produce additive effects. (7) (8)

VI.2.3 Unknowns relating to treatments benefits

The supporting studies included patients between 18-80 years and excluded patients with heart attack in the previous 3 months and renal failure. Therefore, there is no efficacy data available in these populations. The impact of the remained conditions outlined in the safety concerns on efficacy was not specifically studied. (9)

VI.2.4 Summary of safety concerns

Important identified risk

Risk	What is known	Preventability
Worsening of pre-existing heart failure	Bisoprolol action can increase the potential for new-onset or worsening of preexisting condition. (6) Therefore, the treatment of stable chronic heart failure with bisoprolol has to be initiated gradually. Especially in patients with ischaemic heart disease (reduced blood supply to the heart) the cessation of therapy with bisoprolol must not be done abruptly unless clearly indicated, because this may lead to transitional worsening of heart condition. (1)	It is recommended that the treating physician should be experienced in the management of chronic heart failure. The initiation and cessation of treatment with bisoprolol necessitates regular monitoring. (1) Abrupt withdrawal especially in ischaemic heart disease should be avoided. Sudden cessation of bisoprolol can cause a worsening of myocardial ischaemia (reduced blood flow) and therefore gradual reduction of dose is preferable when bisoprolol has to be stopped. Furthermore, ensure heart failure not worsening before increasing dose (10)
AV conduction disturbances (electrical conduction system of the heart)	AV-conduction (electrical conduction system of the heart) disturbances has been reported even if is an uncommon undesirable effect. Bisoprolol is contraindicated in patients with atrioventricular block (conduction between atria and ventricles is disturbed), second or third degree. (6)	In patients with first degree AV block, bisoprolol should be used with caution. (1) Bisoprolol should not be used in combination with calcium antagonists of the verapamil or diltiazem type, with Class I antiarrhythmic drugs (drugs used to suppress abnormal rhythms of the heart) and with centrally acting antihypertensive drugs. (1)
Bradycardia (slow heart rate)	Transient worsening of heart failure, hypotension (low blood pressure), or bradycardia (slow heart rate) may occur. (1) In two	Patients receiving bisoprolol should be monitored for severe bradycardia. During pregnancy, bisoprolol may cause

Risk	What is known	Preventability
	clinical trials with duration of up to 12 weeks, the reported incidence of bradycardia appeared to be dose related. In the 5-20 mg per day group the reported incidence of bradycardia was 0.4%, while the 2.5-40 mg per day group reported 0.5%; placebo (patients with no medicine) was reported at 0%. In some patients, the dizziness can be attributed to orthostatic hypotension (low blood pressure that happens when suddenly standing up from a lying or sitting position) or bradycardia. (6) Concomitant use of drugs that slow the heart rate may increase atrio-ventricular conduction time and the risk of bradycardia as well concomitant use with mefloquine. In pregnancy symptoms of bradycardia are generally to be expected within the first 3 days. (1)	bradycardia and therefore should not be used unless clearly necessary. (1) (9)
Hypotension (low blood pressure)	Orthostatic hypotension has been reported following oral bisoprolol therapy. (6) In 5 of 16 patients given 40 mg bisoprolol as a single dose, a decrease in blood pressure of 20 to 35 mmHg was accompanied by a decrease in heart rate below 50 beats/min. The patients complained of temporary dizziness and tiredness. (6) Dose reduction for 12% (6 of 50) of patients who complained of orthostatic hypotension and intermittent dizziness resulted in correction of the symptom. The patients were receiving chronic	It is recommended that the treating physician should be experienced in the management of chronic heart failure. (1) Bisoprolol should not be used in patients with symptomatic hypotension and patients receiving bisoprolol should be monitored for severe hypotension. (1) Interactions with calcium antagonists of the verapamil type and to a lesser extent of the diltiazem type should be avoided. The following combinations should be used

Risk	What is known	Preventability
	doses of 5 to 40 mg bisoprolol orally daily over 3 months. (6) In some patients, the dizziness can be attributed to orthostatic hypotension. (6)	with caution: calcium antagonists of the dihydropyridine type such as felodipine and amlodipine; Anaesthetic agents and antihypertensive agents as well as with other drugs with blood pressure lowering potential (e.g. tricyclic antidepressants, barbiturates, phenothiazines). (1)
Bronchospasm in patients with bronchial asthma or a history of obstructive airway disease (sudden constriction of the muscles in the lung)	Bisoprolol should usually be avoided in patients with a history of asthma, bronchospasm (sudden constriction of the muscles in the lung) or a history of obstructive airways disease. (10) Furthermore, cases of bronchospasm in patients with bronchial asthma or a history of obstructive airways disease have been reported. (1) However, when there is no alternative, bisoprolol can be given to these patients with caution and under specialist supervision. In such cases the risk of inducing bronchospasm should be appreciated and appropriate precautions taken. (10)	Bisoprolol must be used with caution in bronchospasm (bronchial asthma, obstructive airways diseases) and under specialist supervision. A monitor lung function should be done. (1) (10)
Decreased diabetic control and masking of hypoglycaemic effects (low blood sugar)	Bisoprolol can interfere with carbohydrate metabolism and can produce hypoglycaemia (low blood sugar) or hyperglycaemia (high blood sugar). (11) However, appear to present minimal risk of altering glucose control in nondiabetic patients. Hypoglycemia occurs predominantly in Type-I diabetics (insulin dependent); the hypoglycemic response may be	Bisoprolol must be used with caution in diabetes mellitus with large fluctuations in blood glucose values. Symptoms of hypoglycaemia can be masked. Furthermore may cause neonatal hypoglycaemia and it should not be used in pregnancy. (1) (10) Combinations with insulin and oral antidiabetic drugs increase

Risk	What is known	Preventability
	prolonged, exacerbated, or symptomatically altered. In Type-II diabetics (non-insulin dependent), the incidence of hypoglycemia is much lower. However the alteration in glucose, insulin, and glucagon concentrations in diabetic patients is expected to be small. (6) Regarding pregnancy adverse events like hypoglycaemia may occur in the foetus and newborn infant. Symptoms of hypoglycaemia are generally to be expected within the first 3 days. (1)	of blood sugar lowering effect and bisoprolol may mask symptoms of hypoglycaemia. Therefore these combinations should be used with caution. (1)
Increased sensitivity towards allergens and the severity of anaphylactic reactions (serious allergic reaction) **decreased therapeutic effect of epinephrine treatment**	Bisoprolol may contribute to the severity and reduction in effectiveness of epinephrine drug (used along with emergency medical treatment to treat life-threatening allergic reactions) to treatment of anaphylactic (serious allergic reaction that is rapid in onset and may cause death) or hypersensitivity (allergic) reactions. Normal allergic reactions to known allergens (egg bee venom) may be exaggerated in patients receiving bisoprolol. (6) As with other beta-blockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Furthermore it may reduce response to adrenaline (epinephrine). Therefore, epinephrine treatment does not always yield the expected therapeutic effect. (1) (10)	Caution is advised in patients with a history of hypersensitivity— may increase sensitivity to allergens and result in more serious hypersensitivity response. (10) Bisoprolol must be used with caution in ongoing desensitisation therapy (graduated exposure therapy). (1)
Provoke or worsen psoriasis or induce	Adverse effects like alopecia (hair loss), worsen psoriasis (chronic,	Patients with psoriasis or with a history of psoriasis should only

Risk	What is known	Preventability
psoriasis-like rash (inflammatory disease of the skin)	and recurrent inflammatory disease of the skin characterized by circumscribed, redness of the skin, dry, scaling plaques) or induce psoriasis-like rash (red, itchy) have been reported. (1) Although is incidence is rare a 54-year-old male experienced sudden worsening of psoriasis following the administration of bisoprolol for the treatment of atrial fibrillation (abnormal heart rhythm characterized by rapid and irregular beating). The patient, who had a 20-year history of erythrodermic psoriasis (generalized form of psoriasis), after 72 hours of administration of bisoprolol, he developed inflammation of the skin with deep, skin red plaques. Bisoprolol was discontinued for suspected cause of the psoriasis worsening condition. The patient's condition improved following bisoprolol discontinuation. (6)	be given bisoprolol after carefully balancing the benefits against the risks. (1)

Important potential risks

Risk	What is known	Preventability
Interstitial pneumonitis (severe lung disease with highly productive cough with expectoration of thick mucus, fever, and difficulties breathing)	There are cases report of beta-blockers medicines (class of medications that are particularly used to manage cardiovascular disorders and where bisoprolol is included), namely atenolol, that induce interstitial pneumonitis. (12) (13)	Beta-blockers medicines are generally contra-indicated in patients with airways disease. Reviewers concluded that, given the benefits of beta blockers medicines in cardiovascular disorders, they should not be withheld in patients with risk factors, although patients should be

Risk	What is known	Preventability
		carefully monitored since long-term effects are less clear. (13)
Pulmonary fibrosis (respiratory disease)	Pulmonary fibrosis is a respiratory disease in which the tissue deep in the lungs becomes scarred over time, leading to a thickening of the walls and reduced oxygen supply in the blood. As a consequence patients suffer from perpetual shortness of breath. Therefore Pulmonary fibrosis has significant mortality burden worldwide. (14) It has been reported cases of pulmonary fibrosis with beta-blockers medicines (class of medications that are particularly used to manage cardiovascular disorders and where bisoprolol is included). (13)	Beta-blockers medicines are generally contra-indicated in patients with airways disease. Reviewers concluded that, given the benefits of beta blockers medicines in cardiovascular disorders, they should not be withheld in patients with risk factors, although patients should be carefully monitored since long-term effects are less clear. (13)
Retroperitoneal fibrosis (grow of fibrous tissue in the retroperitoneum, the compartment of the body containing the liver, aorta, renal tract, and various other structures)	The cause of retroperitoneal fibrosis, a rare disease, is unknown. From time to time different drugs have been suggested as a cause, including beta-blockers medicines (class of medications that are particularly used to manage cardiovascular disorders and where bisoprolol is included). (15) It has already been reported cases of retroperitoneal fibrosis with some beta-blockers medicines including atenolol, metoprolol, oxprenolol, propranolol, sotalol, and timolol. Although a review of 100 cases of retroperitoneal fibrosis concluded that beta blockers medicines could not be considered as the cause. (13) The main characteristic and also main complication of this disease is	Not applicable.

Risk	What is known	Preventability
	the absence of symptoms and the progressive involvement of the muscle fibbers that propel urine from the kidneys to the urinary bladder (ureters). (16)	
Peyronie's disease (chronic inflammation in the soft tissue of the penis)	Peyronie's disease is an uncommon condition involving middle-aged men and probably resulting from penile trauma. The injury causes an inflammation in the soft tissue of the penis and ultimately scarring and penile curvature develop. The use of medications such as beta-blockers, like bisoprolol, can sometimes result in Peyronie's disease. In Peyronie's disease, the normal elastic tissue is replaced by scar tissue. The scar tissue in this condition, is not elastic but hard and will not stretch with erection. The side that does not stretch results in penile curvature to the side of the scar. One third of men with Peyronie's disease have painful erections. A low percentage of men with Peyronie's disease develop erectile dysfunction. (17)	The early detection and control of risk factors, namely high cholesterol, abnormally high level of uric acid in the blood (gout or hyperuricemia), and high blood pressure (hypertension), might yield a secondary benefit in preventing the development of Peyronie's disease. (18)

Missing information

Risk	What is known
Paediatric population	There is no paediatric experience with bisoprolol, therefore its use cannot be recommended in paediatric patients. (1)
Use for treatment of heart failure in patients with the following diseases and conditions: **-insulin dependent diabetes mellitus (type I),** **-severely impaired renal**	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 (disease that affect the heart

function **-impaired liver function,** **-restrictive cardiomyopathy,** **-congenital heart disease,** **-haemodynamically significant organic valvular disease,** **-myocardial infarction within 3 months.**	muscle in which the walls are rigid) • congenital heart disease (problem in the structure of the heart) • haemodynamically significant organic valvular disease (condition wherein the heart doesn't function as it should because of any deformity or inflammation) • myocardial infarction (heart attack) within 3 months. (1)

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a SmPC which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package information leaflet (PIL). The measures in these documents are known as routine risk minimisation measures.

The SmPC and the PIL for Theracor 5 mg fil-coated tablets, can be found in the Annex 2 - *Annex 2 - SmPC & PIL.*

This medicine has no additional risk minimisation measures.

VI.2.6. Planned post authorisation development plan (if applicable)

This section is not applicable.

VI.2.7. Summary of changes to the risk management plan over time

Version	Date	Safety Concerns	Comment
0001	10/02/2017	Not applicable.	First version of the RMP
0002	27/07/2017	**Added potential risks:** - Interstitial pneumonitis - Pulmonary fibrosis - Retroperitoneal fibrosis - Peyronie's disease	Revised in response to comments from Denmark regulatory authority

Version	Date	Safety Concerns	Comment
			(RMS)