Products concerned:

Ivabradine Pharmathen (DK/H/2594/001-002/DC)
Ivabradine Genoptim
Vadyrano (DK/H/2601/001-002/DC)

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Angina pectoris is the medical term for chest pain or discomfort due to coronary heart disease. It occurs when the heart muscle doesn't get as much blood as it needs.
Angina usually causes uncomfortable pressure, fullness, squeezing or pain in the center of the chest. Discomfort in the neck, jaw, shoulder, back or arm may also happen. It occurs in both men and women of any age but commonly middle age and older adults. The lifetime risk of developing coronary artery disease (CAD) after 40 years of age is estimated at 49% for men and 32% for women.

Heart cardiac failure (CHF) or **congestive cardiac failure** (CCF) occurs when the heart muscle doesn't pump blood as well as it should. Certain conditions, such as narrowed arteries in the heart (coronary artery disease) or high blood pressure, gradually leave the heart too weak or stiff to fill and pump efficiently. Heart failure is a common and potentially fatal condition. In developed countries, around 2% of adults have heart failure and in those over the age of 65, this increases to 6–10%.

VI.2.2 Summary of treatment benefits

Clinical studies revealed that ivabradine and atenolol both reduced the number of episodes of angina pectoris by two thirds in treated patients. In addition, ivabradine was compared with placebo in 10,917 patients with stable coronary artery disease and left ventricular dysfunction (LVEF <40%). In this study, in patients with a baseline heart rate ≥70 bpm, ivabradine significantly reduced the risk of hospitalization for fatal and nonfatal myocardial infarction by 36%, the risk of coronary revascularization by 30%, and coronary events by 22% compared to patients who have no taken the medicine.
Ivabradine use in patients with heart failure also significantly reduced the risk of hospitalization for worsening heart failure or cardiovascular death compared with patients no treated. These benefits were observed after 3 months of treatment.
Efficacy and tolerability of ivabradine use in long term use has also been studied. The medication was revealed to be well tolerated and efficient.

VI.2.3 Unknowns relating to treatment benefits

There is limited experience of using Ivabradine in patients with severe reduced kidney and liver function and in chronic heart failure patients with intra-ventricular conduction defects.
In addition, safety and efficacy of ivabradine in the treatment of chronic heart failure in children aged below 18 years as well as in pregnant women have not been established

VI.2.4 Summary of safety concerns

Important identified risks		
Risk	**What is known**	**Preventability**
Safety concern in lay language (medical term)	**Brief summary in lay language**	**Whether risk can be minimised or mitigated, and how**
Decrease in heart rate *(Bradycardia)*	Bradycardia is a slow heart rate (resting heart rate of under 60 beats per minute (BPM) in adults). Bradycardia is a common adverse event (may affect more than 1 in 100 people) especially in the first 2 to 3 months after starting treatment. Symptoms related to bradycardia are dizziness, low blood pressure, feeling of weakness or feeling unwell.	Ivabradine is contraindicated in patients with resting heart rate less than 70 beats per minute. Treatment should be avoided in patients taking verabamil or diltiazem. In addition if during treatment, resting heart rate decreases persistently below 50 bpm or the patient experiences symptoms related to bradycardia such as dizziness, fatigue or low blood pressure, the dose must be titrated downward or treatment discontinued.
Luminous visual phenomena *(Phosphenes/ blurred vision)*	A phosphene is a phenomenon characterized by the experience of seeing light without light actually entering the eye. Phosphenes may also be described as a halo, image decomposition (stroboscopic or kaleidoscopic effects), coloured bright lights, or multiple image (retinal persistency). This phenomenon is a very common adverse event (may affect more than 1 in 10 people) especially in the first 2 to 3 months after starting treatment.	Luminous visual phenomena, are linked to the way the medicine works. However, usually are resolved after 2-3 months of treatment. Patients who experienced such as adverse event should be careful when driving or using machines especially when driving at night as changes in light intensity may be suddenly occur.
Irregular heartbeats *(2nd and 3rd degree atrioventricular blocks (AVB II and III)*	Heart block is a problem that occurs with the heart's electrical system. This system controls the rate and rhythm of heartbeats. Heart block occurs	Ivabradine is contraindicated in patients with 3rd degree atrioventricular blocks and should be administered

	if the electrical signal is slowed or disrupted as it moves through the heart. Heart block is classified into three types: first degree, second degree, and third degree. First degree is the least severe, and third degree is the most severe. This adverse event occurs very rarely (may affect less than 1 in 10,000 people)	with caution in case of 2nd degree atrioventricular blocks. Monitoring of heart function is advised.
Increase in blood pressure in patients with high blood pressure *(Increase in blood pressure in hypertensive patients)*	Increase in blood pressure is a common adverse event with ivabradine (may affect more than 1 in 100 people) in patients already suffering from high blood pressure.	Blood pressure should be monitored regularly in patients with heart failure following ivabradine administration
Abnormal heart rhythm characterized by rapid and irregular beating. *(Atrial fibrillation)*	Rapid and irregular beating is a common adverse event with ivabradine treatment (may affect more than 1 in 100 people).	Ivabradine is therefore not recommended in patients with atrial fibrillation. Patient taking concomitantly amiodarone or potent class I anti-arrhythmics should be closely monitored
Abnormal heart tracing in the electrocardiogram *(Prolonged QT interval on ECG)*	Long Q-T syndrome is a disorder of the heart's electrical system. The Q-T interval is the section on the electrocardiogram (ECG) - that represents the time it takes for the electrical system to fire an impulse through the ventricles and then recharge. It is translated to the time it takes for the heart muscle to contract and then recover. This adverse event occurs uncommonly with ivabradine (may affect more than 1 in 1,000 people) and is due to the effect of ivabradine in depressing heart rate	The use of ivabradine in patients with inborn QT syndrome or treated with QT prolonging medicinal products should be avoided.

Important potential risks	
Risk	**What is known (Including reason why it is considered a**

	potential risk)
Supra-ventricular tachyarrhythmia other than atrial fibrillation	Supraventricular tachycardia (SVT) is a common cardiac rhythm disturbance; it usually presents with recurrent episodes of tachycardia, which often increase in frequency and severity with time. In most patients' sudden-onset, rapid and regular palpitations characterise the SVT. Ivabradine is not effective in the treatment or prevention of cardiac arrhythmias and likely loses its efficacy when a tachyarrhythmia occurs (eg. ventricular or supraventricular tachycardia). Ivabradine is therefore not recommended in patients with atrial fibrillation or other cardiac arrhythmias that interfere with sinus node function.
Immune disorders	Ivabradine, as many other drugs, can rarely interact with the immune system and induce a hypersensitivity reaction in the patient. Hypersensitivity reaction symptoms are urticaria, itching, skin reddening and feeling unwell. Ivabradine should be avoided in case of hypersensitivity to the active substance or to any of the excipients listed in SPC
Severe ventricular arrhythmia	Severe ventricular arrhythmias may happen in patients taking ivabradine as per adverse events reported post-marketed of the medication
Myocardial infarction	The preliminary results of a study called SIGNIFY, showed a small but statistically significant increase in the combined risk of cardiovascular death and non-fatal myocardial infarction with ivabradine compared with placebo in a pre-specified subgroup of patients with symptomatic angina CCS (Canadian Cardiovascular Society) class II or more.

Missing information	
Risk	**What is known**
Limited information on use in children under 18 years old	The safety and efficacy of ivabradine in the treatment of chronic heart failure in children aged below 18 years have not been established.
Limited information on use in pregnancy and breastfeeding women	*Women of childbearing potential* Women of child-bearing potential should use appropriate contraceptive measures during treatment. *Pregnancy* There are no or limited amount of data from the use of ivabradine in pregnant women. Studies in animals have shown reproductive toxicity. These studies have shown embryotoxic and teratogenic effects. The potential risk for humans is unknown. Therefore, ivabradine is contra-indicated during pregnancy. *Breast-feeding* Animal studies indicate that ivabradine is excreted in milk. Therefore, ivabradine is contra-indicated during breast-feeding.

	Women that need treatment with ivabradine should stop breast-feeding, and choose for another way of feeding their child.
Severe hepatic insufficiency	No dose adjustment is required in patients with mild hepatic impairment. Caution should be exercised when using ivabradine in patients with moderate hepatic impairment. Ivabradine is contra-indicated for use in patients with severe hepatic insufficiency, since it has not been studied in this population and a large increase in systemic exposure is anticipated.
Severe renal impairment	No dose adjustment is required in patients with renal insufficiency and creatinine clearance above 15 ml/min). No data are available in patients with creatinine clearance below 15 ml/min. Ivabradine should therefore be used with precaution in this population.
Limited information on use in chronic heart failure patients with intra-ventricular conduction defects	The effectiveness and safety of Ivabradine have not been fully studied in this population.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (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 leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan
Not applicable