VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Chronic stable angina pectoris

Stable angina is a heart disease which happens when the heart does not receive enough oxygen. It usually appears between 40 and 50 years of age. The most common symptom of angina is chest pain or chest discomfort. Angina is more likely to happen when the heart beats faster in situations such as exercise, emotion, exposure to the cold or after eating. This increase in heart rate can cause the chest pain in people who suffer from angina.

Chronic heart failure

Chronic heart failure is a heart disease which happens when your heart cannot pump enough blood to the rest of the body. The most common symptoms of heart failure are breathlessness, fatigue, tiredness and ankle swelling.

VI.2.2 Summary of treatment benefits

Carivalan®/Stovadis®/Prescoriel® is a fixed-dose combination of carvedilol and ivabradine, treating angina (except Prescoriel®) and chronic heart failure. This fixed dose combination would allow a simplification of therapy by reducing the number of daily tablets and may enhance the overall therapy compliance.

Chronic stable angina pectoris

The anti-anginal efficacy of carvedilol has been studied in adult patients.

Ivabradine has been studied in five main studies involving over 4,000 adults with long-term stable angina. The medicine was compared with placebo (a dummy treatment) in 360 patients, atenolol (a beta-blocker) in 939 patients and amlodipine (another medicine used to treat angina) in 1,195 patients. It was also compared with placebo as an add-on to atenolol in 889 patients and as an add-on to amlodipine in 728 patients. Each study lasted three to four months. The main measure of effectiveness was how long the patients could exercise on a bicycle or a treadmill, measured at the start and the end of each study.

In patients with long-term stable angina, ivabradine was more effective than placebo at improving exercise capacity and was as effective as atenolol and amlodipine. Ivabradine was also more

effective than placebo when added to atenolol. However, adding ivabradine to amlodipine did not provide an additional benefit.

Chronic heart failure

The efficacy of carvedilol in chronic heart failure has been studied in adult patients.

Ivabradine has been compared with placebo in one main study involving 6,558 patients with long-term moderate to severe heart failure. The main measure of effectiveness was the time until death due to disease of the heart or blood vessels, or hospitalisation due to worsening heart failure.

In patients with long-term heart failure, Ivabradine was more effective than placebo at preventing death due to disease of the heart or blood vessels or hospitalisation due to worsening heart failure: 24.5% (793 out of 3,241) of patients treated with Ivabradine died or were hospitalised for the first time due to worsening heart failure, compared with 28.7% (937 out of 3,264) of patients treated with placebo.

VI.2.3 Unknowns relating to treatment benefits

The populations where experience is limited such as children and adolescents (< 18 years old), pregnant and lactating women, patients with severe kidney problems, patients with severe hepatic problems, patients experiencing irregular heart beats due to intraventricular conduction defects (such as bundle branch blocks) are reflected in the SmPC.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Decrease in heart rate (Bradycardia)	Decrease in heart rate is a common side effect with ivabradine (seen between 1 and 10 patients in 100). This event particularly occurs within the first 2 to 3 months of treatment initiation. Decrease in heart rate is a common side effect with carvedilol (seen between 1 and 10 patients in 100). This may lead to dizziness (commonly), low blood pressure, fainting, feeling of weakness, feeling of faintness (uncommonly), feeling unwell (rarely). Studies performed in current medical practice do not indicate an increased risk in patients treated with carvedilol and ivabradine concurrently.	Dose adaptation according to resting heart rate in accordance with the SmPC. Carivalan®/Stovadis®/Prescoriel® must not be initiated in patients with a pre-treatment resting heart rate below 50 beats per minute.

Risk	What is known	Preventability
Luminous visual phenomena (Phosphenes/blurred vision)	Luminous visual phenomena are very common side effects with ivabradine (seen in more than 1 patient in 10). They are linked to the mechanism of action of ivabradine. These phenomena consist in brief moments of increased brightness, most often caused by sudden changes in light intensity. They generally occur within the first two months of treatment after which they may occur repeatedly and resolve during or after treatment, with no after-effects. Luminous phenomena has not been identified with the use of carvedilol monotherapy, however common (seen between 1 and 10 patients in 100) cases of visual impairment and have been reported with carvedilol.	No
Irregular heartbeats (2nd and 3rd degree Atrioventricular blocks (AVB II and III)	Irregular heartbeats are very rare side effects with ivabradine (seen up to 1 patient in 10,000).	No
Uncontrolled blood pressure (increase in blood pressure in hypertensive patients)	Uncontrolled blood pressure is a common side effect with ivabradine (seen between 1 and 10 patients in 100). This may happen in patient suffering from hypertension (elevated blood pressure), especially after a change in the antihypertensive treatment.	No
Irregular rapid contractions of the upper chambers of the heart (Atrial fibrillation (AF)	Atrial fibrillation is a common side effect with ivabradine (seen between 1 and 10 patients in 100). It happens when the atria (the upper chambers of the heart) contract irregularly and rapidly, resulting in abnormal heart rhythm.	No
Abnormal ECG heart tracing (ECG prolonged QT interval)	Abnormal ECG heart tracing is an uncommon side effect with ivabradine (seen between 1 and 10 patients in 1,000). This event is linked to the lowering effect of ivabradine on heart rate. Based on clinical data, co administration of ivabradine in patients taking beta-blockers did not lead to any prolongation of QTc.	No
Low sugar (glucose) levels in the blood (hypoglycaemia)	Based on data from the literature, low blood sugar levels (hypoglycaemia) is an important identified risk linked to carvedilol. Carvedilol can make hypoglycaemia less noticeable (which can be dangerous, especially for people with diabetes).	When patients with diabetes are given beta-blockers, they should be educated about monitoring for hypoglycaemia and the potential need to adjust the dosage of the hypoglycaemic agents.

Risk	What is known	Preventability
Sudden serious allergic reaction (anaphylaxis) (symptoms: sudden signs of allergy such as rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing)	Based on data from the literature, severe allergic reactions (anaphylactoid/anaphylactic) characterized by symptoms such as pruritus, urticaria, swelling of eyelids, face, lips, tongue or throat, and/or chest pain, difficulty in breathing requiring medical treatment have been reported with carvedilol and other medicinal products of the same class (beta-blockers). Carvedilol may also potentially make anaphylaxis more difficult to treat. Anaphylaxis is a severe and life-threatening condition which can occur at any time. A patient should stop taking carvedilol/ivabradine FDC and consult a doctor if experiencing severe allergic reactions during treatment.	Patients with a history of severe allergic reactions and patients undergoing therapy to desensitize them to agents inducing allergies (allergens) are at increased risk of more severe sudden life-threatening allergic reaction (anaphylaxis) and should follow the precautions for use.

Important potential risks

Risk	What is known
Irregular contractions of the upper chambers of the heart (supra-ventricular tachyarrhythmia (SVT) other than AF)	Based on clinical trial data, supra-ventricular tachyarrhythmia (SVT) other than AF may happen. Studies performed in current medical practice do not indicate an increased risk in patients treated with ivabradine.
Immune disorders	Based on data in animals, ivabradine may cause thymus atrophy. In clinical studies, data do not show any role of ivabradine in the occurrence of immune disorders.
Severe irregular contractions of the lower chambers of the heart (severe ventricular arrhythmia)	Based on post-marketing data, severe ventricular arrhythmias may happen in patients with different risk factors or taking other drugs. Studies performed in current medical practice do not indicate an increased risk in patients treated with ivabradine.
Myocardial infarction	Based on the results of the SIGNIFY study using ivabradine with a different therapeutic scheme, severe bradycardia may lead to myocardial infarction.

Missing information

Risk	What is known
Limited information on use in children < 18 years old	The efficacy and safety of Carivalan®/Stovadis®/Prescoriel® has not been studied in this population.
Limited information on use in pregnancy and breast-feeding women	The efficacy and safety of Carivalan®/Stovadis®/Prescoriel® has not been studied in this population.
Limited information on use in patients with severe hepatic insufficiency	The efficacy and safety of Carivalan®/Stovadis®/Prescoriel® has not been studied in this population.
Limited information on use in patients with severe renal impairment	The efficacy and safety of Carivalan®/Stovadis®/Prescoriel® has not been studied in this population.

Risk	What is known
Limited information on use in chronic heart failure patients with intra-ventricular conduction defects	The efficacy and safety of Carivalan®/Stovadis®/Prescoriel® has not been particularly investigated in this population.

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 leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The SmPC and the PL for Carivalan®/Stovadis®/Prescoriel® can be found on the local regulatory authority website.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable.