VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Ivabradine is a medicine used for two long-term (chronic) heart conditions: to treat symptoms of chronic

stable angina pectoris and to treat chronic heart failure.

Stable angina pectoris (angina) is a heart disease which happens when blood supply to the heart muscle is inadequate, so the heart does not receive enough oxygen. It usually appears between 40 and 50 years of age. The most common symptom of angina is pain in the chest, jaw and back, particularly when the heart beats faster in situations such as exercise, emotion, exposure to the cold or after eating. It is estimated that between 2 and 4% of the population in the EU suffer from stable angina pectoris.

Chronic heart failure is a heart disease in which the heart cannot pump enough blood to the rest of the body. The most common symptoms of heart failure are breathlessness, tiredness and ankle swelling due to fluid build-up. It is estimated to affect between 1 and 2% of the population in the EU.

VI.2.2 Summary of treatment benefits

Ivabradine has been studied in five main studies involving over 4,000 adults with long-term stable angina. The medicine was compared with placebo 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. The studies showed that the medicine 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 it to amlodipine did not provide an additional benefit.

Ivabradine has also 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. It 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

Not applicable

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 in between 1 and 10 patients in 100), especially in the first 2 to 3 months after starting treatment. This may lead to dizziness, low blood pressure, fainting, feeling of weakness, feeling of faintness or feeling unwell.	Doctors should follow the dosing recommendations in the product information and not exceed the maximum recommended dose. Treatment must only be started in patients with heart rate above 70 beats per minute, and must be avoided in patients also taking the medicines verapamil or diltiazem.
Luminous visual phenomena (phosphenes/blurred vision)	Luminous visual phenomena or phosphenes (brief moments of increased brightness, coloured flashes or halos) are very common side effects with Ivabradine (seen in more than 1 patient in 10). They are most often caused by sudden changes in light intensity. They generally occur within the first two months of treatment.	The product information contains warnings for doctors and patients about the possibility of luminous visual phenomena, which are linked to the way the medicine works. Patients should be informed that phosphenes resolve during or after treatment with no after effects. If affected, patients should be warned to be careful when driving or using machines at times when there could be sudden changes in light intensity, especially when driving at night.
Irregular heartbeats (2nd and 3rd degree atrioventricular blocks (AVB II and III)	Irregular heartbeats due to interference with the electrical conduction of the heart are very rare side effects with Ivabradine (seen in less than 1 patient in 10,000).	Patients receiving Ivabradine will normally have their heart function regularly monitored, particularly when starting treatment or changing dose. The product information contains a warning for doctors that Ivabradine is not recommended in patients with existing 2nd degree atrioventricular block and must be avoided in those with existing 3rd degree block.
Uncontrolled blood pressure (increase in blood pressure in hypertensive patients)	Uncontrolled blood pressure is a common side effect with Ivabradine (seen in between 1 and 10 patients in 100). This may happen in patients suffering from hypertension (high blood pressure), especially after a change in their blood pressure treatment.	The product information for Ivabradine warns doctors that when blood pressure treatment is modified in chronic heart failure patients treated with Ivabradine, their blood pressure should be monitored at an appropriate interval.
Irregular rapid	Atrial fibrillation (a rapid, irregular	The product information states that

Risk	**What is known**	**Preventability**
contractions of the upper chambers of the heart (atrial fibrillation)	rhythm of the upper chambers of the heart) is a common side effect with Ivabradine (seen in between 1 and 10 patients in 100).	patients should be informed of signs and symptoms of atrial fibrillation (such as high pulse rate when resting, or irregular pulse rate) and be advised to contact their doctor if these occur. If atrial fibrillation develops during treatment, the balance of benefits and risks of continued ivabradine treatment should be carefully reconsidered.

Abnormal ECG heart tracing (prolonged QT interval on ECG)	A type of abnormal ECG heart tracing known as QT prolongation (reflecting a change in the electrical activity of the heart) is an uncommon side effect with Ivabradine (seen between 1 and 10 patients in 1,000). This event is linked to the effect of ivabradine in lowering heart rate.	The product information warns doctors that use of Ivabradine in patients with inborn alteration in QT interval (congenital QT syndrome) or with other medicines that may also prolong QT interval should be avoided if possible. If Ivabradine is used in such circumstances close monitoring of heart function is needed.

Important potential risks

Risk	**What is known (including reason why it is considered a potential risk)**
Irregular contractions of the upper chambers of the heart (supra-ventricular tachyarrhythmia other than atrial fibrillation)	Based on clinical trial data, supra-ventricular tachyarrhythmia (fast, irregular contractions of the upper chambers of the heart) of types other than atrial fibrillation could occur. However, studies performed in current medical practice reported a similar risk in patients treated with Ivabradine and patients given placebo (dummy treatment).
Immune disorders	Based on data in animals, Ivabradine may cause shrinkage of the thymus gland, which plays a role in the immune system (the body's natural defences). Studies in humans have not so far shown any role of the medicine in the occurrence of immune disorders.
Heart attack (Myocardial infarction)	Based on the preliminary results of a large clinical study called SIGNIFY, in which Ivabradine was given differently than currently authorised, severe slowing of heart rate (bradycardia) caused by the medicine could lead to myocardial infarction.
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. However, clinical studies in humans have not so far shown an increased risk in patients treated with Ivabradine.

Missing information

Risk	**What is known**
Children and adolescents (< 18 years old)	The effectiveness and safety of Ivabradine have not been studied in this population.
Pregnant and lactating women	The effectiveness and safety of Ivabradine have not been studied in this population. Ivabradine must not be used during pregnancy or breastfeeding as studies in animals suggest it can harm the unborn child. Women who are able to have children should use appropriate contraceptive measures while taking the medicine.
Use in patients with severely reduced liver function (Severe hepatic insufficiency)	The effectiveness and safety of Ivabradine have not been studied in this population and it is recommended that they should not be given the medicine.

Use in patients with severely reduced kidney function (Severe renal impairment)	The effectiveness and safety of Ivabradine have not been studied in this population and it should be used with caution.
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.

The Summary of Product Characteristics and the Package leaflet for Ivabradine can be found in the national authority's web page. This medicine has no additional risk minimisation measures.

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

Not applicable

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

Version	Date	Changes	Comment
1	19/Oct/2015	*Following information has been deleted:* Additional pharmacovigilance activities for other MAHs.	This RMP has been updated according to NL/H/3660/001-002/DC NL/H/3661/001-002/DC NL/H/3663/001-002/DC assessment report.