VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Ezetimibe/simvastatin is used to reduce the risk of cardiovascular events in patients with coronary heart disease (CHD). CHD occurs as a result of plaque buildup in the arteries that supply oxygen-rich blood to the heart. The buildup of plaque occurs over many years as a result of hypercholesterolemia and leads to blockages restricting blood flow to the heart. These blockages can result in angina or heart attack. Familial hypercholesterolemia (FH), also called primary hypercholesterolaemia, is a genetic disorder that causes severe elevations in total cholesterol and low-density lipoprotein cholesterol (LDLc). Although moderate hypercholesterolemia is a common finding in industrialized countries, FH occurs in approximately 1 per 500 persons worldwide. Prevalence of FH in the United States and in Europe is approximately the same, though it is more frequent in certain regions, such as Iceland and Finland. Another more rare type called Homozygous Familial Hypercholesterolaemia (HoFH), is also associated with genes but occurs only in 1 patient per million individuals.

VI.2.2 Summary of treatment benefits

HMG-CoA reductase inhibitors (statins) are the medications of choice for the treatment of LDLc elevations in patients with FH because they have the greatest efficacy, are easily tolerated and reduce heart problems and mortality. Even the maximum doses of the strongest statins are usually inadequate for patients with FH, and the addition of one or more nonstatin cholesterol-lowering medications is necessary e.g. ezetimibe. The combination of simvastatin and ezetimibe has been shown effective in clinical trials to lower levels of cholesterol and triglycerides in the blood. Ezetimibe/simvastatin has been shown to reduce major cardiovascular events in patients with coronary heart disease and acute coronary syndrome.

VI.2.3 Unknowns relating to treatment benefits

Based on the currently available data and as stated in the proposed SmPC, efficacy and safety in children, or use during pregnancy and lactation has not yet been established.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Muscle problems, including muscle breakdown (Rhabdomyolysis/Myopathy)	Muscle problems, such as muscle pain, tenderness or weakness, and also serious muscle problems, including muscle breakdown resulting in kidney damage, and very rare death had been observed. Elevation in laboratory blood tests of muscle (CK) function. The risk is higher in certain patients with kidney and thyroid problems, 65 years or older, female gender, previous muscle problems during treatment with cholesterol lowering medicines called statins, or fibrates, family members with hereditary muscle disorders, alcohol abuse.	Yes, by contacting the doctor in case of muscle pain, tenderness or weakness, by talking to the doctor about the following conditions: kidney and thyroid problems, 65 years or older, female gender, previous muscle problems during treatment with cholesterol lowering medicines called statins, or fibrates, family members with hereditary muscle disorders, alcohol abuse. By monitoring muscle problems with tests and taking medicines to diagnose and treat muscle problems.
Liver problems (Abnormal liver function)	Inflammation of the liver with the following symptoms: yellowing of the skin and eyes; itching, dark coloured urine or pale coloured stool, feeling tired or weak, loss of appetite; liver failure had been observed. alterations in some laboratory blood tests for liver function had been observed	Yes, by communicating to the doctor in case of concurrent liver disease, monitoring liver functions

Risk	What is known	Preventability
Allergy (Hypersensitivity)	Rash, hives had been observed following use of with ezetimibe and simvastatin ore with one of the individual components	Yes, by avoiding use in case of ezetimibe simvastatin, or any of the other ingredients of this medicine.
Concomitant use of medicines with an active ingredient to prevent bood clots (Drug interactions with warfarin, another coumarin anticoagulant, or fluindione)	Elevations in the time it takes for blood to clot had been observed during concomitant administration of ezetimibe with anticoagulants (warfarin or fluindione) had been observed. In two studies, patients who was taking simvastatin at the dose of 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants. Very rare cases of elevations in the time it takes for blood to clot had been reported.	Yes, by monitoring time it takes for blood clots.
Concomitant use of ciclosporin (often used in organ transplant patients (Drug interactions with ciclosporin)	Muscle pain, tenderness or weakness and serious muscle problems such us muscle breakdown resulting in kidney damage, and very rare deaths had been observed with the use of ezetimibe simvastatin. These risks are higher in patients in treatment with ciclosporin.	Yes, by contacting your doctor in case of unexpected muscle pain, tenderness or weakness, by avoiding the concomitant use of ciclosporin.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Inflammation of the pancreas often with severe abdominal pain (Pancreatitis)	Inflammation of the pancreas often with severe abdominal pain had been observed following use of ezetimibe simvastatin. However, a large study including over 9000 patients in treatment with simvastatin ezetimibe or placebo demonstrated that there were no differences in the occurrence of pancreatitis between the two groups.
Gallstones or inflammation of the gallbladder (which may cause abdominal pain, nausea, vomiting) (Cholecystitis/cholelithiasis)	Gallstones or inflammation of the gallbladder (which may cause abdominal pain, nausea, vomiting) had been observed. However, a large study including over 9000 patients in treatment with simvastatin ezetimibe or placebo demonstrated that there were no differences in the occurrence of cholecystitis/cholelithiasis between

Risk	What is known (Including reason why it is considered a potential risk)
	the two groups.
Breathing problems including persistent cough and/or shortness of breath or fever (Interstitial lung disease)	Breathing problems, including persistent cough and/or shortness of breath or fever had been observed during treatment with simvastatin, especially with long term therapy
Allergic syndrome with simvastatin (Simvastatin hypersensitivity syndrome)	An apparent hypersensitivity syndrome has been reported rarely which has included some of the following features: angio-oedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopaenia, eosinophilia, red blood cell sedimentation rate increased, arthritis and arthralgia, urticaria, photosensitivity reaction, pyrexia, flushing, dyspnoea and malaise.
Diabetes (New onset diabetes/impaired glucose metabolism)	Diabetes had been observed during treatment with ezetimibe simvastatin.
Stroke with haemorrhage (Haemorrhagic stroke)	In a large study including over 18.000 patients after acute coronary syndromes in treatment with simvastatin-ezetimibe or simvastatin monotherapy, there was an overall benefit for all strokes; however, the rate of haemorrhagic stroke was higher, although non-significant with simvastatin-ezetimibe than with simvastatin monotherapy.

Missing information

Risk	What is known
Limited information on use in pregnancy	No clinical data are available on the use of ezetimibe simvastatin during pregnancy. Animal studies on combination therapy have demonstrated reproduction toxicity.
Limited information on use during lactation	Studies on rats have shown that ezetimibe is present into breast milk. It is not known if the active components of ezetimibe simvastatin are secreted into human breast milk.
Limited information on the use in children	Limited data are available in patient aged 10-17 years old. No data is available for patients aged minor than 10 years-old.

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

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

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	September 2015	Important identified risks - Hypersensitivity - Drug interactions with warfarin, other coumarin anticoagulants, or fluindione - Drug interactions with ciclosporin - Drug interactions with potent CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors (e.g.nelfinavir), boceprevir, telaprevir, and nefazodone) - Drug interactions with fusidic acid - Drug interactions with grapefruit juice - Drug interactions with diltiazem - Drug interactions with verapamil - Drug interactions with amlodipine - Drug interactions with fibrates - Drug interactions with niacin (≥1 g/day) - Drug interactions with danazol - Drug interactions with amiodarone - Myopathy/rhabdomyolysis - Interstitial lung disease - Diabetes mellitus - Liver dysfunction Important potential risks - Pancreatitis - Cholecystitis/cholelithiasis - Simvastatin hypersensitivity syndrome Missing information - Use during pregnancy - Use during lactation - Use in children	
1.1	May 2016	Important identified risks • Rhabdomyolysis/Myopathy • Abnormal liver function • Hypersensitivity • Drug interactions with warfarin, another coumarin anticoagulants, or fluindione	On request of the HA of the RMS the list of safety concerns has been modified and aligned accordingly to the list for the

Version	Date	Safety Concerns	Comment
		• Drug interactions with ciclosporin Important potential risks • Pancreatitis • Cholecystitis/Cholelithiasis • Interstitial lung disease • Simvastatin hypersensitivity syndrome • New onset diabetes/impaired glucose metabolism • Haemorrhagic stroke Missing information • Exposure during pregnancy and lactation • Use in children	reference product.
1.2	November 2016	Important identified risks • Rhabdomyolysis/Myopathy • Abnormal liver function • Hypersensitivity • Drug interactions with warfarin, another coumarin anticoagulants, or fluindione • Drug interactions with ciclosporin Important potential risks • Pancreatitis • Cholecystitis/Cholelithiasis • Interstitial lung disease • Simvastatin hypersensitivity syndrome • New onset diabetes/impaired glucose metabolism • Haemorrhagic stroke Missing information • Exposure during pregnancy and lactation • Use in children	On request of the HA of the RMS, Tables V.1, V.3 and VI.1.4 have been updated with précis of the texts to include reference to all SmPC sections. Minor change in the text in section VI.2.1 and VI.2.3.
1.3	January 2017	Important identified risks • Rhabdomyolysis/Myopathy • Abnormal liver function • Hypersensitivity • Drug interactions with warfarin, another coumarin anticoagulants, or fluindione • Drug interactions with ciclosporin Important potential risks • Pancreatitis • Cholecystitis/Cholelithiasis • Interstitial lung disease • Simvastatin hypersensitivity syndrome • New onset diabetes/impaired glucose metabolism	On request of the HA of the RMS Part I, Part V – tables V.1 and V.3, Part VI.1.4, Parts VI.2.1 and VI.2.2 have been updated in line with the proposed SmPC (Annex 2) expanded to include texts on the indication "Prevention of cardiovascular events".

Version	Date	Safety Concerns	Comment
		• Haemorrhagic stroke Missing information • Exposure during pregnancy and lactation • Use in children	