VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Ezetimibe belongs to a group of medicines that decrease absorption of phytosterols and cholesterol in the small intestine. Its primary clinical effect is reduction of LDL levels. It may be used alone or in combination with other cholesterol-lowering medicines.

Simvastatin belongs to a group of medicines known as statins, which are fat (lipid) regulating medicines.

Simvastatin is used to lower fats known as cholesterol and triglycerides in the blood when a low fat diet and life style changes on their own have failed. Simvastatin can also be used in patients who are at an increased risk of heart disease.

<u>High cholesterol levels (Hypercholesterolaemia)</u>

Cholesterol is carried in the blood by proteins, and when the two combine they are called lipoproteins. There are harmful and protective lipoproteins known as LDL and HDL, or bad and good cholesterol. If there is too much LDL cholesterol for the cells to use, it can build up in the artery walls, leading to disease of the arteries.

Two thirds of the UK population have high cholesterol levels[3].

Heart and circulation disease (Cardiovascular disease)

Heart and circulation diseases include coronary heart disease (chest pain and heart attack), heart failure, inherited heart disease and stroke. If a patient has untreated high cholesterol, this increases the risk of heart disease[1]. It has been estimated that in England 4.9 million people aged 16 or over have cardiovascular disease, this corresponds to 11.73% of the population[4]. Coronary heart disease (a type of cardiovascular disease) is the leading cause of death for both men and women[9]. South Asian people living in the UK have a higher premature death rate from coronary heart disease than other ethnicities[12].

VI.2.2 Summary of treatment benefits

Ezetimibe and simvastatin have been tested in clinical trials individually but also as a combination to evaluate their effectiveness in the indications stated above. Both medicines were found to be effective in lowering cholesterol levels, preventing heart attacks, stroke and the need for bypass surgery.

One study assessed the LDL cholesterol lowering efficacy of the Ezetimibe/Simvastatin combination in comparison to statin treatment alone. Patients with coronary heart disease or type 2 diabetes who did not achieve the target level of LDL cholesterol (<2.5mmol/l) in spite of therapy with simvastatin 20mg or atorvastatin 10mg were selected for the study. Patients were randomly assigned to one of two treatments: they were either given the double statin dose or Ezetimibe/Simvastatin 10/20mg combination tablet. 119 out of 178 (67%) in the Ezetimibe/Simvastatin group and 49 of 189 (26%) in the doube-dose statin group reached target LDL-cholesterol levels. Also a reduction of total cholesterol, total to HDL cholesterol ratio and apoliprotein B was more pronouced in the Ezetimibe/Simvastatin group. Both treatments were well tolerated by patients.

Another study investigated adult patients with type 2 diabetes mellitus and coronary heart disease who were previously prescribed simvastatin 20mg. These patients were randomly assigned to receive either ezetimibe 10mg plus simvastatin 20mg or simvastatin 40mg for six weeks. The Ezetimibe/Simvastatin group achieved a significantly greater decrease in LDL cholesterol and total cholesterol than patients who were treated with simvastatin 40mg alone. Changes in HDL cholesterol and triglycerides were similar between treatments. Both treatments were generally well-tolerated.

VI.2.3 Unknowns relating to treatment benefits

Based on the currently available data, no gaps in knowledge about efficacy in the target population were identified, that would warrant post-authorisation efficacy studies. Furthermore, there is no evidence to suggest that treatment results would be different in any subgroup of the target population, for any of the indications, taking into account factors such as age, sex, race or organ impairment.

However as stated in the proposed SmPC, the safety of use during pregnancy, use during lactation and use in children have not yet been established.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Muscle problems and muscle breakdown (Myopathy/rhabdomyolysis)	This medicine may cause muscle problems. In rare occasions muscle problems can be serious, including muscle breakdown resulting in kidney damage; and very rare deaths have occurred. There may be a greater risk with higher doses and in certain patients such as the elderly, patients with kidney problems, thyroid problems or in women. The risk of muscle problems may be increased with the following medication: -danazol (a man-made hormone used to treat endometriosis, a condition in which the lining of the uterus grows outside the uterus). -medicines with an active ingredient like itraconazole, ketoconazole, fluconazole, posaconazole, or voriconazole (used to treat fungal infections). -fibrates with active ingredients like gemfibrozil and bezafibrate (used to lower cholesterol). -erythromycin, clarithromycin, or telithromycin (used to treat bacterial infections). -fusidic acid to treat a bacterial infection. -HIV protease inhibitors such as indinavir, nelfinavir, ritonavir, and saquinavir (used to treat AIDS). -boceprevir or telaprevir (used to treat hepatitis C virus infection). -nefazodone (used to treat depression). -medicines with the active ingredient cobicistat.	If any muscle pain, weakness or cramps, especially if they are associated with tiredness or fever, occur, the medicine should be stopped and a doctor contacted immediately. Extra monitoring should be undertaken by prescribers in patients with pre-disposing factors for muscle-related side effects. **This is because on rare occasions, muscle problems can be serious, including muscle breakdown resulting in kidney damage; and very rare deaths have occurred.**

Risk	What is known	Preventability
	-amiodarone (used to treat an irregular heartbeat). -verapamil, diltiazem, or amlodipine (used to treat high blood pressure, chest pain associated with heart disease, or other heart conditions). -lomitapide (used to treat a serious and rare genetic cholesterol condition). -large amounts (1 gram or more each day) of niacin or nicotinic acid (also used to lower cholesterol). -colchicine (used to treat gout).	
Abnormal liver function	This medicine may cause liver problems.	Patients should avoid Ezetimibe/Simvastatin if they have had previous liver disease or unexplained abnormal liver function tests. Liver function tests are recommended before treatment begins and during treatment if clinically required. Patients who develop abnormal liver function (increase in transaminase) as shown with a blood test should be monitored until the abnormalities resolve. Should an increase in transaminases of greater than 3 times the upper limit of normal persist, reduction of the dose or withdrawal is recommended.
Allergic reactions (Hypersensitivity)	Patients may develop an allergic reaction to this medicine. Allergic reaction occurs uncommonly with Ezetimibe/Simvastatin and it may affect up to 1 in 100 people.	Patients should not use this medicine if they are allergic to ezetimibe and simvastatin or any of the other ingredients of this medicine. Patients should contact their doctor immediately if they develop signs of an allergic reaction: rash, itching (pruritus), hives (urticaria).
When used together with medicines that prevent blood clots (Drug interactions with warfarin, another coumarin anticoagulant, or fluindione)	Ezetimibe/Simvastatin may increase the risk of bleeding if used together with medicines that prevent blood clots, such as warfarin, fluindione.	Patients should tell their doctor if they are taking any medicines to prevent blood clots. Patients should seek medical attention if they notice: -severe bruising -prolonged nosebleeds (longer than 10 minutes) -unusual headaches Your doctor will monitor your INR-a measure of how fast your blood clots.

Risk	What is known	Preventability
When used together with a drug that reduces the body's defence mechanisms (Drug interaction with ciclosporin)	The risk of muscle problems can be greater if Ezetimibe/Simvastatin is taken with ciclosporin- a medicine that reduces the body's defence mechanisms. This medicine is used to prevent the rejection of transplant organs.	Patients should tell their doctor if they are taking any medicines that prevent the body from rejecting transplanted organs. Ciclosporin should not be taken together (is containdicated) with Ezetimibe/Simvastatin. Patients should seek medical attention if they notice: -muscle pain and swelling (inflammation) -muscle tenderness or weakness -unusual tiredness or weakness -neck pain; -pain in arms and legs -back pain - tendon problems **This is because on rare occasions, muscle problems can be serious, including muscle breakdown resulting in kidney damage; and very rare deaths have occurred.**

Important potential risks

Risk	What is known
Inflammation of the pancreas (Pancreatitis)	Ezetimibe/Simvastatin may potentially cause inflammation of the pancreas, often with severe pain in the abdomen and back.
Cholecystitis/cholelithiasis	Use of Ezetimibe/Simvastatin may potentially result in formation of gallstones and/or inflammation of the gallbladder which may cause abdominal pain, nausea, vomiting.
Inflammation of the lungs (Interstitial lung disease)	This medicine may cause inflammation of the lungs causing breathing problems including persistent cough and/or shortness of breath or fever. It is not known how many people are affected by this. If a patient experiences any of the symptoms of interstitial lung disease (dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever), statin therapy should be discontinued and the patient should go to the doctor.
Simvastatin hypersensitivity syndrome	Simvastatin may be responsible for a potentially life-threatening set of medical signs (simvastatin hypersensitivity syndrome). Signs of this allergic reaction include: swelling of the face, lips, tongue and/or throat which may cause difficulty in breathing or swallowing and requires treatment immediately; pain or inflammation of the joints; inflammation of blood vessels; unusual bruising, skin eruptions and swelling; hives, skin sensitivity to the sun, fever, flushing, shortness of breath and feeling unwell; lupus-like disease picture (including rash, joint disorders and effects on white blood

Risk	What is known
	cells).
Diabetes or abnormal blood sugar levels (New onset diabetes/impaired glucose metabolism)	This group of medicines may increase the risk of developing diabetes, particularly in patients at a high risk such as having high levels of sugars and fats in the blood, being overweight or having high blood pressure. While on this medicine, a doctor will monitor patients with diabetes or who are at risk of developing diabetes closely.
Stroke caused by a bleed (Haemorrhagic stroke)	There is a potential increased risk of having stroke due to a bleed in the brain.

Missing information

Risk	What is known
Use during pregnancy and breastfeeding (Exposure during pregnancy and lactation)	The safety of Ezetimibe/Simvastatin medicine has not been established yet in pregnant women. This medicine should never be used (contraindicated) in pregnancy. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. This medicine should never be used (contraindicated) during lactation. Do not take Ezetimibe/Simvastatin if you are breast-feeding, because it is not known if the medicine is passed into breast milk
Use in children (Limited clinical trial experience in children 10–17 years of age. No clinical trial experience in children less than 10 years of age)	Simvastatin has not been studied in patients younger than 10 years of age. The long-term effects on physical, intellectual, and sexual maturation are unknown.

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

List of studies in post authorisation development plan

Not applicable

Studies which are a condition of the marketing authorisation

Not applicable

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

Not applicable