VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

This medicine is used to lower levels of total cholesterol, LDL cholesterol ("bad" cholesterol), and fatty substances called triglycerides in the blood. In addition, this medicine raises levels of HDL cholesterol ("good" cholesterol). Abnormal cholesterol and triglycerides levels are called dyslipidemia.
Dyslipidemia is a major, modifiable risk factor for cardiovascular disease. Cardiovascular disease is a leading cause of morbidity and mortality in the world; there are an estimated 16.7 million deaths each year from cardiovascular disease worldwide. Dyslipidemia is usually asymptomatic and is not fatal; however, if improperly managed or left untreated, it can eventually contribute to coronary artery disease or peripheral artery disease, both of which can be fatal.

VI.2.2 Summary of treatment benefits

The active substances (simvastatin and ezetimibe) work in different ways and their action have a complementary effect.
Simvastatin belongs to the group called 'statins'. It reduces total blood cholesterol by blocking the action of HMG-CoA reductase, an enzyme in the liver involved in the production of cholesterol. As the liver needs cholesterol to produce bile, the reduced blood cholesterol level causes the liver cells to produce receptors that draw cholesterol from the blood, reducing its level even further. The cholesterol drawn out of the blood in this way is the LDL, or 'bad' cholesterol.

Ezetimibe inhibits intestinal uptake of dietary and biliary cholesterol without affecting the absorption of fat-soluble nutrients. By inhibiting cholesterol absorption at the level of the brush border of the intestine, ezetimibe reduces the amount of lipoprotein cholesterol circulated to the liver. In response to reduced cholesterol delivery, the liver reacts by up-regulating LDLR, which in turn leads to increased clearance of LDL from the blood.

Study which analyzed 27 previously published studies compared effectiveness of combination of simvastatin and ezetimibe and simvastatin alone. Combination of simvastatin and ezetimibe was more effective than simvastatin in lowering total cholesterol, LDL cholesterol and triglycerides levels and in increasing HDL cholesterol levels

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VI.2.3 Unknowns relating to treatment benefits

There was only limited clinical trial experience in children 10 – 17 years of age. Also no clinical trials in children less than 10 years of age were performed.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Muscle disorder **(rhabdomyolysis/myopathy)**	On rare occasions, muscle problems can be serious, including muscle breakdown resulting in kidney damage; and very rare deaths have occurred. The risk of muscle breakdown is greater at higher doses of ezetimibe/simvastatin, particularly the 10/80-mg dose. The risk of muscle breakdown is also greater in certain patients. Like all medicines, ezetimibe/simvastatin can cause side effects, although not everybody gets them. - muscle aches - elevations in laboratory blood muscle (CK) function	Contact your doctor immediately if you experience unexplained muscle pain, tenderness, or weakness. Talk with your doctor if any of the following applies: • you have kidney problems • you have thyroid problems • you are 65 years or older • you are female • you have ever had muscle problems during treatment with cholesterol lowering medicines called "statins" (like simvastatin, atorvastatin, and rosuvastatin) or fibrates (like gemfibrozil and bezafibrate) • you or close family members have a hereditary muscle disorder. Taking ezetimibe/simvastatin with any of these drugs can increase the risk of muscle problems

	Grapefruit juice contains one or more components that alter the metabolism of some medications, including ezetimibe/simvastatin.	• ciclosporin (a medicine often used in organ transplant patients) • danazol (a man-made hormone used to treat endometriosis) • medicines like itraconazole, ketoconazole, fluconazole or posaconazole (medicines for fungal infections) • fibrates like gemfibrozil and bezafibrate (medicines for lowering cholesterol) • erythromycin, clarithromycin, telithromycin, or fusidic acid (medicines for bacterial infections) • HIV protease inhibitors such as indinavir, nelfinavir, ritonavir, and saquinavir (medicines for AIDS) • boceprevir or telaprevir (medicines for hepatitis C virus infection) • nefazodone (a medicine for depression) • amiodarone (a medicine for an irregular heartbeat) • verapamil, diltiazem, or amlodipine

		(medicines for high blood pressure, chest pain associated with heart disease, or other heart conditions) • large amounts (1 gram or more each day) of niacin or nicotinic acid (medicines for lowering cholesterol) • colchicine (a medicine used to treat gout). If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist. Consuming grapefruit juice should be avoided as it may increase your risk of muscle problems. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
Liver disease or unexplained persistant elevation in some enzymes **(Abnormal liver function)**	Like all medicines, ezetimibe/simvastatin can cause side effects, although not everybody gets them. The following common side effects were reported • elevations in laboratory blood tests of liver (transaminases) • inflammation of the liver with the following symptoms: yellowing of	Your doctor should do a blood test before you start taking ezetimibe/simvastatin and if you have any symptoms of liver problems while you take ezetimibe/simvastatin. This is to check how

	the skin and eyes, itching, dark coloured urine or pale coloured stool, feeling tired or weak, loss of appetite; liver failure; gallstones or inflammation of the gallbladder (which may cause abdominal pain, nausea, vomiting)	well your liver is working. Do not take ezetimibe/simvastatin if: • you currently have liver problems Your doctor may also want you to have blood tests to check how well your liver is working after you start taking ezetimibe/simvastatin. If any of the side effects gets serious, or if you notice any side effects not listed in leaflet, please tell your doctor or pharmacist.
Hypersensitivity	These medications may cause allergic reactions as all medicines can.	Yes, by monitoring for early symptoms and avoiding the drugs you are already known to be allergic of. Please tell your doctor if you are undergoing or are planning to undergo desensitisation therapy. Be careful and tell your doctor if you have experienced symptoms such as sudden wheeziness, chest pain, shortness of breath or difficulty in breathing, swelling of eyelids, face or lips, severe skin reactions or other allergic reactions.

Drug interaction with warfarin, another coumarin anticoagulant, or fluindione	Both active components in ezetimibe/simvastatin can effect warfarin action but very rare cases of elevated INR (prothrombin time) have been reported. So it is important that doctor monitor INR before starting therapy and more frequently during early therapy to ensure that no significant alteration of prothrombin time occurs.	Yes, by monitoring for early symptoms. Tell your doctor if you are taking any other drugs. You should take your medicine at the same time each day with a drink of water.
Concomitant administration of ciclosporin	Taking ezetimibe/simvastatin with other drugs can increase the risk of some side effects.	Do not take ezetimibe/simvastatin if: you are taking one or more than one of the following drugs at the same time: • gemfibrozil (a medicine for lowering cholesterol) • ciclosporin (a medicine often used in organ transplant patients) • danazol (a man-made hormone used to treat endometriosis). Ask your doctor if you are not sure if your medicine is listed above.

Important potential risks:

Risk	**What is known (including reason why it is considered a potential risk)**
Inflammation of the pancreas **(Pancreatitis)**	Simvastatin can cause inflammation of the pancreas, which is presented as pain in the upper abdomen.

Inflammation of the gallbladder/gallstones **(Cholecystitis/cholelithiasis)**	Ezetimibe is an active component of ezetimibe/simvastatin. Concomitant fenofibrate or gemfibrozil administration modestly increased ezetimibe concentrations (ezetimibe is In patients receiving fenofibrate and Ezoleta, physicians should be aware of the possible risk of cholelithiasis and gallbladder disease. If cholelithiasis is suspected in a patient receiving ezetimibe and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued. Coadministration of ezetimibe with other fibrates has not been studied. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In animal studies, ezetimibe sometimes increased cholesterol in the gallbladder bile, but not in all species.
Different lung condition **(Interstitial lung disease)**	Simvastatin, active component of ezetimibe/simvastatin, belongs to the group called 'statins'. Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy. Symptoms of interstitial lung disease include breathing problems including persistent cough and/or shortness of breath or fever. Interstitial lung disease describes a large group of disorders, most of which cause progressive scarring of lung tissue and can have severe outcome. Tell your doctor if you have severe lung disease.
Simvastatin hypersensitivity syndrome	These medications may cause allergic reactions as all medicines can. The doctor or pharmacist should be informed if you have allergic reactions to other simvastatin containing medicine.
New onset diabetes/impaired glucose metabolism	Simvastatin, active component of ezetimibe/simvastatin, belongs to the group called 'statins'. Some evidence suggests that statins as a group raise blood glucose (sugar) and in some patients, at high risk of developing future diabetes, may produce a level of hyperglycaemia (high levels of sugars) where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping treatment with this medicine. While you are on this medicine your doctor will monitor you closely if you have diabetes or are at risk of developing

	diabetes. You are likely to be at risk of developing diabetes if you have high levels of sugars and fats in your blood, are overweight and have high blood pressure.
Haemorrhagic stroke	Talk to your doctor or pharmacist before taking this medicinal product if you have had a previous stroke with bleeding into the brain, or have small pockets of fluid in the brain from previous strokes. All types of stroke are dangerous, but a few of them are notorious for causing severe disability and/or a rapid progression to death. Take special care with if you have had a previous stroke with bleeding into the brain, or have small pockets of fluid in the brain from previous strokes.

Missing information

Risk	**What is known**
Pregnancy and breastfeeding **(Exposure during pregnancy and lactation)**	Some drugs used during pregnancy and breastfeeding can have temporary or permanent effects on the fetus. The safety of simvastatin in pregnant women has not been established. No clinical data are available on the use of ezetimibe during pregnancy. Do not take ezetimibe/simvastatin if you are pregnant, are trying to get pregnant or think you may be pregnant as there is not enough information on the safety of the drug. If you get pregnant while taking ezetimibe/simvastatin, stop taking it immediately and tell your doctor. 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 experience in children < 10 years of age)	As insufficient data on the safety and efficacy of the drug is not available, the drug is not recommended for children under age 10.

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 this product can be found at the agency's EPAR page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable. No postauthorisation studies are planned.

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

Not applicable.