VI.2 ELEMENTS FOR A PUBLIC SUMMARY

VI.2.1 Overview of Disease Epidemiology

Hypercholesterolemia (or hyperlipidaemia) refers to high blood cholesterol levels. Cholesterol is a waxy, fatty substance (also known as lipid) that the body needs the appropriate amounts of to work properly. It is obtained from food and is also made by the liver.

There are a few different types of cholesterol, including:

Total cholesterol (all the cholesterol combined; Total-C)

Low-density lipoprotein cholesterol (LDL-C): also called "bad" cholesterol because it is the main source of cholesterol buildup and blockage in the blood vessels.

High-density lipoprotein cholesterol (HDL-C) also called "good" cholesterol because it helps keep cholesterol from building up in the blood vessels.

Triglycerides: are types of fat found in blood. Body uses them for energy.

High blood cholesterol levels, particularly high LDL-C and triglyceride levels, may lead to a build-up of cholesterol and fat along the inner walls of the blood vessels of the heart (coronary heart disease) and brain (cerebrovascular disease) which increases the risk of heart disease and stroke.

The most common cause of hypercholesterolemia is an interaction between genes and dietary and other factors, such as smoking and physical inactivity. This is called primary non-familial hypercholesterolemia. Primary non-familial hypercholesterolemia affects about 34% of men (ranging from 21% - 41% in different regions) and 40% in women (ranging from 26% - 47% in different regions). [Ref. 5.4: 03QJDC]

Homozygous and heterozygous familial hypercholesterolaemia (HoFH and HeFH) are genetic diseases which are passed down from parents which cause very high levels of bad cholesterol. The defect makes the body unable to remove LDL-C from the blood. Most people with FH inherit a defective gene for FH from only one parent and are therefore called heterozygous (HeFH). Rarely, a person may inherit the genetic defect from both parents and thus have homozygous FH (HoFH). About 1 per 500 people [Ref. 5.4: 03PJWM, 03QJFY, 03QJFZ] and 1 per 1,000,000 [Ref. 5.4: 03QJFZ] people have HeFH and HoFH respectively. It is more commonly found in Afrikaner, French Canadians, Ashkenazi Jews, and Lebanese populations [Ref. 5.4: 03QKW2]. The rates of HeFH and HoFH are the same for both men and women. Individuals with familial hypercholesterolemia tend to get coronary artery disease at earlier ages and those with HoFH tend to have a decreased life span.

Homozygous sitosterolaemia (phytosterolaemia) is a very rare inherited genetic disorder. In normal individuals, plant sterols (present in small amounts in fruits, vegetables, nuts, seeds, and cereals) are poorly absorbed and usually removed by the digestive system. However, in this disorder, excessive absorption and decreased removal of dietary plant sterols takes place. The blood cholesterol levels may be normal or raised; however, plant sterols are elevated which increases the risk of coronary heart disease. It is not known how many people are affected by this disorder, but it is likely to be a few hundred to a few thousand worldwide .

The potential health risk due to all type of hypercholesterolaemia includes risk of heart attack, stroke, chest pain (angina), reduced blood flow to heart (ischaemic heart disease), and death related to heart and blood vessel (cardiovascular) problems. According to the World Health Organization

over 30% of deaths worldwide are related to cardiovascular disease [Ref. 5.4: 03QJG9]. Cardiovascular disease causes nearly half of all deaths in Europe [Ref. 5.4: 03QJD3].

Ezetimibe is also used to reduce the risk of cardiovascular events in patients with coronary heart disease and a history of a heart attack or unstable angina. Coronary heart disease (CHD) is a result of plaque buildup in the arteries that supply oxygen-rich blood to your heart. The buildup of plaque occurs over many years as a result of hypercholesterolemia and leads to blockages restricting blood flow to the heart. If the flow of oxygen-rich blood to your heart muscle is reduced or blocked, angina or a heart attack can occur. Angina is chest pain or discomfort. A heart attack occurs if the flow of oxygen-rich blood to a section of heart muscle is cut off causing damage to the heart. About 6.2% of adults in the United States [Ref. 5.4: 042MCN] and 5.7% of men and 3.5% of women in the UK [Ref. 5.4: 04CGKK] have CHD.

VI.2.2 Summary of Treatment Benefits

Ezetimibe works by selectively inhibiting the intestinal absorption of cholesterol and related plant sterols. Ezetimibe has been approved as monotherapy or to be given in combination with statins for the treatment of familial and non-familial hypercholesterolemia, and as adjunctive therapy for the treatment of homozygous familial sitosterolemia. An extensive clinical program has been conducted with ezetimibe administered alone, and in combination with statins. Ezetimibe either as monotherapy or co-administered with a statin significantly reduced total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), and triglycerides (TG) and increased high-density lipoprotein cholesterol (HDL-C) in patients with hypercholesterolaemia.

In adults with hypercholesterolaemia, ezetimibe was evaluated in an 8-week study that enrolled 769 patients. Patients were randomly assigned to receive additional treatment of ezetimibe or placebo (pill without active medicine), in addition to their ongoing statin therapy. LDL-C was reduced by 25% in patients receiving ezetimibe as compared to 4% in patients receiving placebo. In two other 12-week studies involving 1719 adult patients with primary hypercholesterolaemia, as compared to placebo, ezetimibe reduced LDL-C by 19%. In adults with homozygous FH, ezetimibe was evaluated in a 12-week study that enrolled 50 patients who were receiving atorvastatin or simvastatin (40 mg) with or without concomitant LDL apheresis. Patients were randomly assigned to receive additional treatment of ezetimibe or placebo, in addition to their ongoing statin. Ezetimibe co-administered with atorvastatin (40 or 80 mg) or simvastatin (40 or 80 mg), significantly reduced LDL-C compared with increasing the dose of simvastatin or atorvastatin monotherapy from 40 to 80 mg. In an 8-week study that randomly assigned 37 patients with homozygous sitosterolaemia to ezetimibe or placebo, ezetimibe lowered the two major plant sterols, sitosterol and campesterol, by 21% and 24%, respectively. In adult patients with homozygous sitosterolaemia, ezetimibe was evaluated in an 8-week study that enrolled 37 patients. Patients were randomised to receive ezetimibe 10 mg (n=30) or placebo (n=7). Ezetimibe lowered the two major plant sterols, sitosterol and campesterol, by 21% and 24%, respectively. The effects of decreasing sitosterol on morbidity and mortality in this population are not known.

Studies in children

Ezetimibe was tested in 138 children, 6 to 10 years of age, with heterozygous FH or non-familial hypercholesterolaemia. At week 12 of therapy, ezetimibe reduced LDL-C by 28% as compared to 1% with placebo, and other types of cholesterol by 26% as compared to 0% with placebo. Similar results were obtained in another study that enrolled 248 children, 10 to 17 years of age, with

heterozygous FH. It was seen that reduction of cholesterol was maintained even at 53 weeks of treatment.

The safety and efficacy of ezetimibe co-administered with doses of simvastatin above 40 mg daily have not been studied in paediatric patients 10 to 17 years of age. The safety and efficacy of ezetimibe co-administered with simvastatin have not been studied in paediatric patients < 10years of age. The long-term efficacy of therapy with Ezetrol in patients below 17 years of age to reduce morbidity and mortality in adulthood has not been studied.

IMPROVE-IT was a randomized, double-blind, parallel group, multicenter study of ezetimibe/simvastatin (combination tablet) versus simvastatin monotherapy, designed to assess the clinical benefit of the 2 therapies in the incidence of the composite endpoint in a stabilized acute coronary syndrome (ACS) subject population. Subjects were initially randomized in a 1:1 ratio to receive either ezetimibe/simvastatin 10/40 mg or simvastatin 40 mg daily and subsequently uptitrated in a blinded manner to ezetimibe./simvastatin 10/80 mg or simvastatin 80 mg daily based on LDL-C levels. The primary composite endpoint was CV death, non-fatal MI, documented unstable angina that requires admission into a hospital, and all coronary revascularization with either PCI or CABG occurring at least 30 days after randomized treatment assignment, and non-fatal stroke. IMPROVE-IT randomized a total of 18,144 subjects with stabilized high-risk ACS. The protocol-defined intent-to-treat (ITT) population included 9,067 subjects in the ezetimibe/simvastatin group and 9,077 subjects in the simvastatin monotherapy group. All subjects were to be followed for a minimum of 2.5 years. The median length of follow-up for the primary endpoint in the ITT population was 56.9 mos (4.7 years). Overall, the trial achieved 104,135.0 patient-years of follow-up for all-cause mortality. The study met its primary and all secondary composite efficacy endpoints and based on the design of the study, these benefits are attributable to ezetimibe.

Specifically, ezetimibe/simvastatin treatment significantly reduced the incidence of the following endpoints, compared to treatment with simvastatin monotherapy:

- the composite endpoint of death due to all causes, major coronary events, and non-fatal stroke.
- the composite endpoint of death due to coronary heart disease (CHD), non-fatal myocardial infarction (MI), and urgent coronary revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) occurring at least 30 days after randomization.
- the composite endpoint of cardiovascular death, non-fatal MI, documented unstable angina that requires admission into a hospital, all revascularization (including both coronary and non-coronary) occurring at least 30 days after randomization, and non-fatal stroke.

VI.2.3 Unknowns Relating to Treatment Benefits

The safety and efficacy of ezetimibe has not been studied in:

- children less than 6 years of age
- children less than 10 years of age receiving ezetimibe simultaneously with simvastatin
- children 10 to 17 years of age receiving ezetimibe simultaneously with doses of simvastatin above 40 mg daily
- long-term studies in children
- pregnant and breast-feeding women

VI.2.4 Summary of Safety Concerns

Important Identified Risks

Important identified risks are safety issues or undesirable effects for which there is sufficient proof of an association or link with the use of this medicine.

Table 54 provides information on the important identified risks and their preventability.

Table 54 Summary of Important Identified Risks

Risk	What is known	Preventability
Muscle injury (Rhabdomyolysis/myopathy)	Muscle injury is a rare but known effect of statins and other lipid-lowering medicines. It may be mild to severe, ranging from muscle pain, tenderness and weakness to muscle inflammation (myositis) and muscle breakdown (rhabdomyolysis). Serious cases of muscle injury did not occur in clinical studies when ezetimibe was given alone. However, rarely (reported in less than 1 in 1000 patients), serious cases of muscle injury were reported when ezetimibe was used along with statins. These events were generally mild to moderate in intensity. The mechanism by which statins and ezetimibe cause muscle injury is not known. It is not clearly known which patients are at risk of developing muscle injury with ezetimibe use. However, muscle injury may occur more frequently in patients who: are of advanced age have a small body frame and are weak have low thyroid hormone levels (hypothyroidism) have diseases affecting more than one system of the body are on a number of medicines have recently undergone surgery consume large quantities of alcohol are taking high doses of statins	Patients should promptly report signs and symptoms of muscle injury, should these occur. Creatine kinase is an enzyme that is released by damaged muscle. Patients in whom muscle injury is diagnosed clinically or on the basis of a rise in creatine kinase levels should immediately discontinue treatment with statins as well as ezetimibe and contact their doctor.
Abnormal liver function (Abnormal liver function)	Effects on the liver (such as raised liver enzymes or abnormal liver function tests, liver inflammation and liver failure) have been observed in patients treated with ezetimibe, but these events are uncommon (reported in less than 1 in 100 patients). Serious liver function abnormalities	Ezetimibe should not be used in patients with moderate or severe liver impairment. Ezetimibe should not be used along with a statin in patients with active liver disease or persistently raised liver enzymes of unknown cause.

Table 54 Summary of Important Identified Risks

Risk	What is known	Preventability
	were uncommon in clinical studies of ezetimibe. Most cases of abnormal liver function were mild to moderate in intensity and resolved upon stopping the medicine. The mechanism by which abnormal liver function associated with ezetimibe occurs is not known. It is not clearly known which patients are at risk of developing abnormalities in liver function with ezetimibe. However, patients who are generally at risk of abnormal liver function may have higher chances of developing abnormal liver function during ezetimibe use. Undesirable changes in liver function are generally seen in patients who: are of advanced age are men have a large waist circumference consume alcohol in large amounts are receiving treatment with certain medicines (such as painkillers, anti-seizure medicines, anti-tubercular medicines, herbal medications, or use illicit drugs) have liver disease (such as fatty liver disease, hepatitis B and C and other forms of liver inflammation) have certain medical conditions (such as autoimmune diseases, haemochromatosis, Wilson's disease, congestive heart failure, coeliac disease, hypothyroidism, Addison's disease and glycogen storage disease).	It is recommended to perform liver function tests before starting treatment with ezetimibe and whenever required during treatment. Patients receiving ezetimibe with a statin should have liver function tests performed before starting treatment and regularly during treatment. Immediately contact your doctor if any symptoms of liver problems such as feeling tired or weak, dark colored urine, pale colored stool, loss of appetite, or yellow discoloration of the eyes occur.
Allergic reactions (Hypersensitivity)	Allergic reactions can occur with any medicine and are known to occur with ezetimibe use. Allergic reactions, such as rashes; itching; reddish itchy bumps on the skin (hives); difficulty in breathing and/or swallowing; congestion of the nose; and swelling of the face,	Ezetimibe should not be used by patients who are allergic to ezetimibe or any of the inactive ingredients of the drug product. Patients who develop signs and symptoms of allergic reactions

Table 54 Summary of Important Identified Risks

Risk	What is known	Preventability
	tongue, throat, lips, eyes, hands and feet, may occur rarely with the use of ezetimibe. Serious allergic reactions were rare (reported in less than 1 in 1000 patients) in clinical studies. These may include whole body reaction (anaphylaxis) or swelling under the skin (angioedema). Most cases of allergic reactions with ezetimibe were mild to moderate and resolved upon stopping the medicine.	should promptly stop taking the medicine and seek medical attention immediately.

Table 54 Summary of Important Identified Risks

Risk	What is known	Preventability
Drug interaction with medicines often used in organ transplant patients to prevent organ rejection (ciclosporin)	Clinical studies have shown an increased level of ezetimibe in renal transplant patients taking ezetimibe and ciclosporin. In a study of healthy subjects, administration of ezetimibe and ciclosporin resulted in an increase in the level of ciclosporin.	Interactions can be prevented by avoiding the use of ezetimibe at the same time as ciclosporine. Side effects due to this interaction can be prevented by monitoring of the concentration of ciclosporin in the blood. Patients should talk to their doctor/pharmacist about any other medicines they are taking or might be taking.
Drug interaction with medicines used to prevent blood clots (warfarin, phenprocoumon, acenocoumarol or fluindione; anticoagulants)	A study in healthy adults showed no significant effect on warfarin levels and prothrombin time with co- administration of ezetimibe. There have been post-marketing reports of increased International Normalized Ratio (INR) in patients who had ezetimibe added to warfarin or fluindione. Most of these patients were also on other medications. Prothrombin time and INR are blood tests used to monitor patients taking warfarin.	If warfarin, another coumarin anticoagulant, or fluindione is administered along with ezetimibe, the INR or prothrombin time should be appropriately monitored to reduce the risk of bleeding events associated with these drugs. Patients should talk to their doctor/pharmacist about any other medicines they are taking or might be taking.

Important Potential Risks

Important potential risks are safety issues or undesirable effects for which there is some basis for suspicion of a link with the use of medicine of interest, but this association has not been confirmed.

Table 55 provides information on the important potential risks identified with the medicinal product.

Table 55 Summary of Important Potential Risks

Risk	What is known
Gallbladder inflammation/gallstones (Cholecystitis/cholelithiasis)	It is not known with surety if gallstones/gallbladder inflammation occurs due to the use of ezetimibe. Gallstones (cholelithiasis) and gallbladder inflammation (cholecystitis) were uncommon adverse effects (reported in less than 1 in 100 patients) in clinical studies of ezetimibe. The mechanism of gallstone formation or gallbladder inflammation associated with the use of ezetimibe is thought to be due to increased cholesterol removal in the bile because of ezetimibe. However, the exact mechanism is unknown. Signs and symptoms of gallbladder inflammation and gallstones are sharp, cramping, dull or steady pain in the upper abdomen; clay-coloured stools; fever; nausea and vomiting; and yellowing of the skins and whites of the eyes (jaundice). It is not clearly known which patients are at risk of developing gallstones/gallbladder inflammation with ezetimibe use. However, patients who are generally at risk of gallstones/gallbladder inflammation may have higher chances of developing gallstones/gallbladder inflammation during ezetimibe use. Gallstones/gallbladder inflammation are generally seen in patients who: have a family history of gallstones/gallbladder disease are of advanced age are women are overweight or obese have recently lost weight rapidly are physically inactive have metabolic syndrome (high blood sugar, high blood pressure, high triglyceride levels and a large waistline). Most of the cases of gallstones/gallbladder inflammation that occurred in clinical studies were moderate to severe in intensity. Ezetimibe is not recommended to be used together with fibrates (another class of lipid-lowering medicines), as the risk of gallstones/gallbladder inflammation may be increased.
Inflammation of the pancreas (Pancreatitis)	It is not known with surety if pancreatitis, or inflammation of the pancreas, occurs due to the use of ezetimibe. No cases of pancreatitis were observed in clinical studies of ezetimibe. Pancreatitis has been reported rarely after the medicine has been marketed. The mechanism of pancreatitis associated with the use of ezetimibe is unknown. It is also not clearly known which patients are at risk of pancreatitis with ezetimibe use. Pancreatitis is generally seen in patients who: are of advanced age have gallstones consume alcohol in large amounts have high amounts of triglycerides in their blood (hypertriglyceridemia) Signs and symptoms of pancreatitis are pain in the upper part of the abdomen that radiates to the back; swelling and tenderness of the abdomen; nausea and vomiting; fever; and increased heart rate.

Missing Information

Missing information is information about the safety of a medicine or pill which is not available at the time of submission of a particular risk management plan.

Examples of missing information include populations not studied (e.g. pregnant women or patients with severe renal impairment) or where there is a high likelihood of off-label use (pill used for indication other than what it is approved for).

Table 56 provides missing information with the medicinal product.

Table 56 Summary of Missing Information

Missing information	What is known
Use in pregnancy and breastfeeding (Exposure during pregnancy and lactation)	Ezetimibe has not been studied in pregnant and breast-feeding women. Ezetimibe should not be used during pregnancy and breastfeeding.
Use in children (Limited clinical trial experience in children age 10 to 17 years old beyond 1 year and in children 6 to 10 years old beyond 12 weeks. No clinical trial experience in children less than 6 years of age)	Ezetimibe has not been studied in children less than 6 years of age and should not be used in children of this age group. Simultaneous use of ezetimibe and simvastatin has not been studied in children less than 10 years of age. Ezetimibe has not been studied in children 10 to 17 years of age receiving a higher than the standard dose of simvastatin simultaneously. There is only limited exposure in children of 6-17 years of age. Long-term effects of ezetimibe therapy in children are not known.

VI.2.5 Summary of Risk Minimization Measures by Safety Concern

This medicine has no additional risk minimization measures.

VI.2.6 Planned Post-Authorization Development Plan

VI.2.6.1 List of Studies in Post-Authorization Development Plan

Table 57 List of Studies in Post-authorization Development Plan

Actions	Objectives	Efficacy Concerns Addressed	Milestones/ Exposure	Study Status	Milestones /Calendar Time
Clinical Study P04103 IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial)	A randomized, active-control, double-blind study of subjects with stabilized high-risk acute coronary syndrome. The primary objective was to evaluate the clinical benefit of ezetimibe/simvastati	IMPROVE-IT assessed the additional clinical benefit of ezetimibe when taken with simvastatin, compared to simvastatin monotherapy,	Randomized 18,144 patients. The primary endpoint event occurred in 5314 patients, meeting projected number of events. All patients followed for a minimum of 2.5 years and the	Completed	FPE: Oct 2005 Study Completion Sep-2014 CSR: Mar-2015

Table 57 List of Studies in Post-authorization Development Plan

Actions	Objectives	Efficacy Concerns Addressed	Milestones/ Exposure	Study Status	Milestones /Calendar Time
	n combination compared with Simvastatin monotherapy. Clinical benefit is defined as the reduction in the risk of the occurrence of the composite endpoint of CV death, non-fatal MI, documented unstable angina that requires admission into a hospital, and all coronary revascularization with either PCI or CABG occurring at least 30 days after randomized treatment assignment, and non-fatal stroke.	in the risk reduction for the occurrence of CV outcomes	median follow-up for mortality was greater than 6 years.		

VI.2.6.2 Studies which are a Condition of the Marketing Authorisation

None of the studies in the table above are a condition of the marketing authorisation.

VI.2.7 Summary of Changes to the Risk Management Plan Over Time

Table 58 Major Changes to the Risk Management Plan

RMP Version	Date	Safety Concerns	Comment
2.0	31-DEC-2010		Addition of Non clinical finding for Nonglandular stomach/esophagus. Update for Study P05522 Indication/Target Population: CHD/Ischemic Stroke
2.1	31-DEC-2012		A study in children was completed, and the results included in this version of the RMP. The safety and efficacy results in children were comparable to those in adults. Information from the completed SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) follow-up study was added. Results did not confirm an increased risk of cancer or increased risk of dying from cancer in patients treated with ezetimibe and simvastatin. The revised date of completion of the IMPROVE-IT study was added.
3.0	24-MAR-2015	Removal of cancer (Malignancy) as an Important Potential Risk.	▪ Updated based on results of completed trial (IMPROVE-IT). Update for SEAS Follow -Up Study.
3.1	01-OCT-2015		Version 3.1 is an administrative update and includes the previously recognized (Version 2.1) Important Identified Risks of Drug interaction with ciclosporin and Drug interaction with warfarin, another coumarin anticoagulant, or fluindione in the appropriate sections of the document.
3.2	29-FEB-2016		Version 3.2 is an administrative update regarding the indication for use.

Key Points

- This medication is used to reduce blood cholesterol levels in patients with raised cholesterol level in blood or elevated fat levels in blood. It may also be used to reduce the risk of cardiovascular events in patients with coronary heart disease and a history of acute coronary syndrome.
- Muscle injury is a known risk associated with the use of statins and ezetimibe. Patients should be alert to any signs or symptoms of muscle injury and seek medical attention immediately, should these occur.
- Abnormal liver function is a known risk associated with the use of ezetimibe. Before starting treatment with ezetimibe, blood tests to check liver function are recommended. Patients should be alert to any signs or symptoms of abnormal liver function and seek medical attention, should these occur.
- This medicine should not be used by those who have moderate or severe liver failure.
- This medicine should not be used by those who have a history of allergic reactions to ezetimibe or any inactive ingredient of the drug product.
- Caution should be exercised while simultaneously administering ciclosporin (an immunosuppressant used in organ transplantation) with ezetimibe.
- Bleeding time should be monitored while simultaneously administering anticoagulants (such as warfarin, coumarins and fluindione) with ezetimibe.
- Gallstones, gallbladder inflammation and pancreas inflammation may occur in patients using ezetimibe. Patients should be alert to any signs and symptoms of gallstones, gallbladder inflammation and pancreas inflammation and should seek medical attention promptly, should these occur.
- This medicine should not be used by pregnant or breastfeeding women.