VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Cardiovascular disease (CVD) is responsible for one-third of global deaths and is a leading and increasing contributor to the global disease burden. The costs associated with the the condition are enormous, with the cost of CVD and stroke in the US in 2007 estimated at 431.8 milliard dollar. (3)

One of the highly prevalent risk factor for CVD is **hyperlipidemia** or **hyperlipoproteinemia** including **hypercholesterolemia** which are extremely common in the general population.
Among the dislipidemias hypercholesterolemia is the most important risk for the development of coronary heart disease and the main responsible lipoprotein in coronary atherosclerosis is low density lipoprotein (LDL) which carries the most of plasma cholesterol in the blood.

The guidelines of the American Heart Association and the NCEP Adult Treatment Panel III (ATP III) define hypercholesterolemia as a blood cholesterol concentration of greater than or equal to 6.2 mmol/l (240 mg/dl). Desirable cholesterol concentrations are less than 5.2 mmol/l (200 mg/dl). The National Health and Nutrition Examination Survey III, performed from 1988-1991, found that 26% of American adults had high blood cholesterol concentrations and 49% had desirable values. (4)

In 2001-2002 a survey found the overall prevalence of hypercholesterolemia was 47%, when hypercholesterolemia was defined as a low-density lipoprotein cholesterol level of ≥3.4 mmol/l (≥130 mg/dl) [or ≥2.6 mmol/l (≥100 mg/dl) if DM or CVD was present] or on treatment.

Serum cholesterol concentrations vary widely throughout the world. Generally, countries associated with low serum cholesterol concentrations (eg, Japan) have lower CHD event rates, while countries associated with very high serum cholesterol concentrations (eg, Finland) have very high CHD event rates. However, some populations with similar total cholesterol levels have very different CHD event rates, as would be expected given that other risk factors (e.g. prevalence of smoking or diabetes mellitus) also influence CHD risk. The cholesterol levels in developing countries tend to increase as western dietary habits (the MacDonald's syndrome) replace traditional diets.

Race
Among adults, National Health and Nutrition Examination Survey III data (1988-1992) show more frank hypercholesterolemia among non-Hispanic white persons (19%) than Mexican Americans (15%) or non-Hispanic black persons (16%).

Sex
Hypercholesterolemia is more common in men younger than 55 years and in women older than 55 years.

Age
In adults, hypercholesterolemia increases with advancing age. (4)

VI.2.2 Summary of treatment benefits

The association between elevated serum cholesterol levels and risk of cardiovascular disease has been well established through a number of epidemiologic studies, such as the Framingham Heart Study and the Seven Countries Study. Multiple randomized controlled trials over the past two decades have consistently shown that treatment with 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) in dyslipidemic patients with and without established vascular disease effectively lowers low-density lipoprotein cholesterol (LDL-C) levels and reduces major cardiovascular events. Based upon these lines of evidence, the National Cholesterol Education Program (NCEP) through the Adult Treatment Panel (ATP) III has recommended reducing LDL-C levels as the primary goal and supports the use of statins as the initial preferred therapy.8 Recent trials have suggested that more aggressive lowering of LDL-C to levels of ,70 mg/dL may result in incremental cardiovascular benefit. Therefore, ATP III was updated to include an optional LDL-C goal of ,70 mg/dL in very high-risk patients that have established cardiovascular disease with multiple cardiac risk factors.(5)

Despite growing evidence supporting a lower-is-better approach for LDL-C, treatment with statin therapy alone may not be sufficient to achieve optimal LDL-C targets, with some patients requiring greater than a 50% reduction. Institutional surveys have shown that only two-thirds of vascular disease patients are at an LDL-C goal of, 100 mg/dL and less than a third of very high-risk patients are able to reach an LDL-C goal of, 70 mg/dL. Based upon these treatment failures, combination therapies using multiple cholesterol-lowering agents including ezetimibe in addition to statin therapy have been investigated. While ATP III recommends statin therapy as the first-line agent for the treatment of elevated LDL-C, alternative therapies such as ezetimibe, niacin, bile-acid sequestrants, and ileal bypass surgery can also effectively lower LDL-C. A recent meta-analysis has shown that these nonstatin-based treatments can lower cardiac events similar to statin therapies, with an equivalent observed relationship between degree of LDL-C lowering and reduction in coronary heart disease (CHD) risk. These data suggest that the addition of these therapies to a background of statin treatment may produce an incremental lowering of LDL-C, and possibly result in a further reduction in cardiovascular events. (5)

VI.2.3 Unknowns relating to treatment benefits

Hepatic insufficiency

After a single 10 mg dose of ezetimibe, the mean AUC for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic insufficiency (Child Pugh score 5 or 6), compared to healthy subjects. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency (Child Pugh score 7 to 9), the mean AUC for total ezetimibe was increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects.
Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child Pugh score >9) hepatic insufficiency, ezetimibe is not recommended in these patients. (6)

1.8.2 Risk Management System	

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Muscle breakdown/ Pain or weakness in muscles **(Rhabdomyolysis / Myopathy)**	Patients starting therapy with ezetimibe have an increased risk for development of muscle diseases, like pain or weakness in muscles (myopathy), or in severe cases, muscle breakdown (rhabdomyolysis). Based on the current experiences, a high percent of these reactions occurred in those patients, who used Ezetimibe together with statins (which are also drugs used to lower blood cholesterol levels) or with other drugs also known to cause such reactions. Myopathy is a condition when the muscles do not function normally resulting in muscular weakness, muscle aches, like pain in arms and legs, unusual tiredness or weakness, muscle cramps or muscle stiffness. Muscle breakdown (rhabdomyolysis) means such a condition in which damaged skeletal muscle tissue breaks down rapidly and their contents release into the bloodstream. One of the early complications of a muscle breakdown can be a very high level of potassium in the blood (called hyperkalaemia), which can lead to disturbances in the heart rhythm or in very severe cases, it can cause cardiac arrest (when the heart stops beating). In other cases, the liver can also be injured. On rare occasions, muscle breakdown resulting in kidney	In rare cases, these situations (especially when they lead to kidney damage or heart problems), can be potentially life threatening. However, when treated in time, most of these reactions have a good outcome. For this reason, early recognition of these conditions is essential. Therefore, patients should contact their doctors immediately if they experience unexplained muscle pain, tenderness or weakness, or muscle cramps and stiffness, as these symptoms can draw the attention to these possible undesirable effects. If such a muscle disorder is suspected based on muscle symptoms or is confirmed by medical and laboratory examinations, Ezetimibe (and also statins or any other drugs which are known to also cause muscle breakdown in patients taking these medications simultaneously), should be discontinued immediately and an appropriate treatment should be initiated to avoid more severe consequences.

Risk	What is known	Preventability
	damage can be serious and may become a potentially life-threatening condition**.** However, if recognized and treated correctly in time, these reactions often have good outcomes.	
Liver damage, elevations in some laboratory blood tests of liver **(Abnormal liver function)**	The liver supports almost every organ in the body and is vital for survival. The liver plays a central role in transforming and clearing chemicals/medicaments and due to its unique metabolism and close relationship with the gastrointestinal tracts, it is susceptible to the toxicity from these agents. Certain medicinal agents, when taken in overdoses and sometimes even when introduced within therapeutic ranges, may injure the organ. During treatment with Ezetimibe liver damages may occur. These problems occur more likely when ezetime is administered together with statins (which are also drugs used to lower blood cholesterol levels). The classic symptoms of liver damage include the following: pale stools, dark urine, jaundice (yellowing eyes/skin), swelling of the abdomen, ankles and feet, persistent nausea/vomiting, stomach/abdominal pain, fatigue, bruising. In several cases, liver function alterations might not be accompanied with any symptom (called as asymptomatic liver function alteration). Liver damages can be diagnosed by laboratory blood tests called liver function tests, which show elevated values in these cases.	Liver function disorders may occur more likely when ezetime is administered together with statins (which are also drugs used to lower blood cholesterol levels). For this reason, Patients' doctors should order a blood test before starting treatment of ezetimibe with a statin to check how well the liver is working. These kinds of blood tests might be repeated after starting treatment of ezetimibe with a statin. Patients who currently have liver problems or whose laboratory blood test results show an abnormal liver function for a longer period without any known reason should not take ezetimibe together with a statin. According to the current knowledge, there is no need to modify the standard dosage of ezetimibe in patients who have mild liver impairment. However, in patients with moderate or severe liver problems, the use of ezetimibe is not recommended. Patients should inform their doctors before starting the ezetimibe treatment if they know about any previous liver diseases (or they should discuss it when they are not

Risk	What is known	Preventability
	In most of the cases, these liver function abnormalities disappear after the ezetimibe treatment is stopped or sometimes even when the ezetimibe treatment is continued.	sure about it), and patients should immediately seek medical advice if any symptom of a liver damage, like pale stools, dark urine, jaundice, swelling of the abdomen, ankles and feet, stomach/abdominal pain, long-standing nausea/vomiting, fatigue and/or bruising occurs.
Allergic reaction **(Hypersensitivity)**	Like all medicines, ezetimibe can cause allergic reactions in patients who are susceptible for such events. Allergic reactions including rash and hives; raised red rash, sometimes with target-shaped lesions (erythema multiforme) have been reported in general use. Severe allergic reactions, including swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing (which requires treatment right away) have also been reported in connection with the use of ezetimibe. Patients who are allergic to ezetimibe or any of the other ingredients of this medicine must not take ezetimibe.	Patients who are allergic to ezetimibe or any of the other ingredients of this medicine must not take this medicament. Patients should always inform their doctors about any allergies they have before starting the treatment with this product. Patients should be advised to remain alert for any symptoms compatible with an allergic reaction (e.g. difficulty in breathing, itching, hives and swelling (especially of the face and/or throat), etc.) and to stop ezetimibe and seek medical advice immediately if such symptoms occur.
Simultaneous use of other medications which are used to prevent blood clots (anticoagulants) during treatment with ezetimibe **(Drug interaction with warfarin, another coumarin anticoagulant or fluindione)**	A drug interaction is a situation in which a medicine affects the activity of another drug when both are administered together. There have been drug interactions reported when ezetimibe was used together with medicines that prevent blood clots (called anticoagulants, like warfarin or fluindione). In these cases, a	Patients should always inform their doctors about taking any medicines together with ezetimibe, especially if they take any medicines which are used to prevent blood clots, such as warfarin, phenprocoumon, acenocoumarol or fluindione (called anticoagulants). If ezetimibe is added to these

Risk	What is known	Preventability
	laboratory test called International Normalised Ratio (INR) showed increased values, that draws attention to an increased risk of bleeding in these patients.	medicines, the laboratory blood test called INR (International Normalised Ratio) should be regularly checked. In some cases, modification of the dose of these medicines might be necessary.
Simultaneous use of ciclosporin (a medicine often used in organ transplant patients) during treatment with ezetimibe **(Drug interaction with ciclosporin)**	Ciclosporin is a medicine that is often used in renal transplant patients to prevent any disorder (rejection) of the transplanted foreign organ. There have been reports in which ciclosporin level increased in patients who started treatment with ezetimibe simultaneously. High level of ciclosoprin may cause several serious side effects therefore the blood concentrations of this medicine should be monitored in patients receiving ezetimibe and ciclosporin simultaneously.	Patients should always inform their doctors about taking any medicines together with ezetimibe, especially if they take ciclosporin, which is a medicine often used in organ transplant patients. Ciclosporin concentrations should be regularly checked in those patients who receive ezetimibe and ciclosporin simultaneously.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Inflammation of the gallbladder/ Gallstones **(Cholecystitis/ Cholelithiasis)**	Cholelithiasis is the medical term for gallstone disease. Gallstones are concretions that form in the biliary tract, usually in the gallbladder. Gallstones develop insidiously, and they may remain asymptomatic for decades. Cholecystitis is the inflammation of the gallbladder, which occurs most commonly due to blockage of the cystic duct with gall stones leading to increased pressure in the gallbladder, stagnation of bile and consecutive infection. Gallbladder infections can occur with a sudden onset called acute cholecystitis. On rare occasions serious complications might occur like gall bladder perforation which is a rare but life-threatening complication of the gallbladder infection of sudden onset or bacteria can spread rapidly back up the ductal system into the liver which can result in a life-threatening infection called ascending cholangitis. Therefore early diagnosis and treatment of an acute cholecystitis is of high priority..

Risk	**What is known (Including reason why it is considered a potential risk)**
	Chronically, gallstones in the gallbladder may cause progressive fibrosis and loss of function of the gallbladder, a condition known as chronic cholecystitis. (2) Gallstones and/or inflammation of the gallbladder usually present with pain in the right upper quadrant of the abdomen, nausea, vomiting and fever. For most patients diagnosed with acute cholecystitis, the definitive treatment is surgical removal of the gallbladder, called cholecystectomy. Ezetimibe is often used in combination with fibrates (medicines also used for lowering cholesterol). Based on animal studies fibrates may increase cholesterol excretion into the bile, leading to gallstone formation. In a clinical study cholecystectomy was carried out more often in patients who were treated with the combination of ezetimibe and fenofibrate. The safety and efficacy of the combined use of ezetimibe and fibrates have not been established. A risk of increased gall stone formation associated with the therapeutic use of ezetimibe cannot be ruled out. Patients and physicians should be aware of the possible risk of gallbladder diseases (gallstone formation and inflammation) when fenofibrate and ezetimibe are administered simultaneously. Therefore, patients should always inform their doctors about taking any medicines together with ezetimibe, especially if they take fibrates. If a gallstone disease (cholelithiasis) is suspected in a patient receiving ezetimibe and fenofibrate (on the basis of either medical test results or typical symptoms), patients should contact their doctors. In these cases gallbladder investigations are indicated and this therapy should be stopped.
Inflammation of pancreas (Pancreatitis)	Pancreatitis is the medical term for the inflammation of the pancreas. It can be manifested with a sudden onset accompanied with intensive symptoms called acute pancreatitis or can occur over several years often with moderate and non-specific symptoms (especially in the first period), the latter called as chronic pancreatitis. Acute inflammation of the pancreas are often associated with gallstones. The most common symptoms of pancreatitis are severe upper abdominal burning pain radiating to the back, nausea, and vomiting that is worsened with eating. Acute pancreatitis might be manifested in mild or more severe form with complications leading to a potentially life-threatening condition. After ezetimibe products were put on the market, there were

Risk	What is known (Including reason why it is considered a potential risk)
	reports about inflammation of the pancreas (pancreatitis) which occurred during treatment with ezetimibe. Patients receiving ezetimibe and their doctors should be aware of the possible risk of pancreatitis. If patients experience symptoms typical for pancreatitis (such as severe abdominal pain which radiates to the back, jaundice, fever, severe nausea nad vomiting, etc.), they should immediately contact their doctors, as early diagnosis and treatment of this condition is essential for a better outcome.

Missing information

Risk	What is known
Limited information on use of Ezetimibe during pregnancy **(Exposure during pregnancy)**	In the animal studies (which are generally conducted during a relative early phase of the drug development), ezetimibe, when administered alone, did not cause relevant malformations in the developing offspring and no direct or indirect harmful effects were seen on the pregnancy, birth or after-birth development of offspring. However, In animal studies simultaneous administration of ezetimibe with lovastatin (a medicine also used to lower blood cholesterol) resulted in some deaths of the developing embryos. Since there are no sufficient data on the safe use of the product during human pregnancies (since its use was not examined during human pregnancies), therefore taking ezetimibe is not recommended in women who are actually or might be pregnant. Ezetimibe should be given to pregnant women only if clearly necessary. Simultaneous therapy with ezetimibe and a statin is prohibited during pregnancy, therefore patients should not take ezetimibe with a statin if they are pregnant, are trying to get pregnant or think they may be pregnant. Patients who get pregnant while taking ezetimibe together with a statin, should stop taking both medicines immediately and contact their doctor. Patients who are pregnant or breast-feeding, or who think they may be pregnant or who are planning to get pregnant, should consult their doctors or pharmacist before starting the treatment with ezetimibe.
Limited exposure in children between 6 and 17 years of age	There is limited data on the safe and effective use of ezetimibe in children between 6 and 10 years of age. During the development of this medicine, the use of ezetimibe (regarding its effectiveness

Risk	What is known
(Limited exposure in children between 6 and 17 years of age)	and safety) was studied during a 12-week treatment period in about 140 children of 6 to 10 years of age. However, effects of ezetimibe for treatment periods over 12 weeks have not been studied in this age group. There is no clinical experience with co-administration of ezetimibe and a statin (another medication used for the treatment of high blood cholesterol levels) in children under 10 years of age. There is limited clinical experience about the use of ezetimibe in adolescent patients (aged 10-17 years old). During the development of this medicine, a study involving about 250 boys and girls of 10 to 17 years of age was carried out, where the patients were treated with ezetimibe and simvastatin (another medicine for the treatment of high blood cholesterol level) together. In this study, there was generally no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. However, the effects of ezetimibe for a longer treatment period (over 33 weeks) on growth and sexual maturation have not been studied. The long-term effectiveness of the ezetimibe therapy regarding its further positive effects for the adulthood in patients below 17 years of age has not been studied. The daily dose of ezetimibe in adolescents and children (6 to 17 years of age) is the same as for adults. The ways the body absorbs, distributes and gets rid of ezetimibe are similar between children over 6 years and adults. Starting a treatment with ezetimibe in children, must be controlled by a specialist. When treating a child with the combination of ezetimibe and a statin (which is also a medicine used to lower blood cholesterol), the dosage instructions for the statin should be considered. Close follow-up is recommended in this age-group.
Exposure in children less than 6 years of age (Exposure in children less than 6 years of age)	There is no available data on the safe and effective use of ezetimibe in children younger than 6 years.

VI.2.5 Summary of additional 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) / patient information leaflet (PIL). The measures in these documents are known as routine risk minimisation measures.

Appropriate labelling is planned for the management of all the above listed safety concerns of Gedeon Richter Plc.'s product of Ezetimibe 10 mg tablets.

The Summary of Product Characteristics and the Package Leaflet for of Ezetimibe 10 mg tablets can be found in "***Annex 2 - SmPC & Package Leaflet***".

Ezetimibe 10 mg tablets has no additional risk minimisation measures.

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

No post-authorisation studies are planned by the MAH for its product of Ezetimibe 10 mg tablets.

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

Not applicable, since this is the first RMP on Ezetimibe 10 mg tablets compiled by Gedeon Richter Plc under the Decentralised Procedure of DK/H/2467/001/DC.