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. 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.

Primary Hypercholesterolaemia

Serum cholesterol concentrations vary widely throughout the world. Generally, countries associated with low serum cholesterol concentrations (eg, Japan) have lower coronary heart disease (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 (eg, prevalence of smoking or diabetes mellitus) also influence CHD risk. The cholesterol levels in developing countries tend to increase as western dietary habits (McDonald's syndrome) replace traditional diets[1].

Homozygous Familial Hypercholesterolaemia (HoFH)

The prevalence (proportion of individuals in a population having HoFH) of heterozygous FH in Europe approximates that of the United States 1 case per 500 persons), but certain regions, such as Iceland and Finland, or populations have a higher incidence (measure of the probability of occurrence of HoFH in a population within a specified period of time). The prevalence of heterozygous FH among French Canadians is 1 case per 270 persons and is 1 case per 170 persons in Christian Lebanese. Due to the founder effect and relatively isolated populations, 3 distinct populations within South Africa have an extremely high prevalence of FH: 1 case per 67 in Ashkenazi Jews and 1 case per 100 persons in both Afrikaners and South African Indians.

Homozygous Sitosterolaemia (phytosterolaemia)

Sitosterolemia is thought to be a very rare disorder. Only approximately 40 patients had been identified worldwide by 2000. More than likely, sitosterolemia is significantly underdiagnosed. Many patients are probably misdiagnosed with hyperlipidemia; therefore, assay of plasma sterol levels, the definitive diagnostic test for sitosterolemia, is not performed. Only approximately 40 patients with sitosterolemia had been reported worldwide as of the year 2000; therefore, very little information on racial or ethnic predilection is available, especially because bias of ascertainment is likely. No ethnic predilection is apparent in sitosterolemia, although the small number of patients diagnosed makes it premature to draw any conclusions No sex predilection is noted. Males may be more prone to the severe complications of sitosterolemia. The condition can manifest at any age.

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 studies. Based upon these lines of evidence, the National Cholesterol Education Program (NCEP) through the Adult Treatment Panel (ATP) III has recommended reducing LDL-C (low-density lipoprotein cholesterol) levels as the primary goal and supports the use of statins as the initial preferred therapy. 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. 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 firstline agent for the treatment of elevated LDL-C, alternative therapies such as ezetimibe can also effectively lower LDL-C. A recent study 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.

VI.2.3 Unknowns relating to treatment benefits

No clinical data are available on the use of ezetimibe during pregnancy. Animal studies on the use of ezetimibe in monotherapy have shown no evidence of direct or indirect harmful effects on pregnancy, embryofoetal development, birth or postnatal development.
The clinical experience in paediatric and adolescent patients (aged 10-17 years old) is limited. There is limited data on safety and efficacy in children >6 and < 10 years.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What Is Known**	**Preventability**
Muscle problems, including muscle breakdown resulting in kidney damage (Rhabdomyolysis/myo pathy)	On rare occasions, muscle problems, including muscle breakdown resulting in kidney damage, can be serious and may become a potentially life-threatening condition.	Contact your doctor immediately if you experience unexplained muscle pain, tenderness, or weakness.
Elevations in some laboratory blood tests of liver (Abnormal liver function)	Ezetimibe may cause elevations in some laboratory blood tests of liver (transaminases)	Your doctor should do a blood test before you start taking ezetimibe with a statin. This is to check how well your liver is working. Your doctor may also want you to have blood tests to check how well your liver is working after you start taking ezetimibe with a

Risk	What Is Known	Preventability
		statin.
Allergic reactions (Hypersensitivity)	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 been reported in general use.	Do not take ezetimibe if: you are allergic (hypersensitive) to ezetimibe or any of the other ingredients of this medicine
Drug interaction with ciclosporin	Caution should be exercised when initiating ezetimibe in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving Ezetimibe and ciclosporin.	Tell your doctor if you are taking cyclosporin (often used in organ transplant patients).
Drug interaction with warfarin, another coumarin anticoagulant, or fluindione.	There have been post-marketing reports of increased International Normalised Ratio (INR) in patients who had ezetimibe added to warfarin or fluindione. If ezetimibe is added to warfarin, another coumarin anticoagulant, or fluindione, INR should be appropriately monitored.	Tell your doctor if you are taking medicines with an active ingredient to prevent blood clots, such as warfarin, phenprocoumon, acenocoumarol or fluindione (anticoagulants).

Important potential risks

Risk	What is Known
Gallstones or inflammation of the gallbladder (Cholecystitis/choletithiasis)	Ezetimibe may cause gallstones or inflammation of the gallbladder (which may cause abdominal pain, nausea, vomiting).
Inflammation of the pancreas (Pancreatitis)	Ezetimibe may cause inflammation of the pancreas often with severe abdominal pain

Missing information

Risk	What is Known
Exposure during pregnancy	There is no experience from the use of ezetimibe without a statin during pregnancy.
Limited exposure in children age 10 to 17 beyong 1 year and limited exposure in children less than 10 years of age	The clinical experience in paediatric and adolescent patients (aged 10-17 years old) is limited.There is limited data on safety and efficacy in children >6 and < 10 years.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a SmPC which provides physicians, pharmacists, and other healthcare professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package information leaflet (PIL). The measures in this documents as well as the prescription-only status are known as routine risk minimization measures which are considered sufficient for this medicinal product. No additional risk minimization measures are proposed.

VI.2.6 Planned post authorisation development plan

Not Applicable

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

Not Applicable