4.2 Part VI.2 Elements for a Public Summary

4.2.1 Part VI.2.1 Overview of disease epidemiology

Ezetimibe/simvastatin is used together with diet to lower high cholesterol levels in patients with hypercholesterolaemia and Homozygous Familial Hypercholesterolaemia (HoFH), as highblood fat levels block the arteries and can cause coronary heart disease, stroke, chest pain, etc. Ezetimibe/simvastatin is also used to reduce the risk of cardiovascular events in patients with coronary heart disease and a history of acute coronary syndrome.

1. **Hypercholesterolemia**

Hypercholesterolemia is the most common cause of high blood fat levels. The condition is aggravated by life style factors, including excessive intake of saturated fat, obesity, and sedentary lifestyle ("couch potato").

The primary consequence of hypercholesterolemia is increased coronary heart disease (CHD) risk. 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 higher CHD event rates. However, some populations with similar total cholesterol blood levels have 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 replace traditional diets. In USA an estimated 71 million (33.5%) US adults aged 20 years or older has high LDL-C, but only 34 million (48.1%) are treated [Anastasopoulou C, 2015].

2. **Homozygous Familial Hypercholesterolemia**

This kind of hypercholesterolemia is a genetic disorder inherited from both parents [Marais D, 2004]. The risk of diseases such as coronary heart disease, stroke, chest pain is very high in these patients and most do not survive adulthood beyond age 30 years unless treated. Children are at risk of early coronary events, and sudden death or acute myocardial infarction may occur in patients as young as 1-2 years.

Homozygous Familial Hypercholesterolemia occurs in 1 case per 1 million persons, though it occurs more often in relatively isolated populations [Citkowitz E, 2013].

3. **Prevention of Cardiovascular Events**

Cardiovascular disease (CVD) is a group of diseases that include both the heart and blood vessels (1), thereby including coronary heart disease (CHD) and coronary artery disease (CAD), and acute coronary syndrome (ACS) among several other conditions. CHD is a major cause of death and disability in developed countries. Although the mortality for this condition has gradually declined over the last decades in western countries, it still causes about one-third of all deaths in people older than 35 years. The 2016 Heart Disease and Stroke Statistics update of the American Heart Association (AHA) has recently reported that 15.5 million persons ≥20 years of age in the USA have CHD [Sanchis-Gomar F, 2016].

4.2.2 Part VI.2.2 Summary of treatment benefits

There have been several studies on the fat lowering effect and safety of the combination of ezetimibe/simvastatin. The safety profile was similar to the therapies with a single product, however the effect on the reduction of the blood fat was higher. Ezetimibe/simvastatin has been shown in one large study to reduce major cardiovascular events in patients with coronary heart disease and ACS event history. There was an overall benefit for all strokes; however there was a small non-significant increase in haemorrhagic stroke among patients taking ezetimibe-simvastatin compared to patients taking simvastatin alone

4.2.3 Part VI.2.3 Unknowns relating to treatment benefits

There is limited clinical trial experience in children aged 10-17 and no clinical trial experience in children less than 10 years of age. Drug interaction studies have only been performed in adults.

No clinical data are available on the use of ezetimibe simvastatin during pregnancy. Animal studies on combination therapy have demonstrated reproduction toxicity.

No controlled clinical trials with simvastatin have been conducted in pregnant women.

No clinical data are available on the use of ezetimibe during pregnancy.

4.2.4 Part VI.2.4 Summary of safety concerns

Table 4-1 Important identified risks

Risk	What is known	Preventability
Allergy (hypersensitivity)	The following symptoms: rash, itchy skin rash, severe allergic responses and swollen face, lips, throat or tongue can occur. This may affect up to 1 in 100 people.	Patients should not take simvastatin/ezetimibe if they are allergic to ezetimibe, simvastatin, or any of the other ingredients of this medicine.
Prescribed along with drugs that prevent clotting of blood (Drug interactions warfarin, another coumarin anticoagulant, or fluindione)	Blood clotting time could increase (increased INR) in patients taking ezetimibe together with medicines to prevent blood clots	It is particularly important to tell the doctor if patient is taking medicine(s) with any of the mentioned active ingredients.
Prescribed along with medicine often used in organ transplant patients (Drug interactions with ciclosporin)	Taking simvastatin/ezetimibe together with ciclosporin increases the risk of muscular weakness.	It is particularly important to tell the doctor if patient is taking medicine(s) with ciclosporin.
Muscular weakness/ breakdown of muscles (Myopathy/rhabdomyolysis)	Muscle aches may affect up to 1 in 10 people.	Patients should contact their doctor immediately if they experience unexplained muscle pain, tenderness, or weakness.
Abnormal liver function	Abnormal liver function has been reported, elevations in laboratory blood tests of liver (transaminases) has been reported in 1 of 100	Patients should contact their doctor for monitoring the liver function tests

Risk	What is known	Preventability
	patients.	

Table 4-2 Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Inflammation of the pancreas (pancreatitis)	The adverse reaction has been reported.
Inflammation of the gall bladder or gallstones (cholecystitis/cholelithiasis)	The adverse reactions have been reported.
Lung disease affecting the tissue and space around the air sacs of the lungs (Interstitial lung disease)	Shortness of breath has been reported.
Simvastatin induced allergic reactions (Simvastatin hypersensitivity syndrome)	Simvastatin/ezetimibe should not be given to patients who have allergy to simvastatin. A hypersensitivity syndrome has been reported rarely.
Newly developed condition of high blood sugar levels over a prolonged period / Pre-state of such condition associated with reduction in body's ability to breakdown glucose (simple sugars) for energy (New onset diabetes / Impaired glucose metabolism)	High blood sugar has been reported.
Brain attack due to bleeding within the brain tissue (Hemorrhagic stroke)	There are still insufficient data on an association of ezetimibe/simvastatin and the occurrence of a brain attack due to bleeding within the brain tissue.

Table 4-3 Missing information

Risk	What is known
Exposure with drug during pregnancy and breast-feeding (Exposure during pregnancy and lactation)	No clinical data are available on the use of ezetimibe/ simvastatin during pregnancy. Animal studies on combination therapy have demonstrated reproduction toxicity. It is unknown if ezetimibe/simvastatin are secreted into human breast milk, in rats it has been shown that ezetimibe is excreted 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 available. Drug interaction studies have only been performed in adults.

4.2.5 Part VI.2.5 Summary of additional risk minimization 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 minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet. The measures in these documents are known as routine risk minimization measures.

This medicine has no additional risk minimization measures.

4.2.6 Part VI.2.6 Planned post authorization development plan

No post-authorization safety or efficacy studies are ongoing or are planned to be conducted for ezetimibe/simvastatin.

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

Not applicable (first submission)