Ezetimibe

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Summary of safety concerns	
Important identified risks	• Rhabdomyolysis/myopathy • Abnormal liver function • Hypersensitivity • Drug interaction with ciclosporin • Drug interaction with warfarin, another coumarin anticoagulant, or fluindione.
Important potential risks	• Cholecystitis/choletithiasis • Pancreatitis
Missing information	• Exposure during pregnancy • Limited exposure inchildren age 10 to 17 beyong 1 year and limited exposure in children less than 10 years of age

VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

No additional pharmacovigilance activities are planned

VI.1.3 Summary of Post authorisation efficacy development plan

No Post authorisation efficacy studies are planned

VI.1.4 Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Rhabdomyolysis/myopathy	This safety concern has been covered under SPC Section 4.4 Special warnings and Precautions of Use and SPC Section 4.8 Undesirable effects). *4.4 Special warnings and Precautions of Use* *Skeletal muscle* In post-marketing experience with Ezetimibe, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin	None Proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	concomitantly with Ezetimibe. However, rhabdomyolysis has been reported very rarely with Ezetimibe monotherapy and very rarely with the addition of Ezetimibe to other agents known to be associated with increased risk of rhabdomyolysis. If myopathy is suspected based on muscle symptoms or is confirmed by a creatine phosphokinase (CPK) level >10 times the ULN, Ezetimibe, any statin, and any of these other agents that the patient is taking concomitantly should be immediately discontinued. All patients starting therapy with Ezetimibe should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness (see section 4.8). In a clinical trial in which over 9000 patients with chronic kidney disease were randomized to receive Ezetimibe 10 mg combined with simvastatin 20 mg daily (n=4650) or placebo (n=4620) (median follow-up 4.9 years), the incidence of myopathy/rhabdomyolysis was 0.2% for Ezetimibe combined with simvastatin and 0.1% for placebo (See section 4.8). *4.8 Undesirable effects* Post-marketing Experience (with or without a statin) Musculoskeletal and connective tissue disorder; myalgia; myopathy/rhabdomyolysis (see section 4.4)-Frequency: Not known Prescription only medicine	
Abnormal liver function	This safety concern has been covered under SPC Section 4.3 Contraindications, SPC Section 4.4 Special warnings and Precautions of Use and SPC Section 4.8 Undesirable effects). *4.3 Contraindications* Ezetimibe co-administered with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.	None Proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	4.4 Special warnings and Precautions of Use *Liver enzymes* In controlled co-administration trials in patients receiving Ezetimibe with a statin, consecutive transaminase elevations (≥3 X the upper limit of normal [ULN]) have been observed. When Ezetimibe is co-administered with a statin, liver function tests should be performed at initiation of therapy and according to the recommendations of the statin. (See section 4.8.) In a controlled clinical study in which over 9000 patients with chronic kidney disease were randomized to receive Ezetimibe 10 mg combined with simvastatin 20 mg daily (n=4650) or placebo (n=4620), (median follow-up period of 4.9 years), the incidence of consecutive elevations of transaminases (>3 X ULN) was 0.7% for Ezetimibe combined with simvastatin and 0.6% for placebo (see section 4.8). *4.8 Undesirable effects* *Ezetimibe monotherapy* Investigations; ALT and/or AST increased; blood CPK increased; gammaglutamyltransferase increased; liver function test abnormal-Frequency; Uncommon Prescription only medicine	
Hypersensitivity	This safety concern has been covered under SPC Section 4.3 Contraindications and SPC Section 4.8 Undesirable effects). *4.3 Contraindications* Hypersensitivity to the active substance or to any of the excipients. *4.8 Undesirable effects* *Post-marketing Experience (with or without a statin)* Immune system disorders; hypersensitivity, including rash, urticaria, anaphylaxis and angioedema-Frequency; Not known	None Proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Prescription only medicine	
Drug interaction with ciclosporin	This safety concern has been covered under SPC Section 4.4 Special warnings and Precautions of Use and SPC Section 4.5 Interaction with other medicinal products and other forms of interaction. *4.4 Special warnings and Precautions of Use* *Ciclosporin* Caution should be exercised when initiating Ezetimibe in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving Ezetimibe and ciclosporin (see section 4.5). *4.5 Interaction with other medicinal products and other forms of interaction* *Ciclosporin*: In a study of eight post-renal transplant patients with creatinine clearance of >50 mL/min on a stable dose of ciclosporin, a single 10-mg dose of Ezetimibe resulted in a 3.4-fold (range 2.3 to 7.9-fold) increase in the mean AUC for total ezetimibe compared to a healthy control population, receiving ezetimibe alone, from another study (n=17). In a different study, a renal transplant patient with severe renal insufficiency who was receiving ciclosporin and multiple other medications, demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls receiving ezetimibe alone. In a two- period crossover study in twelve healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100-mg dose of ciclosporin on Day 7 resulted in a mean 15 % increase in ciclosporin AUC (range 10 % decrease to 51 % increase) compared to a single 100-mg dose of ciclosporin alone. A controlled study on the effect of co- administered ezetimibe on ciclosporin exposure in renal transplant patients has not been conducted. Caution should be exercised when initiating Ezetimibe in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving Ezetimibe	None Proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	and ciclosporin (see section 4.4). Prescription only medicine	
Drug interaction with warfarin, another coumarin anticoagulant, or fluindione	This safety concern has been covered under SPC Section 4.4 Special warnings and Precautions of Use and SPC Section 4.5 Interaction with other medicinal products and other forms of interaction. *4.4 Special warnings and Precautions of Use* *Anticoagulants* If Ezetimibe is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalised Ratio (INR) should be appropriately monitored (see section 4.5). *4.5 Interaction with other medicinal products and other forms of interaction* Anticoagulants: Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males. However, 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 (see Section 4.4). Prescription only medicine	None Proposed
Cholecystitis/choletithiasis	This safety concern has been covered under SPC Section 4.8 Undesirable effects. *4.8 Undesirable effects* Post-marketing Experience (with or without a statin) Hepatobiliary disorders; hepatitis; cholelithiasis; cholecystitis-Frequency; Not known Prescription only medicine	None Proposed
Pancreatitis	This safety concern has been covered under	None Proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	SPC Section 4.8 Undesirable effects. *4.8 Undesirable effects* Post-marketing Experience (with or without a statin) Gastrointestinal disorders; pancreatitis; constipation. Frequency; Not known Prescription only medicine	
Exposure during pregnancy	This safety concern has been covered under SPC Section 4.8 Undesirable effects. *4.3 Contraindications* Therapy with Ezetimibe co-administered with a statin is contraindicated during pregnancy and lactation. *4.6 Fertility, pregnancy and lactation* Ezetimibe co-administered with a statin is contraindicated during pregnancy and lactation (see section 4.3), please refer to the SPC for that particular statin. Pregnancy: Ezetimibe should be given to pregnant women only if clearly necessary. 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 (see section 5.3). Prescription only medicine	None Proposed
Limited exposure in children age 10 to 17 beyong 1 year and limited exposure in children less than 10 years of age	This safety concern has been covered under SPC Section 4.2 Posology and method of administration, 4.4 Special warnings and Precautions of Use, SPC Section 5.1 Pharmacodynamic properties and 5.2 Pharmacokinetic properties. 4.2 Posology and method of administration *Paediatric population* Initiation of treatment must be performed	None Proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	under review of a specialist. Children and adolescents ≥ 6: The safety and efficacy of ezetimibe in children aged 6 to 17 years has not been established. Current available data are described in sections 4.4, 4.8, 5.1 and 5.2 but no recommendation on a posology can be made. When ezetimibe is administered with a statin, the dosage instructions for the statin in children should be consulted. Children <6 years: The safety and efficacy of Ezetimibe in children aged < 6 years has not been established. No data are available. *4.4 Special warnings and Precautions of Use* <u>Paediatric population</u> Efficacy and safety of ezetimibe in patients 6 to10 years of age with heterozygous familial or non-familial hypercholesterolemia have been evaluated in a 12-week placebo- controlled clinical trial. Effects of ezetimibe for treatment periods > 12 weeks have not been studied in this age group (see sections 4.2, 4.8, 5.1 and 5.2). Ezetimibe has not been studied in patients younger than 6 years of age (see sections 4.2 and 4.8.). Efficacy and safety of ezetimibe co-administered with simvastatin in patients 10 to 17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial in adolescent boys (Tanner stage II or above) and in girls who were at least one year post-menarche. In this limited controlled 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 treatment period > 33 weeks on growth and sexual maturation have not been studied (see sections 4.2 and 4.8). The safety and efficacy of ezetimibe co-	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	administered with doses of simvastatin above 40mg 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 < 10 years of age (see sections 4.2 and 4.8). The long-term efficacy of therapy with <invented name> in patients below 17 years of age to reduce morbidity and mortality in adulthood has not been studied. *5.1 Pharmacodynamic properties* 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 <invented name> co- administered with simvastatin have not been studied in paediatric patients < 10years of age. The long-term efficacy of therapy with <invented name> in patients below 17 years of age to reduce morbidity and mortality in adulthood has not been studied. *5.2 Pharmacokinetic properties* *Special Populations* Paediatric population The pharmacokinetics of ezetimibe are similar between children ≥6 years and adults. Pharmacokinetic data in the paediatric population < 6 years of age are not available. Clinical experience in paediatric and adolescent patients includes patients with HoFH, HeFH, or sitosterolaemia. Prescription only medicine	

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