PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

VI.1 Elements for summary tables in the European Public Assessment Report (EPAR)

VI.1.1 Summary table of Safety concerns

Important identified risk (s)	• Rhabdomyolysis / Myopathy • Abnormal liver function • Hypersensitivity • Drug interaction with warfarin, another coumarin anticoagulant, or fluindione • Drug interaction with ciclosporin
Important potential risk (s)	• Cholecystitis / Cholelithiasis • Pancreatitis
Missing information	• Exposure during pregnancy and lactation • Limited clinical experience in paediatric population age 10-17 years old beyond 1 year and in children 6-10 years old beyond 12 weeks. No clinical experience in children less than 6 years of age

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

Not applicable.

VI.1.3 Summary of Post authorisation efficacy development plan

Not applicable.

VI.1.4 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk: Rhabdomyolysis / Myopathy	Information in SmPC section: - 4.4 Special warnings and precaution for use - 4.8 Undesirable effects Associated wording included in the PIL Prescription only medicine	None
Important identified risk: Abnormal liver function	Information in SmPC section: - 4.2: Posology and method of administration - 4.3: Contraindications - 4.4: Special warnings and precaution for use - 4.8: Undesirable effects - 5.2 : Pharmacokinetic properties Associated wording included in the PIL Prescription only medicine	None
Important identified risk: Hypersensitivity	Information in SmPC section: - 4.3: Contraindications - 4.8: Undesirable effects Associated wording included in	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	the PIL Prescription only medicine	
Important identified risk: Drug interaction with warfarin, another coumarin anticoagulant, or fluindione	Information in SmPC section: - 4.4 Special warnings and precaution for use - 4.5 Interaction with other medicinal products and other forms of interaction Associated wording included in the PIL Prescription only medicine	None
Important identified risk: Drug interaction with ciclosporin	Information in SmPC section: - 4.4 Special warnings and precaution for use - 4.5 Interaction with other medicinal products and other forms of interaction Associated wording included in the PIL Prescription only medicine	None
Important potential risk: Cholecystitis / Cholelithiasis	Information in SmPC section: - 4.3: Contraindications -4.4: Special warnings and precaution for use -4.5 Interaction with other	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	medicinal products and other forms of interaction - 4.8: Undesirable effects Associated wording included in the PIL Prescription only medicine	
Important potential risk: Pancreatitis	Information in SmPC section: - 4.8 Undesirable effects Associated wording included in the PIL Prescription only medicine	None
Missing information: Exposure during pregnancy and lactation	Information in SmPC section: - 4.3 Contraindications - 4.6 Fertility, pregnancy and lactation - 5.3 Preclinical safety data Associated wording included in the PIL Prescription only medicine	None
Missing information: Limited clinical experience in paediatric population age 10-	Information in SmPC section: - 4.2: Posology and method of administration - 4.4: Special warnings and precaution for use	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
17 years old beyond 1 year and in children 6-10 years old beyond 12 weeks. No clinical experience in children less than 6 years of age	- 4.8: Undesirable effects - 5.1 : Pharmacodynamic properties - 5.2 : Pharmacokinetic properties Associated wording included in the PIL Prescription only medicine	

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Primary hypercholesterolaemia (high blood cholesterol)

People with high blood cholesterol levels have a greater risk of having a heart attack, stroke (lack of blood supply to brain causing damage to brain cells) or other related diseases of heart and blood vessel. This is because cholesterol and other fatty substances (lipids) may build up on the inside wall of blood vessels causing them to narrow. Sometimes blood clots form which block the blood vessels completely. Diseases such as strokes and heart attacks cause almost 1 in 3 deaths worldwide each year. High cholesterol levels are common throughout the world, but are more common in high income than low-income regions. In high-income regions such as Europe, the United States, Canada and Japan, more than half of adults have high cholesterol levels. Sometimes cholesterol levels can be lowered with changes in diet and increased exercise. However, cholesterol levels are often affected by things that cannot be changed, such as age, sex, or family history. Cholesterol levels usually rise steadily with age, but stabilise after middle age.

Homozygous Familial Hypercholesterolaemia

Familial hypercholesterolemia (FH) is a condition of high cholesterol that runs in the family occurring in about 1 in 100 people. Individuals with FH are at significantly increased risk for premature heart related disease and higher frequencies in French Canadians, Afrikaners in South Africa, or Christian Lebanese. FH estimated 620,000 individuals affected in the United States (US). Heterozygous FH (HeFH) means inherited the disease that causes high cholesterol levels from only one parent, is the most common form of the disease and present in 1 in 500 means that approximately 110,000 people are affected in UK. Homozygous FH (HoFH) means inherited the disease that causes high cholesterol levels from both parents is a very rare and present in 1 in 1 million persons. Homozygous FH often does not respond to medical therapy and may require LDL apheresis (removal of cholesterol in a method similar to dialysis) and occasionally liver transplantation.

Homozygous Sitosterolaemia (Phytosterolaemia)

Homozygous Sitosterolaemia is a very rare genetic disorder of lipid metabolism where excessive amounts of sterols (a type of lipid) are absorbed and not removed from the body resulting in a build up in the blood. It is characterized by tendon xanthomas (i.e. a deposition of yellowish cholesterol-rich material in tendons or other body parts in various disease states) that can occur in childhood and in unusual locations (heels, knees, elbows and buttocks). There may be premature hardening of arteries which can lead to heart attack and sudden death. Increased plasma concentrations of plant sterols (especially sitosterol, campesterol, and stigmasterol) are observed once foods with plant sterols are included in the diet and have accumulated in the body. Current treatment therapies focus on the diet low in shellfish sterols and plant sterols (i.e., avoidance of vegetable oils, margarine, nuts, seeds, avocados, chocolate, and shellfish) in conjunction with ezetimibe or other medications.

Prevention of cardiovascular events

Cardiovascular diseases (CVD) are a group of disorders of the heart and blood vessels which causes 17.3 million deaths per year. The main causes of CVD death are

coronary heart disease (CHD - is occurred when heart's blood supply is blocked or interrupted by a build-up of fatty substances in the coronary arteries). There are 80,000 (1 in 5 men and 1 in 7 women) deaths from CHD in the United Kingdom (UK) each year. In the UK, there are an estimated 2.3 million people living with CHD. Acute coronary syndrome (ACS) refers to a group of conditions due to decreased blood flow in the coronary arteries such that part of the heart muscle is unable to function properly or dies. In the UK, about 114,000 patients with ACS are admitted to hospital each year. Treatment for CVD can include eating a healthy diet, controlling blood cholesterol, regular exercise, stopping smoking, medication such as ezetimibe and heart surgery.

VI.2.2 Summary of treatment benefits

Ezetimibe is a medicine used to lower levels of LDL cholesterol, (and fatty substances called triglycerides in the blood. In addition, ezetimibe raises levels of HDL cholesterol

Primary hypercholesterolaemia

In an 8-week clinical study, 769 patients with hypercholesterolaemia already receiving statin therapy were receiving either ezetimibe tablets 10 mg or dummy medication in addition to their on-going statin therapy. The patients on ezetimibe tablets showed more reduction in LDL-cholesterol compared to dummy medication.

In another study, 720 patients with hypercholesterolemia received either ezetimibe 10 mg in combination with simvastatin 80 mg or simvastatin 80 mg alone for 2 years. The result demonstrated that ezetimibe with simvastatin lowered cholesterol and triglyceride significantly more than simvastatin alone.

Studies in Children (6 to 17 years of age)

In a study, 138 patients (59 boys and 79 girls) of 6 to 10 years of age were received either Ezetimibe tablets 10 mg or dummy medication for 12 weeks. At week 12, Ezetimibe tablets significantly reduced cholesterol and other type of fats compared to dummy medication.

In another study, with 142 boys and 106 girls (post-menstrual cycle), 10 to 17 years of age with hypercholesterolemia were received either ezetimibe tablets with simvastatin or simvastatin alone for 6 weeks. In patients receiving ezetimibe tablets and 40 mg simvastatin, cholesterol reduced more compared to those receiving 40 mg simvastatin alone.

Homozygous Familial Hypercholesterolaemia (HoFH)

In one of the study 50 patients received atorvastatin or simvastatin. Ezetimibe tablets taken with atorvastatin or simvastatin, significantly reduced cholesterol compared with increasing the dose of simvastatin or atorvastatin single therapy.

Homozygous sitosterolaemia (phytosterolaemia)

In a study, 37 patients with homozygous sitosterolaemia were received ezetimibe tablets 10 mg or dummy medication. Ezetimibe significantly lowered sterols from its baseline.

Prevention of cardiovascular events

In a study, 18,144 patients with coronary heart disease and ACS event history were received ezetimibe/simvastatin 10/40 mg daily (n=9067) or simvastatin 40 mg daily (n=9077). Ezetimibe with a statin is effective in reducing the risk of cardiovascular events (cardiovascular death, major coronary events and non-fatal stroke) in patients with coronary heart disease and ACS event history compared to statins alone.

VI.2.3 Unknowns relating to treatment benefits

The benefits of ezetimibe use during pregnancy and lactation have not been established yet. There is limited clinical experience about the use of ezetimibe in children and adolescents between 10-17 years old beyond 1 year and 6-10 years old beyond 12 weeks. There is no available data of use of ezetimibe in children less than 6 years of age.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Muscle breakdown / Pain or weakness in muscles (Rhabdomyolysis / Myopathy)	When used alone, elevations in some laboratory blood tests of muscle (CK) function, muscle spasms. Additionally, when used with a statin, elevations in some laboratory blood tests, headache; muscle pain; tenderness or muscle weakness. On rare occasions, muscle problems, including muscle breakdown resulting in kidney damage, can be serious and may become a potentially life-threatening condition.	Contact the doctor immediately in case of unexplained muscle pain, tenderness, or weakness.
Abnormal liver function	Side effects on the liver like elevations in some laboratory blood tests of liver (transaminases) have been observed in patients treated with ezetimibe, but these events are uncommon (reported in less than 1 in 100 patients). Additionally, when used with statin,	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
	elevations in some laboratory blood tests of liver function (transaminases) was reported.	statin. Do not take Ezetimibe Accord together with a statin if you currently have liver problems. If you have moderate or severe liver problems, ask your doctor before taking Ezetimibe Accord / Astron.
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.	Tell your doctor about all your medical conditions including allergies.
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	There have been post-marketing reports of increased a blood test to check blood clotting ability (international normalised ratio (INR)) in patients who had ezetimibe added to warfarin or fluindione.	Tell your doctor or pharmacist if you are taking or have recently taken medicines to prevent blood clots, such as warfarin, phenprocoumon, acenocoumarol or fluindione (anticoagulants).
Simultaneous use of ciclosporin (a medicine	Patient receiving ezetimibe with ciclosporin and	Tell your doctor or pharmacist if you are

Risk	What is known	Preventability
used in organ transplant patients) during treatment with ezetimibe (Drug interaction with ciclosporin)	multiple other medications, concentration of ezetimibe in blood is increases compared to patient receiving ezetimibe alone.	taking or have recently taken ciclosporin (a medicine often used in organ transplant patients). Ciclosporin concentrations should be monitored in patients receiving ezetimibe and ciclosporin.

Important potential risks

Risk	What is known
Gallstones or inflammation of the gallbladder (Cholecystitis / Cholelithiasis)	Side effects have been reported in general use are gallstones or inflammation of the gallbladder (which may cause abdominal pain, nausea, vomiting).
Inflammation of the pancreas (Pancreatitis)	Side effects have been reported in general use is inflammation of the pancreas often with severe abdominal pain.

Missing information

Risk	What is known
Exposure during pregnancy and lactation	Do not take ezetimibe with a statin if you are pregnant, are trying to get pregnant or think you may be pregnant. If you get pregnant while taking ezetimibe with a statin, stop taking both medicines immediately and tell the doctor. There is no experience from the use of ezetimibe

Risk	What is known
	without a statin during pregnancy. Do not take Ezetimibe with a statin if you are breast-feeding, because it is not known if the medicines are passed into breast milk. Ezetimibe without a statin should not be used if you are breast-feeding.
Limited clinical experience in paediatric population age 10-17 years old beyond 1 year and in children 6-10 years old beyond 12 weeks. No clinical experience in children less than 6 years of age	Do not give this medicine to children and adolescents between 6 and 17 years unless prescribed by a specialist because there are limited data on safety and efficacy. Do not give this medicine to children less than 6 years old because there is no information in this age group. Ezetimibe co-administered with simvastatin in patients 10 to 17 years of age with heterozygous familial hypercholesterolemia revealed that 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. Ezetimibe has not been studied in patients 10 to 17 years of aged receiving doses of simvastatin above 40 mg daily simultaneously.

VI.2.5 Summary of 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). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No studies planned.

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

Version	Date	Safety Concern	Comment
6.0	20 April 2016	There were no changes to safety concerns.	Indication – Prevention of cardiovascular events has been added in Ezetimibe Accord/Astron SmPC and PIL and relevant changes were made accordingly.
5.0	18 January 2016	Below important potential risk has been deleted from this RMP: • Use in patients with hypersensitivity to acetylsalicylic acid or other NSAIDs	As per Day 120 assessment report for Ezetimibe Accord / Astron, the RMP has been updated.
4.0	03 September 2015	Below important potential risk has been deleted from this RMP: • Co-administration of ezetimibe with other fibrates Below important potential risk has been added to this RMP: • Use in patients with	As per Day 70 and Day 100 assessment report for Ezetimibe Accord / Astron, the RMP has been updated.

Version	Date	Safety Concern	Comment
		hypersensitivity to acetylsalicylic acid or other NSAIDs Below missing information has been change. • Limited exposure in children and adolescents of age 6 to 17 years and in children less than 6 years of age" has been changed to "limited clinical experience in paediatric population age 10-17 years old beyond 1 year and in children 6-10 years old beyond 12 weeks. No clinical experience in children less than 6 years of age.	
3.0	18 May 2015	There were no safety concerns related changes in this RMP.	Indication - Homozygous sitosterolaemia (phytosterolaemia) has been removed from Ezetimibe Accord/Astron SmPC and PIL and relevant changes were made accordingly.
2.0	04 May 2015 1.1.1	There were no safety concerns related changes in this RMP.	To update product information for Ezetimibe Astron

Version	Date	Safety Concern	Comment
			(ES/H/0330/001/DC).