Summary of activities in the risk management plan by medicinal product

A separate RMP Part VI should be provided for each product in the RMP.

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Summary of safety concerns	
Important identified risks	• Abnormal liver function • Rhabdomyolysis/myopathy • Hypersnsitivity • Drug interaction with ciclosporin • Drug interaction with warfarin, another coumarin anticoagulant, or fluindione
Important potential risks	• Cholecystitis/cholelithiasis • Pancreatitis
Important missing information	• Use during pregnancy and lactation • Limited clinical trial experience in children aged 10-17 years old beyond 1 year of treatment and in children 6-10 years old beyond 12 weeks of treatment. No clinical trial experience in children less than 6 years of age.

VI.1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance 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**
Abnormal liver function	Information in SPC - Ezetimibe with statin is contraindicated in patients with elevated serum transaminases. (section 4.3.) - Use of ezetimibe is not recommended in moderate or severe hepatic insufficiency. (section 4.4.)	N/A

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	- There have been reports of elevated transaminases mostly in combination with statins. (section 4.4.) Prescription only medicine	
Rhabdomyolysis/myopathy	Information in SPC - There have been reports of rhabdomyolysis after ezetimibe therapy. Most patients who developed rhabdomyolysis were taking a statin concomitantly with ezetimibe. If a creatine phosphokinase (CPK) level is >10 times the ULN, ezetimibe should be immediately discontinued. (section 4.4) Prescription only medicine	N/A
Hypersensitivity	Information in SPC Information on contraindication in patients with known hypersensitivity in section 4.3 This reaction is listed in section 4.8 Prescription only medicine	N/A
Drug interaction with ciclosporin	Information in SPC Information on this interaction is specified in sections 4.4 and 4.5 Prescription only medicine	N/A
Drug interaction with warfarin, another coumarin anticoagulant, or fluindione	Information in SPC Information on this interaction is specified in sections 4.4 and 4.5 Prescription only medicine	N/A
Cholecystitis/cholelithiasis	Information in SPC This adverse reaction is listed in section 4.8. Prescription only medicine	N/A
Pancreatitis	Information in SPC This adverse reaction is listed in section 4.8. Prescription only medicine	N/A

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Use during pregnancy and lactation	Information in SPC - Ezetimibe with statin is contraindicated during pregnancy and lactation. (section 4.3.) - Pregnancy: animal data showed no harm, there is lack of human data. (section 4.6.) - Lactation: animal data showed that ezetimibe passes into breast milk. No human data are available. (section 4.6.) Prescription only medicine	N/A
Use in children and adolescents	Information in SPC Children **<10 years** Ezetimibe is not recommended for use in children below age 10 due to insufficient data on safety and efficacy (section 4.2., 4.4.) **10-17 years** Limited data are available on effect on growth or sexual maturation, only for a treatment period up to 33 weeks. (section 4.4.) The safety and efficacy of ezetimibe co-administered with doses simvastatin above 40 mg daily have not been studied in paediatric patients 10 to 17 years of age. (section 4.4.) Prescription only medicine	N/A

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Currently, approximately over half of people in Europe (54% for both sexes) have elevated total cholesterol, compared to slightly less in Americas (48% for both sexes) [1].

Primary hypercholesterolaemia (heterozygous familial and non-familial) is an elevation of plasma low density lipoprotein-cholesterol (LDL-cholesterol) which is not secondary to environmental, dietary, or other underlying diseases.

It has been associated with the development of atherosclerosis and premature cardiovascular disease [2].

Homozygous familial hypercholesterolaemia

Familial hypercholesterolemia (FH) is an inherited autosomal dominant disorder that causes severe elevations in total cholesterol and low-density lipoprotein cholesterol (LDLc).

The prevalence of homozygous FH is 1 case per 1 million persons [2].

Homozygous sitosterolaemia (phytosterolaemia)

Sitosterolemia is an inherited autosomal recessive condition.

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.

Sitosterolemia is characterized by tendon and tuberous xanthomas and by a strong propensity toward premature coronary atherosclerosis. [1]

Treatment

The currently available lipid-lowering drugs include [5]

Drugs of choice [6]:

- inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (statins)

o Statins at doses that effectively reduce LDL cholesterol by 50% also seem to halt progression or even contribute to regression of coronary atherosclerosis. Therefore, they should be used as the drugs of first choice in patients with hypercholesterolaemia or combined hyperlipidaemia.

Other options [6]:

- fibrates

o Fibrates, particularly fenofibrate, may be useful, not only for decreasing high triglyceride concentrations and increasing low HDL cholesterol, but can further lower LDL cholesterol when applied together with a statin.

- niacin (nicotinic acid)

o Combinations of niacin and a statin increase HDL cholesterol and decrease triglycerides better than either of these drugs alone, but flushing is the main adverse effect of niacin, which may affect compliance. Adding laropiprant to niacin might help in reducing the incidence of this adverse effect.

- bile acid sequestrants (anion exchange resins)

o Combinations of a statin and a bile acid sequestrant can be used for greater reduction of LDL cholesterol than can be achieved with either drug alone.

• selective cholesterol absorption inhibitors (including ezetimibe)

o Combinations of a statin and ezetimibe can be used for greater reduction of LDL cholesterol than can be achieved with either drug alone.

Furthermore, according to NICE guidance [6], ezetimibe is to be used as an option to monotherapy with statins in the following cases:

• Treatment of adults with primary (heterozygous-familial or non-familial) hypercholesterolaemia who are unable to be initiated on statin because of contraindications.

• Treatment of adults with primary (heterozygous-familial or non-familial) hypercholesterolaemia who are intolerant to statin therapy.

• Treatment of adults with primary (heterozygous-familial or non-familial) hypercholesterolaemia who have been initiated on statin therapy and serum total or low-density lipoprotein (LDL)cholesterol concentration is not appropriately controlled.

VI.2.2 Summary of treatment benefits

The effect of ezetimibe on lowering of serum cholesterol has been demonstrated in several clinical studies in patients with the following diagnoses:

- Primary hypercholesterolaemia
    - Ezetimibe, co-administered with an HMG-CoA reductase inhibitor (statin) is considered effective as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia who are not appropriately controlled with a statin alone.
    - Ezetimibe monotherapy is considered effective as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated.

- Homozygous Familial Hypercholesterolaemia (HoFH)
    - Ezetimibe co-administered with a statin, is effective as adjunctive therapy to diet for use in patients with HoFH.

- Homozygous sitosterolaemia (phytosterolaemia)
    - Ezetimibe is considered effective in lowering cholesterol as adjunctive therapy to diet for use in patients with homozygous familial sitosterolaemia.

VI.2.3 Unknowns relating to treatment benefits

<u>Effect on cardiovascular morbitidy and mortality</u>

In various clinical studies, effect of ezetimibe on lowering of serum cholesterol was proven. However, a beneficial effect of ezetimibe on cardiovascular morbidity and mortality has not yet been demonstrated.

<u>Children and adolescents</u>

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 long-term efficacy of therapy with Ezetimibe in patients below 17 years of age to reduce morbidity and mortality in adulthood has not been studied.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Abnormal liver function/liver damage (Abnormal liver function/liver damage)	Ezetimibe together with statin (another lipid lowering drug) may increase blood test for liver function signalizing liver damage.	Yes, partly - contraindication in liver impairment - monitoring of liver function during the therapy
Muscle damage (Rhabdomyolysis/myopathy)	Ezetimibe together with statin (another lipid lowering drug) may increase blood test signalizing muscle damage.	Yes, partly - monitoring of creatine kinase (blood test) during the therapy - discontinuation in case of high elevation
Allergic reaction (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.	Yes, partly - contraindication in patients with known allergy to ezetibime
Interaction with ciclosporin (medicine used in organ transplant patients)	Concomitant use of ciclosporine and ezetimibe may cause higher exposure to ezetimibe than in patients who use ezetimibe alone.	Caution should be exercised when initiating ezetimibe in patients who are concomitantly treated with ciclosporin. Ciclosporin concentrations should be monitored in patients receiving ezetimibe and ciclosporin.
Interaction with warfarin, another coumarin anticoagulant or fluindione (medicines for prevention of blood clots)	Concomitant use of warfarin or fluindione (medicines used to prevent blood clots) may cause increased INR (international normalised ration). This is a sign of increased possibility to bleed.	INR should be propriety monitored in patients who use these medicines concomitantly.

Important potential risks

Risk	What is known
Inflammation of the gall bladder/ stones in gall bladder (Cholecystitis/cholelithiasis)	Inflammation of the gall bladder or gall stones which may cause abdominal pain, nausea or vomiting were reported in general use of the product.
Inflammation of pancreas (Pancreatitis)	Inflammation of the pancreas often with severe abdominal pain was reported in general use of the product.

Important missing information

Risk	What is known
Limited information on use in during pregnancy and lactation (Missing information: Use during pregnancy and lactation)	- Ezetimibe with statin is contraindicated during pregnancy and lactation. **Pregnancy**: - animal data - no harm - human data – lacking **Lactation:** - animal data - ezetimibe passes into breast milk - human data - lacking
Limited information on use in children and adolescents (Missing information: • Limited clinical trial experience in children aged 10-17 years old beyond 1 year of treatment and in children 6-10 years old beyond 12 weeks of treatment. No clinical trial experience in children less than 6 years of age.)	**<10 years** Ezetimibe is not recommended for use in children below age 10 due to insufficient data on safety and efficacy. **10-17 years** Limited data are available on effect on growth or sexual maturation, only for a treatment period up to 33 weeks. The safety and efficacy of ezetimibe co-administered with doses simvastatin above 40 mg daily have not been studied in paediatric patients 10 to 17 years of age.

VI.2.5 Summary of additional risk minimisation measures by safety concern

The product has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable

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

Table 1. Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1	11/06/2013	**Identified Risks** 1) Transaminases increased on combination with statin therapy 2) Creatine kinase elevation on combination with statin therapy **Potential Risks**	-

Version	Date	Safety Concerns	Comment
		- **Missing information** 1) Use during pregnancy and lactation Use in children and adolescents	
1.0A	28/10/2013	**Identified Risks** 1) Abnormal liver function/liver damage on combination with statin therapy 2) Rhabdomyolysis/myopathy on combination with statin therapy **Potential Risks** - **Missing information** 1) Use during pregnancy and lactation Use in children and adolescents	This version No. 1.0A is an update due to comments that resulted from the procedure CZ/H/219/001/II/001. The appropriate terms defining the risks (important risks) were used in this new version of RMP.
1.0B	14/07/2016	**Identified Risks** 1) Abnormal liver function/liver damage on combination with statin therapy 2) Rhabdomyolysis/myopathy on combination with statin therapy **Potential Risks** - **Missing information** 1) Use during pregnancy and lactation Use in children and adolescents	This version No. 1.0B is an update due to German NCA validation issues regarding RMP prepared for procedure CZ/H/219/001/II/001 to be used for MRP. MAHs, product concerned names and invented name in EEA sections updated.
2.0	23/01/2017	**Identified Risks** 1) Abnormal liver function/liver damage 2) Rhabdomyolysis/myopathy 3) Hypersensitivity 4) Drug interaction with ciclosporin 5) Drug interaction with warfarin, another coumarin anticoagulant, or fluindione **Potential Risks** 1) Cholecystitis/ cholecystolithiasis 2) Pancreatitis **Missing information** 1) Use during pregnancy and lactation 2) Limited clinical trial experience in children aged 10-17 years old beyond 1 year of	New version was created with updated List of Safety Concerns and part concerning post-authorisation experience with the molecule. This update was agreed within procedure CZ/H/219/001/II/001 as a post-authorisation commitment.

Version	Date	Safety Concerns	Comment
		treatment and in children 6-10 years old beyond 12 weeks of treatment. No clinical trial experience in children less than 6 years of age	