Part VI: Summary of activities in the risk management plan by product

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Important identified risks	• Musculoskeletal and connective disorders • Hepatobiliary disorders • Renal and urinary disorders • Thromboembolic events • Cholelithiasis • Pancreatitis • Diabetes mellitus aggravated

Important potential risks	• Increased risk of myopathy • Increased risk of hepatic events • Increased risk of pancreatic events • Blood homocysteine increased • Interstitial pneumopathy • Phototoxicity • Off label use • Inappropriate monitoring during treatment

Important missing information	• Patients above the age of 75 years. • Long-term safety profile of the product. • Uncontrolled hypertension (SBP > 160 mmHg or DBP > 95 mmHg) under blood pressure treatment. • Diabetes requiring insulin. • Uncontrolled diabetes with HbA1c > 8.5%. • Patients who had an acute cardiovascular episode within the 6 months previous to the start of the trial (3 months or with a history of coronary angioplasty with mounting of a stent within the past 6 months). • Other ethnical subgroup population than Caucasian • Neoplasm

VI.1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan (if applicable)

Study/Activity type, Title and category	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports
A European, observational, three-year cohort comparative study on the safety of the fixed-dose combination pravastatin 40 mg/fenofibrate 160 mg (Pravafenix®) versus statin alone in real clinical practice	**Primary objective**: The primary objective is to estimate the hazard ratio for the main safety endpoints (considering the time of first occurrence) between patients treated by Pravafenix® or by a statin in monotherapy in real clinical practice conditions within a three-year follow-up period. **Secondary objectives:** • To estimate the proportion of patients with at least one occurrence of each safety endpoints. • To estimate the event-free follow-up time for each safety endpoints. • To estimate the hazard ratio for main safety endpoints considering the time to each event. • To describe the adverse events reported and the proportion of patients presenting laboratory abnormalities. • To estimate the occurrence rates of cardiovascular events • To describe the patients' characteristics. • To describe the participating physicians' characteristics. To describe the patterns of use of Pravafenix® and to assess the routine risk minimisation.	Mainly the following safety concerns will be identified and quantified during this study: - Musculoskeletal and connective tissue disorders - Hepatobiliary disorders - Renal and urinary disorders - Thromboembolic events - Cholelithiasis - Pancreatitis - Diabetes mellitus aggravated - Off label use - Inappropriate monitoring during treatment.	Study protocol was accepted by the PRAC in September 2014. A feasibility study is currently being performed to allow SMB to consolidate the protocol of the PASS study.	An interim analysis report will be provided after one year.

VI.1.3 Summary of Post authorisation efficacy development plan (if applicable)

Not applicable

VI.1.4 Summary table of risk minimisation measures

IMPORTANT IDENTIFIED RISKS

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
MUSCULOSKELETAL AND CONNECTIVE DISORDERS: Myopathy, myositis, myalgia, muscle disorder, blood creatine phosphokinase abnormal, muscle enzyme increase, immune-mediated necrotizing myopathy	Labelling EU SmPC ▪ Section 4.3 Contraindications ▪ Section 4.4 Special warnings and precaution for use ▪ Listed as adverse reaction (section 4.8). Other Risk minimisation measure: • Prescription only medicine	NA.
HEPATOBILIARY DISORDERS: Transaminases increased, hepatic failure, hepatic pain, hepatotoxicity, hepatitis, blood bilirubin abnormal, hepatic enzyme abnormal, gamma-glutamyltransferase abnormal, transaminases abnormal	Labelling EU SmPC ▪ Section 4.2 Posology and method of administration ▪ Section 4.3 Contraindications ▪ Section 4.4. Special warnings and precaution for use ▪ Listed as adverse reaction (section 4.8) with the experience of the combination Other Risk minimisation measure: • Prescription only medicine	NA.
RENAL AND URINARY DISORDERS: Blood creatine abnormal, blood creatinine abnormal, creatinine renal clearance abnormal, renal failure, renal disorder, blood urea abnormal, glomerular filtration rate abnormal, red blood cells urine positive, urine analysis abnormal.	Labelling EU SmPC ▪ Section 4.2 Posology and method of administration ▪ Section 4.3 Contraindications: ▪ Section 4.4. Special warnings and precaution for use ▪ Listed as adverse reaction (section 4.8) Other Risk minimisation measure: • Prescription only medicine	NA.
CHOLELITHIASIS: Cholelithiasis, Gallbladder disorder.	Labelling EU SmPC ▪ Section 4.3 Contraindications ▪ Section 4.4 Special warnings and precaution for use ▪ Listed as adverse reaction in section 4.8	NA.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Other Risk minimisation measure: • Prescription only medicine	
THROMBOEMBOLIC EVENTS: Pulmonary embolism, Deep vein thrombosis.	Labelling EU SmPC ▪ Section 4.4 Special warnings and precaution for use ▪ Listed as adverse reaction in section 4.8 Other Risk minimisation measure: • Prescription only medicine	NA.
PANCREATITIS: Pancreatitis, pancreatitis acute, pancreatic disorder, pancreatic enzymes abnormal, blood amylase increased.	Labelling EU SmPC ▪ Section 4.3 Contraindications ▪ Section 4.4. Special warnings and precaution for use ▪ mentioned as adverse reaction in section 4.8 Other Risk minimisation measure: • Prescription only medicine	NA.
DIABETES MELLITUS AGGRAVATED: Diabetes mellitus aggravated, diabetes mellitus exacerbated, worsening of diabetes, hyperglycaemia, blood glucose abnormal and new onset diabetes.	Labelling EU SmPC ▪ Section 4.4 Special warnings and precaution for use ▪ Section 4.8 – Undesirable effects Other Risk minimisation measure: • Prescription only medicine	NA.

IMPORTANT POTENTIAL RISKS

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
INCREASED RISK OF MYOPATHY: Rhabdomyolysis	Labelling EU SmPC ▪ Section 4.3 Contraindications ▪ 4.4. Special warnings and precaution for use ▪ Listed as adverse reaction (section 4.8). Other Risk minimisation measure: • Prescription only medicine	NA.
INCREASED RISK OF HEPATIC EVENTS: Hepatic failure	Labelling EU SmPC ▪ Section 4.2 Posology and method of administration ▪ Section 4.3 Contraindications ▪ Section 4.4. Special warnings and precaution for use ▪ Listed as adverse reaction (section 4.8) with the experience of the combination Other Risk minimisation measure: • Prescription only medicine	NA.
INCREASED RISK OF PANCREATIC EVENTS: Pancreatitis	Labelling EU SmPC ▪ Section 4.3 Contraindications ▪ Section 4.4. Special warnings and precaution for use ▪ Mentioned as adverse reaction in section 4.8 Other Risk minimisation measure: • Prescription only medicine	NA.
BLOOD HOMOCYSTEINE INCREASED: Blood homocysteine increased, blood homocysteine abnormal, hyperhomocysteinaemia**.**	Labelling EU SmPC ▪ Section 4.4. Special warnings and precaution for use Other Risk minimisation measure: • Prescription only medicine	NA.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
INTERSTITIAL PNEUMOPATHY DISEASE: Interstitial lung disease, pulmonary fibrosis.	Labelling EU SmPC ▪ Section 4.4 Special warnings and precautions for use ▪ Section 4.8 – Undesirable effects Other Risk minimisation measure: • Prescription only medicine	NA.
PHOTOTOXICITY: Photosensivity reaction, photosensitivity allergic reaction, retinal phototoxicity.	Labelling EU SmPC ▪ Section 4.3 Contra indications ▪ Section 4.8 – Undesirable effects ▪ Other Risk minimisation measure: • Prescription only medicine	NA.
OFF LABEL USE: Off label use	Labelling EU SmPC Section 4.1 Therapeutic indications Other Risk minimisation measure: • Prescription only medicine	NA.
INAPPROPRIATE MONITORING DURING TREATMENT: Medication monitoring errors	NA.	NA.

IMPORTANT MISSING INFORMATION

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
PATIENTS ABOVE THE AGE OF 75 YEARS	Labelling EU SmPC: • 4.2 Posology and method of administration: Other Risk minimisation measure: • Prescription only medicine	NA.
LONG-TERM SAFETY PROFILE OF THE PRODUCT	NA.	NA.
EXCLUSION'S CRITERIA (Patients not studied during clinical trials)	NA.	NA.
OTHER ETHNICAL SUBGROUP POPULATION THAN CAUCASIAN	NA.	NA.

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Cardiovascular disease (CVD) is the leading cause of death in the western countries and lipid disorders are well-documented major modifiable factors. The association between lipid disorders (dyslipidemia) and particularly an excess of cholesterol and the occurrence of coronary heart disease (CHD) is well established. Among the most notable elevated risk factors for the development of atherosclerotic cardiovascular disease (CV) are elevated levels of LDL-C (the so called "bad-cholesterol) and reduced levels of HDL-C (the so-called "good cholesterol"). Although the relationship is not as strong, an excess of triglycerides in the blood (hypertriglyceridemia) is also associated with an increased risk of atherosclerotic disease.

Overall prevalence of mixed hyperlipidaemia (patient with an increase in both cholesterol and other lipids) varies between 10 and 25% with many cases being the result of secondary causes, such as a sedentary lifestyle with excessive dietary intake of saturated fat and cholesterol. Other common secondary causes include diabetes mellitus, alcohol overuse, chronic kidney disease, etc. Familial mixed hyperlipidaemia is one of the most common hereditary disorders predisposing to early coronary death. It affects 1 to 3% of the adult population and up to 20% of patients with premature myocardial infarction (MI) and about 30% of MI survivors. Many patients have polygenic mixed hyperlipidaemia and/or insulin resistance or diabetes mellitus, while a small number of patients (0.2%) have monogenic hyperlipidaemia. Patients with polygenic or monogenic mixed hyperlipidaemia form a high-risk group for development of atherosclerosis especially coronary heart disease (CHD).

VI.2.2 Summary of treatment benefits

The treatment of patients with lipid disorders is highly dependent on the patient himself, the cause (primary of secondary lipid disorders), which lipids have abnormal values in the blood (too high or too low), what is the extent of the cardiovascular risk of the patient, etc. Elevated LDL-cholesterol is present in most of these patients and is the primary target for therapies. The golden treatment standard to reduce LDL-cholesterol is the use of statins, but always in combination with lifestyle changes, including exercise, weight loss and dietary measures. There are many different statins, with slightly different properties and the choice of statin is mainly based on patient characteristics, LDL-cholesterol levels, etc.

The use of PRAVAFENIX® can be considered in adult patients with a high risk for developing coronary heart disease and whose lipid disorder is characterised by high triglyceride levels, low HDL-cholesterol levels and LDL-cholesterol levels that were under control with Pravastatin treatment alone.

During the clinical development of PRAVAFENIX®, 1637 patients participated to the different clinical studies. These included four international phase III studies in which the use of PRAVAFENIX® was compared with the use of pravastatin, simvastatin, or fenofibrate alone. In these study populations, the use of PRAVAFENIX® provided sufficient evidence to be superior to statin monotherapy and fenofibrate monotherapy to reduce non-HDL cholesterol. Moreover, PRAVAFENIX® has shown good tolerability and a satisfactory safety profile.

VI.2.3 Unknowns relating to treatment benefits

Although extensive evidence supports the use of statins and fibrate monotherapy for reducing cardiovascular risk in patients with diabetes, data on the efficacy and safety of this combination are more limited. Prospective, long-term outcome studies with this combination are needed. Data from the lipid-lowering arm of the ongoing Action to Control Cardiovascular Risk in Diabetes (ACCORD) study – which involved approximately 5,500 patients with type 2 diabetes and compares treatment with simvastatin (20 mg/day) plus fenofibrate (160 mg/day) or simvastatin alone on cardiovascular mortality, did not reveal an increase of these safety concerns and the safety profile is more on line with the literature data and the long experience of these molecules[24].

VI.2.4 Summary of safety concerns

IMPORTANT IDENTIFIED RISKS

Risk	What is known	Preventability
Muscle pain Myopathy, myositis, myalgia, muscle disorder, blood creatine phosphokinase abnormal, muscle enzyme increase, immune-mediated necrotizing myopathy.	Muscle toxicity such as myopathy is one of the most well known adverse effects of statins and fibrates. Muscle symptoms may vary from very mild symptoms such as pain, tenderness or weakness with or without creatine kinase (CK) elevation, to the most severe condition of rhabdomyolysis. All statins can cause muscle toxicity and is more likely with higher doses and the individual strength of the statin. Pravastatin is generally considered as a weaker statin with a lower risk of developing muscle related problems.	Patients who are known to have muscle related problems while under treatment with statins of fibrates should not take PRAVAFENIX®. Patients that are at higher risk for developing muscle problems, such as elderly patients (> 70 years), patients with a history of muscle related problems, patients with kidney, liver or thyroid problems and patients with a history of alcohol abuse should be monitored closely by the treating physician for muscle related problems before and during treatment with PRAVAFENIX®.
Liver problems Transaminases increased, hepatic failure, hepatic pain, hepatotoxicity, hepatitis, blood bilirubin abnormal, hepatic enzyme abnormal, gamma-glutamyltransferase abnormal, transaminases abnormal	Elevation of several enzymes of the liver (transaminases) is another well known adverse effect of statins and fenofibrate. This increase often passes without showing any symptoms. It has been questioned whether the effect on transaminases indicates liver toxicity or just a reaction of the liver to a greater reduction in lipid levels as all lipid-lowering drugs may increase liver enzymes.	Patients with severe liver problems, should not take PRAVAFENIX®. Furthermore, it is recommended that transaminase levels are monitored by the physician on several moments during treatment with PRAVAFENIX®.

24 ACCORD LIPID STUDY, N. Engl. J. Med.2010

Risk	What is known	Preventability
Kidney problems Blood creatine abnormal, blood creatinine abnormal, creatinine renal clearance abnormal, renal failure, renal disorder, blood urea abnormal, glomerular filtration rate abnormal, red blood cells urine positive, urine analysis abnormal	Mainly high potency statins are more likely to cause more serious kidney problems such as acute kidney injury. Pravastatin is however considered as a low potency statin. The effect of fenofibrate on the kidney function is still more controversial and requires further studies.	Patients with moderate to severe kidney impairment should not be treated with PRAVAFENIX®. Furthermore it is recommended to systematically assess the patient's renal function at the initiation of the treatment and every 3 months during the first 12 months of the combination. Afterwards, the physician should decide to check the patient's renal function.
Gall stones Cholelithiasis, Gallbladder disorder	The use of fibrates, such as fenofibrate are likely to cause gallbladder problems such as gall stones by increasing cholesterol excretion into the bile.	Patients with gall bladder disease should not start PRAVAFENIX® treatment. If during treatment gall stones are suspected, gallbladder studies should be performed.
Inflammation of the pancreas Pancreatitis, Pancreatitis acute, Pancreatic disorder, Pancreatic enzymes abnormal, Blood amylase increased	Statin-induced inflammation of the pancreas can occur at any time of treatment but seems to be very uncommon early on and more likely to occur after many months of therapy. Fenofibrate can also cause pancreatitis and could point out to a lack of treatment efficacy in cases of severe hyper-triglyceridaemia, a direct drug effect, or a secondary effect caused by a gallstone.	Patients with a chronic or acute inflammation of the pancreas should not start PRAVAFENIX® treatment, unless it is caused by a severe hypertriglyceridaemia.
Formation of clots in a blood vessel (Thromboembolic events) Pulmonary embolism, Deep vein thrombosis	It is generally accepted that fibrates such as fenofibrate increase the risk for venous thromboembolic events and that statins reduce this risk, but the exact mechanisms are yet to be determined.	Caution should be exercised in patients with a history of thromboembolic events.
Worsening of Diabetes mellitus Diabetes mellitus aggravated, diabetes mellitus exacerbated, worsening of diabetes, hyperglycaemia, blood glucose abnormal and new onset diabetes.	Statin therapy in general and intensive statin therapy in particular is associated with a slightly increased risk of developing diabetes, but this risk was very small in absolute terms and relative to the benefits in terms of reducing coronary events.	Patients at risk should be monitored carefully by their treating physician, but their risk of developing diabetes is outweighed by the reduction in cardiovascular risk so there is no need for stopping treatment with PRAVAFENIX®.

IMPORTANT POTENTIAL RISKS

Risk	What is known (Including reason why it is considered a potential risk)
Increased risk of muscle disorders	Both active ingredients are known to cause muscle related problems. Adding a fibrate, such a fenofibrate, to statin therapy can therefore likely increase the occurrence of muscle related disorders such as myopathy or rhabdomyolysis.
Increased risk of liver problems	As both active ingredients are known to induce liver associated problems, the combination of Pravastatin with Fenofibrate could further increase this risk.
Increased risk of pancreatic events	As both active substances of PRAVAFENIX® can induce inflammation of the pancreas, it is possible that the combination of pravastatin and fenofibrate further increases this risk.
Blood homocysteine increased	Fenofibrate is known to increase homocysteine, but the clinical implications of this increase are not completely defined. Nevertheless it is an important potential risk as it could be a risk factor for cardiovascular disease.
Interstitial lung disease Interstitial pneumopathy	Interstitial lung disease seems to be a possible adverse effect that is common for all statins, but it is not clear how statins cause this effect.
Skin sensitivity to light Phototoxicity	Both statins and fenofibrate can make your skin sensitive to light. Subsequent exposure to heavy sunlight may cause skin problems.
Off label use	As the indication for PRAVAFENIX® is limited to patients with severe lipid disorders whose LDL-cholesterol is managed with Pravastatin 40 mg, but whose triglycerides are still too high and HDL-cholesterol is low, it is possible that patients who are taking other statins than pravastatin will start taking PRAVAFENIX®. Adding Fenofibrate to any statin therapy is indeed accepted by the European Medicines Agency.
Inappropriate monitoring during treatment	Patients at risk for muscle, liver or renal problems, pancreatitis, interstitial lung disease, cholelithiasis or Venothromboembolic events, should be monitored closely by their treating physician. There is a possibility that these recommendations are not followed.

IMPORTANT MISSING INFORMATION

Risk	What is known
Patients above the age of 75 years	Only limited safety data is available on the use of PRAVAFENIX® in patients older than 75 years. Caution should be exercised when starting treatment in these patients.
Long term safety profile of the product	Limited information on the long-term safety of PRAVAFENIX® is available as patients in clinical studies have been exposed to PRAVAFENIX® for a maximum period of 64 weeks.
Uncontrolled hypertension under blood pressure treatment	As these patients were not included in the clinical studies with PRAVAFENIX®, only limited safety information on this group of patients is available.
Diabetes requiring insulin or uncontrolled diabetes	Diabetic patients under PRAVAFENIX® can experience a worsening of their diabetes. This risk however, does not weigh up against the

Risk	What is known
	benefits of PRAVAFENIX® treatment.
Patients who had an acute cardiovascular episode within the 6 months previous to the start of the trial	As these patients were not included in the clinical studies with PRAVAFENIX®, only limited safety information on this group of patients is available.
Other ethnical subgroup population than Caucasian	As these patients were not included in the clinical studies with PRAVAFENIX®, only limited safety information on this group of patients is available.
Cancer	The links between the use of PRAVAFENIX® and the development of different kinds of cancer is not established. However, literature studies suggest that statins might have a protective role against the development of some cancers.

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

Not applicable.

VI.2.6 Planned post authorisation development plan (if applicable)

Not applicable

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

Major changes to the Risk Management Plan over time

Version	Date	Safety concern	Comment
2.0	01/2011	- Diabetes mellitus aggravated was moved from important potential to an important identified risk.	- This change was made following the evaluation of the third PSUR on PRAVAFENIX® by the PRAC.
3.0	10/2013	- Update of the Post Authorisation Safety Study.	- Evolution into the new RMP template.
4.0	07/2015	- The risk of immune-mediated necrotizing myopathy was added to the safety information of PRAVAFENIX®. - Additional information on off label use was added.	- The signal of immune-mediated necrotizing myopathy was analyzed by the PRAC and considered a class effect of statins. - There is a certain extent of off label use of PRAVAFENIX® (i.e. PRAVAFENIX® treatment initiation without prior pravastatin therapy). The adverse events reported besides the off label use were mostly listed adverse reactions linked to the Pravafenix therapy and do not appear to be related to the so called off label use.