

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pravafenix 40 mg/160 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 40 mg pravastatin sodium and 160 mg fenofibrate.

Excipient(s) with known effect:

Each hard capsule contains 19 mg of lactose monohydrate and 33.3 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Hard capsule, with light green body and olive cap, containing a waxy white beige mass and a tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pravafenix is indicated as an adjunct to diet and other non-pharmacological treatment (e.g. exercise, weight reduction) for the treatment of mixed hyperlipidaemia in adult patients at high cardiovascular risk to reduce triglycerides and increase HDL-C when LDL-C levels are adequately controlled while on a treatment with pravastatin 40 mg monotherapy.

4.2 Posology and method of administration

Prior to initiating Pravafenix, secondary causes of combined dyslipidaemia should be excluded and patients should be placed on a standard cholesterol and triglycerides-lowering diet which should be continued during treatment.

Posology

The recommended dose is one capsule per day. Dietary restrictions instituted before therapy should be continued.

Response to therapy should be monitored by determination of serum lipid values. Rapid reduction of serum lipid levels usually follows Pravafenix treatment, but treatment should be discontinued if an adequate response has not been achieved within three months.

Special populations

Elderly patients (≥ 65 years old)

Treatment initiation with Pravafenix should be decided after renal function has been evaluated (see section 4.4 Renal and urinary disorders). Limited safety data on Pravafenix is available in patients >75 years of age and care should be exercised.

Renal impairment

Pravafenix is contraindicated in patients with moderate to severe renal impairment (defined as a creatinine clearance < 60 ml/min) (see section 4.3.)

No modification of posology should be necessary in patients with mild renal impairment.

Hepatic impairment

Pravafenix is not recommended in patients with moderate hepatic impairment and is contraindicated in patients with severe hepatic impairment (see section 4.3.). No posology adjustment is required in patients with mild hepatic impairment.

Paediatric population (< 18 years old)

There is no relevant use of Pravafenix in the paediatric population (< 18 years old) for the indication of mixed dyslipidaemia (see section 4.3).

Method of administration

Oral use.

The recommended dose is one capsule taken daily during the evening meal. Since it is less well absorbed from an empty stomach, Pravafenix should always be taken with food (see sections 4.5. and 5.2).

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Severe hepatic impairment including biliary cirrhosis or active liver disease including unexplained persistent elevations in liver function tests (including serum transaminase elevation) exceeding 3 fold the upper limit of normal (ULN) (see section 4.4).
- Children and adolescents (age below 18 years).
- Moderate to severe renal impairment (defined as an estimated creatinine clearance < 60 ml/min).
- Known photo allergy or photo toxic reaction during treatment with fibrates or ketoprofen.
- Gallbladder disease (see section 4.4).
- Chronic or acute pancreatitis with the exception of acute pancreatitis due to severe hypertriglyceridaemia (see section 4.4).
- Pregnancy and breast-feeding (see section 4.6).
- Personal history of myopathy and/or rhabdomyolysis with statins and/or fibrates or confirmed creatine phosphokinase (CK) elevation above 5 times the ULN under previous statin treatment (see section 4.4).

4.4 Special warnings and precautions for use

The pharmacokinetics properties of Pravafenix are not completely identical to the co-administration of the existing monotherapies when taken with fat-meal or in fasting state. Patients should not be switched from a free co-administration of fenofibrate and pravastatin preparation to Pravafenix (see section 5.2.).

Nervous system disorders

In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia (see section 4.8). Pravafenix should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

Musculoskeletal and connective tissue disorders

As with other lipid lowering substances, pravastatin or fenofibrate have been associated with the onset of myalgia, myopathy and very rarely rhabdomyolysis with or without secondary renal insufficiency. Rhabdomyolysis is an acute potentially fatal condition of skeletal muscle, which may develop at any time during treatment and is characterised by massive muscle destruction associated with major increase in CK (usually > 30 or 40 times the ULN) leading to myoglobinuria.

The risk of muscle toxicity is increased when a fibrate and a 3-hydroxy-3-methyl-glutaryl-Coenzyme A (HMG-CoA) reductase inhibitor are administered together. Myopathy must be considered in any patient presenting with unexplained muscle symptoms such as pain or tenderness, muscle weakness, or muscle cramps. In such cases CK levels should be measured (see below).

Consequently, the potential benefit/risk ratio of Pravafenix should be closely assessed before treatment initiation and patients should be monitored for any signs of muscle toxicity. Certain predisposing factors such as age > 70, renal impairment, hepatic impairment, hypothyroidism, personal history of muscular toxicity with a statin or fibrate, personal or familial history of hereditary muscular disorders or alcohol abuse may increase the risk of muscular toxicity and therefore CK measurement is indicated before starting the combination therapy in these patients (see below).

Statins including pravastatin must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination (see section 4.5). The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness.

Statin therapy may be re-introduced seven days after the last dose of fusidic acid.

In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g., for the treatment of severe infections, the need for co-administration of Pravafenix and fusidic acid should only be considered on a case by case basis and under close medical supervision.

Before treatment initiation

CK levels should be measured prior to initiation of therapy. The baseline CK levels may also be useful as a reference in the event of a later increase during the combination therapy. When measured, CK levels should be interpreted in the context of other potential factors that can cause transient muscle damage, such as strenuous exercise or muscle trauma and repeated if necessary.

If CK levels are significantly elevated > 5 times the ULN at baseline, the results should be controlled after 5-7 days. If confirmed, the treatment should definitively not be initiated (see section 4.3).

During treatment

Routine monitoring of CK is systematically recommended every 3 months during the first 12 months of the combination therapy and let to the appreciation of the clinician beyond this initial period.

Patients should be advised to report promptly unexplained muscle pain, tenderness, weakness or cramps. In these cases, CK levels should be measured.

If a markedly elevated (> 5 times the ULN) CK level is detected and confirmed, Pravafenix therapy must be discontinued. Treatment discontinuation should also be considered if the muscular symptoms are severe and cause daily discomfort (whatever CK levels). If a hereditary muscular disease is suspected in such patients, restarting Pravafenix therapy is not recommended.

There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterized by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

Hepatobiliary disorders

As with other lipid lowering medicinal products, moderate increases in transaminase levels have been reported in some patients treated with pravastatin or fenofibrate. In the majority of cases, liver transaminase levels have returned to their baseline value without the need for treatment discontinuation.

It is recommended that transaminase levels be monitored every 3 months during the first 12 months of treatment and let to the appreciation of the clinician beyond this initial period.

Special attention should be paid to patients who develop increase in transaminase levels and therapy should be discontinued if increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) exceed 3 times the ULN and persist.

Caution should be exercised when Pravafenix is administered to patients with a history of liver disease or heavy alcohol ingestion.

Pancreatitis

Pancreatitis has been reported in patients taking fenofibrate or pravastatin (see sections 4.3). This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridaemia, a direct medicinal product effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation, resulting in the obstruction of the common bile duct.

Renal and urinary disorders

Pravafenix is contraindicated in moderate to severe renal impairment (section 4.3).

It is recommended to systematically assess the estimated creatinine clearance at the initiation of the treatment and every 3 months during the first 12 months of the combination therapy then let to the appreciation of the clinician beyond this period.

Treatment should be discontinued in case of an estimated creatinine clearance < 60 ml/min.

Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, Pravafenix therapy should be discontinued.

Cholelithiasis

Fenofibrate may increase cholesterol excretion into the bile, potentially leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Pravafenix should be discontinued if gallstones are found.

Venothromboembolic events

In the FIELD study, a statistically significant increase was reported in the incidence of pulmonary embolism (0.7% in the placebo group versus 1.1% in the fenofibrate group; $p=0.022$) and a statistically non significant increase in deep vein thrombosis (placebo 1.0% 48/4,900 patients) versus fenofibrate 1.4% (67/4,895); $p=0.074$. The increased risk of venous thrombotic events may be related to the increased homocysteine level, a risk factor for thrombosis and other unidentified factors. The clinical significance of this is not clear. Therefore, caution should be exercised in patients with history of pulmonary embolism.

Diabetes Mellitus

Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI > 30 kg/m², raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Concomitant use with glecaprevir/pibrentasvir

The use of Pravafenix is not recommended in patients treated with glecaprevir/pibrentasvir. Concomitant use of pravastatin and glecaprevir/pibrentasvir may increase the plasma concentration of pravastatin and may lead to an increase of dose-dependent adverse events including myopathy risk. Patients treated with glecaprevir/pibrentasvir should not exceed 20 mg per day of pravastatin.

Lactose

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium

This medicinal product contains 33.3 mg sodium per capsule (excipients and active substance), equivalent to 1.7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

There have been no formal interaction studies for Pravafenix; however the concomitant use of the active substances in patients in clinical studies has not resulted in any unexpected interactions. The following statements reflect the information available on the individual active substances (fenofibrate and pravastatin).

Interactions relevant to pravastatin

Colestyramine/Colestipol

Concomitant administration resulted in approximately 40 to 50% decrease in the bioavailability of pravastatin. There was no clinically significant decrease in bioavailability or therapeutic effect when pravastatin was administered one hour before or four hours after colestyramine or one hour before colestipol.

Ciclosporin

Concomitant administration of pravastatin and ciclosporin leads to an approximately 4 fold increase in pravastatin systemic exposure. In some patients, however, the increase in pravastatin exposure may be larger. Clinical and biochemical monitoring of patients receiving this combination is recommended.

Medicinal products metabolised by cytochrome P450

Pravastatin is not metabolised to a clinically significant extent by the cytochrome P450 system. This is why medicinal products that are metabolised by, or are inhibitors of, the cytochrome P450 system can be added to a stable regimen of pravastatin without causing significant changes in the plasma levels of pravastatin, as have been seen with other statins. The absence of a significant pharmacokinetic interaction with pravastatin has been specifically demonstrated for several medicinal products, particularly those that are substrates/inhibitors of CYP3A4 e.g. diltiazem, verapamil, itraconazole, ketoconazole, protease inhibitors, grapefruit juice and CYP2C9 inhibitors (e.g. fluconazole).

In one of two interaction studies with pravastatin and erythromycin a statistically significant increase in the area under the curve (AUC) (70%) and C_{max} (121%) of pravastatin was observed. In a similar study with clarithromycin a statistically significant increase in AUC (110%) and C_{max} (127%) was observed. Although these changes were minor, caution should be exercised when associating pravastatin with erythromycin or clarithromycin.

Fusidic acid

The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination.

If treatment with systemic fusidic acid is necessary, pravastatin treatment should be discontinued throughout the duration of the fusidic acid treatment. Also see section 4.4.

Glecaprevir/pibrentasvir

Concomitant use of pravastatin and glecaprevir/pibrentasvir may increase the plasma concentration of pravastatin and may lead to an increase of dose-dependent adverse events including myopathy risk.

Patients treated with glecaprevir/pibrentasvir should not exceed 20 mg per day of pravastatin.

Therefore Pravafenix is not recommended in those patients.

Other medicinal products

In interaction studies, no statistically significant differences in bioavailability were observed when pravastatin was administered with acetylsalicylic acid, antacids (when given one hour prior to pravastatin), nicotinic acid or probucol.

Interactions relevant to fenofibrate

Bile acid resin

Bile acid binding resins frequently reduce the absorption of medicinal products and when resins are being co-administered, fenofibrate should be taken 1 hour before, or 4 to 6 hours after, the resin so as not to impede the absorption of fenofibrate.

Oral anticoagulants

Fenofibrate enhances oral anticoagulant effect and may increase risk of bleeding. It is recommended that the dose of anticoagulants is reduced by about one third at the start of treatment and then gradually adjusted if necessary according to INR (International Normalised Ratio) monitoring. This combination is, therefore, not recommended.

Ciclosporin

Some severe cases of reversible renal function impairment have been reported during concomitant administration of fenofibrate and ciclosporin. The renal function of these patients must therefore be closely monitored and the treatment with fenofibrate stopped in the case of severe alteration of laboratory parameters.

Glitazones

Some cases of reversible paradoxical reduction of HDL-cholesterol have been reported during concomitant administration of fenofibrate and glitazones. Therefore, it is recommended to monitor HDL-cholesterol if Pravafenix is co-administered with a glitazone and to stop one of the two treatments if HDL-cholesterol is too low.

Food interaction

Pravafenix must be taken with food, as food enhances the bioavailability of fenofibrate (see sections 4.2 and 5.2).

In all clinical trials, patients were instructed to take Pravafenix daily during the evening meal and dietary restrictions instituted before therapy should be continued. Since current safety and efficacy data are based upon administration with food and with dietary restrictions, it is recommended that Pravafenix is administered with food. (see sections 4.2 and 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

Pravafenix

There are no data from the combined use of pravastatin and fenofibrate in pregnant women. The combination has not been tested in reproductive toxicity studies. The potential risk for humans is unknown. Therefore, as far as pravastatin is contra indicated (see below), Pravafenix is contraindicated during pregnancy (see section 4.3).

Pravastatin sodium

Pravastatin is contraindicated during pregnancy and should be administered to women of childbearing potential only when such patients are unlikely to conceive and have been informed of the potential risk. Special caution is recommended in women of childbearing potential to ensure proper understanding of the potential risk associated with pravastatin therapy during pregnancy. If a patient plans to become pregnant or becomes pregnant, the physician has to be informed immediately and pravastatin should be discontinued because of the potential risk to the foetus.

Fenofibrate

There are no data from the use of fenofibrate in pregnant women. Animal studies have not demonstrated any teratogenic effects. Embryotoxic effects have been shown at doses in the range of maternal toxicity (see section 5.3). The potential risk for humans is unknown.

Breastfeeding

Pravafenix

No studies in lactating animals have been conducted with Pravafenix. Therefore, taking into account the contra indication of pravastatin during lactation, Pravafenix is contraindicated during breastfeeding (see section 4.3).

Pravastatin sodium

A small amount of pravastatin is excreted in human breast milk; therefore pravastatin is contraindicated during breastfeeding (see section 4.3).

Fenofibrate

Fenofibrate is excreted in milk of female rat.

There are no data on the excretion of fenofibrate and/or its metabolites into human breast milk.

Fertility

No effect on fertility in reproductive toxicity studies have been observed with both fenofibrate and pravastatin (see section 5.3)

There are no data on fertility from the combined use of fenofibrate and pravastatin

4.7 Effects on ability to drive and use machines

Pravafenix has no or negligible influence on the ability to drive and use machines. However, when driving vehicles or using machines, it should be taken into account that dizziness and visual disturbances may occur during treatment.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions (ADRs) during Pravafenix therapy are increased transaminase and gastrointestinal disorders.

Tabulated list of adverse reactions

In clinical trials, over 1,566 patients received Pravafenix. Adverse reactions have usually been mild and transient.

The frequencies of adverse reactions are ranked according to the following: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1,000$ to $< 1/100$), Rare ($\geq 1/10,000$ to $< 1/1,000$), Very rare ($< 1/10,000$).

System organ class	Adverse reaction	Frequency
Immune system disorders	Hypersensitivity reactions	Uncommon
Metabolism and nutrition disorders	Diabetes mellitus aggravated, Obesity	Uncommon
Psychiatric disorders	Sleep disturbance including insomnia and nightmares	Uncommon
Nervous system disorders	Dizziness, headache, paraesthesia	Uncommon
Cardiac disorders	Palpitations	Uncommon
Gastrointestinal disorders	Abdominal distension, abdominal pain, abdominal pain upper, constipation, diarrhoea, dry mouth, dyspepsia, eructation, flatulence, nausea, abdominal discomfort, vomiting.	Common
Hepatobiliary disorders	Transaminases increased.	Common
	Hepatic pain, gammaglutamyl transferase increased.	Uncommon
Skin and subcutaneous tissue disorders	Pruritus, urticaria	Uncommon

Musculoskeletal, connective tissue and bone disorders	Arthralgia, back pain, blood creatine phosphokinase increased, muscle spasms, musculoskeletal pain, myalgia, pain in extremity.	Uncommon
Renal and urinary disorders	Blood creatinine increased, creatinine renal clearance decreased, creatinine renal clearance increased, Renal failure	Uncommon
General disorders and administration site conditions	Asthenia, fatigue, influenza like illness	Uncommon
Investigation	Blood cholesterol increased, blood triglycerides increased, low-density lipoprotein increased, weight increased.	Uncommon

Description of selected adverse reactions

Skeletal muscle: Marked and persistent increases of creatine phosphokinase (CK) have been reported infrequently. In clinical studies, the incidence of important elevations in creatine phosphokinase ($CK \geq 3$ times the ULN, ≤ 5 times the ULN) was 1.92% for patients treated with Pravafenix. Clinically important elevations in creatine phosphokinase ($CK \geq 5$ times the ULN, ≤ 10 times the ULN without muscular symptoms) were seen in 0.38% of the patients treated with Pravafenix. Clinically important elevation ($CK \geq 10$ times the ULN without muscular symptoms) was seen in 0.06% of the patients treated with Pravafenix. (see section 4.4).

Liver reactions: Marked and persistent increases of serum transaminases have been reported infrequently. In clinical studies, the incidence of important elevations in serum transaminases (ALT and/or AST ≥ 3 times the ULN, ≤ 5 times the ULN) was 0.83% for patients treated with Pravafenix. Clinically important elevations in serum transaminases (ALT and/or AST ≥ 5 times the ULN) were seen in 0.38% of the patients treated with Pravafenix. (see section 4.4).

Additional information on the individual active substances of the fixed dose combination

Pravafenix contains pravastatin and fenofibrate. Additional adverse reactions associated with the use of medicinal products containing pravastatin or fenofibrate observed in clinical trials and post-marketing experience that may potentially occur with Pravafenix are listed below. Frequency categories are based on information available from pravastatin and fenofibrate Summary of Product characteristics available in the EU.

System Organ Class	Adverse reaction (fenofibrate)	Adverse reaction (Pravastatin)	Frequency
Blood and lymphatic system disorders	Haemoglobin decreased, White blood cell count decreased		Rare
Nervous system disorders	Fatigue and vertigo		Rare
		Peripheral polyneuropathy	Very Rare
		Myasthenia gravis	Not known
Eye disorders		Vision disturbance (including blurred vision and diplopia)	Uncommon
		Ocular myasthenia	Not known
Vascular disorders	Thromboembolism (pulmonary embolism, deep vein thrombosis)*		Uncommon
Respiratory, thoracic and mediastinal disorders	Interstitial pneumopathies		Not known
Hepatobiliary disorders	Cholelithiasis		Uncommon

		Jaundice, fulminant hepatic necrosis, hepatitis	Very rare
	Jaundice, complications of cholelithiasis (e.g. cholecystitis, cholangitis, biliary colic, etc).		Not known
Skin and subcutaneous tissue disorders		Skin rash, Scalp/hair abnormality (including alopecia)	Uncommon
		Dermatomyositis	Very rare
	Alopecia, photosensitivity reactions		Rare
		Lichenoid eruption	Not known
Musculoskeletal, connective tissue and bone disorders	Muscle disorder (e.g. myositis, muscular weakness)		Uncommon
		Muscle rupture	Not known
		Rhabdomyolysis, which can be associated with acute renal failure secondary to myoglobinuria, myopathy (see section 4.4); myositis, polymyositis. Isolated cases of tendon disorders, sometimes complicated by rupture. Erythematous lupus like syndrome.	Very rare
	Rhabdomyolysis	Immune-mediated necrotizing myopathy (see section 4.4).	Not known
Renal and urinary disorders:		Abnormal urination (including dysuria, frequency, nocturia)	Uncommon
Reproductive system and breast disorders	Sexual dysfunction	Sexual dysfunction	Uncommon
General disorders:		Fatigue	Uncommon
Investigations	Blood urea increased		Rare

* In the FIELD-study (fenofibrate study), a randomised placebo-controlled trial performed in 9,795 patients with type 2 diabetes mellitus, a statistically significant increase in pancreatitis cases was observed in patients receiving fenofibrate versus patients receiving placebo (0.8% versus 0.5%; $p = 0.031$). In the same study, a statistically significant increase was reported in the incidence of pulmonary embolism (0.7% in the placebo group versus 1.1% in the fenofibrate group; $p = 0.022$) and a statistically non-significant increase in deep vein thromboses (placebo: 1.0 % [48/4,900 patients] versus fenofibrate 1.4% [67/4,895 patients]; $p = 0.074$).

The following adverse events have been reported with some statins:

- Nightmares
- Memory loss
- Depression
- Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4).
- Diabetes Mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI > 30 kg/m², raised triglycerides, history of hypertension).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

In the event of an overdose, symptomatic and supportive measures should be employed.

Pravastatin

Reported cases of overdose were asymptomatic and did not give rise to abnormal laboratory tests. No specific antidote is known. If overdose is suspected, treat symptomatically and institute appropriate supportive measures as required.

Fenofibrate

No specific antidote is known. If an overdose is suspected, treat symptomatically and institute appropriate supportive measures as required. Fenofibrate cannot be eliminated by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Lipid modifying agents, HMG CoA reductase inhibitors in combination with other lipid modifying agents, ATC code: C10BA03

Pharmacodynamic effects

Pravafenix contains fenofibrate and pravastatin, which have different modes of action and show additive effects in terms of reduction of serum lipid. The following statements reflect the pharmacodynamic/pharmacokinetic properties of the individual active substances of Pravafenix.

Fenofibrate

Fenofibrate is a fibric acid derivative whose lipid modifying effects reported in humans are mediated via activation of Peroxisome Proliferator Activated Receptor type alpha (PPAR α). Studies with fenofibrate on lipoprotein fractions show decreases in levels of LDL and VLDL cholesterol. HDL cholesterol levels are frequently increased. LDL and VLDL triglycerides are reduced. The overall effect is a decrease in the ratio of low and very low-density lipoproteins to high-density lipoproteins.

The lipid-lowering properties of fenofibrate seen in clinical practice have been explained in vivo in transgenic mice and in human hepatocyte cultures by activation of Peroxisome Proliferator Activated Receptor type α (PPAR α). Through this mechanism, fenofibrate increases lipolysis and elimination of triglyceride rich particles from plasma by activating lipoprotein lipase and reducing production of Apoprotein C-III. Activation of PPAR α also induces an increase in the synthesis of Apoproteins A-I, A-II and of HDL cholesterol.

There is evidence that treatment with fibrates may reduce coronary heart disease events but they have not been shown to decrease all cause mortality in the primary or secondary prevention of cardiovascular disease.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid trial was a randomized placebo-controlled study of 5,518 patients with type 2 diabetes mellitus treated with fenofibrate in addition to simvastatin. Fenofibrate plus simvastatin therapy did not show any significant differences compared to simvastatin monotherapy in the composite primary outcome of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death (hazard ratio [HR] 0.92, 95% CI 0.79-1.08, $p = 0.32$; absolute risk reduction: 0.74%). In the pre-specified subgroup of dyslipidaemic patients, defined as those in the lowest tertile of HDL-C (≤ 34 mg/dl or 0.88 mmol/L) and highest tertile of TG (≥ 204 mg/dl or 2.3 mmol/L) at baseline, fenofibrate plus simvastatin therapy demonstrated a 31% relative reduction compared to simvastatin monotherapy for the composite primary outcome (hazard ratio [HR] 0.69, 95% CI 0.49-0.97, $p = 0.03$; absolute risk reduction: 4.95%). Another prespecified subgroup analysis identified a statistically significant treatment-by-gender interaction ($p = 0.01$)

indicating a possible treatment benefit of combination therapy in men ($p=0.037$) but a potentially higher risk for the primary outcome in women treated with combination therapy compared to simvastatin monotherapy ($p=0.069$). This was not observed in the aforementioned subgroup of patients with dyslipidaemia but there was also no clear evidence of benefit in dyslipidaemic women treated with fenofibrate plus simvastatin, and a possible harmful effect in this subgroup could not be excluded.

Plasma uric acid levels are increased in approximately 20% of hyperlipidaemic patients, particularly in those with type IV disease. Fenofibrate has a uricosuric effect and is therefore of additional benefit in such patients.

Pravastatin

Pravastatin is a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme catalysing the early rate-limiting step in cholesterol biosynthesis, and produces its lipid-lowering effect in two ways. Firstly, with the reversible and specific competitive inhibition of HMG-CoA reductase, it effects modest reduction in the synthesis of intracellular cholesterol. This results in an increase in the number of LDL-receptors on cell surfaces and enhanced receptor-mediated catabolism and clearance of circulating LDL-cholesterol.

Secondly, pravastatin inhibits LDL production by inhibiting the hepatic synthesis of VLDL-cholesterol, the LDL-cholesterol precursor.

In both healthy subjects and patients with hypercholesterolaemia, pravastatin lowers the following lipid values: total cholesterol, LDL-cholesterol, apolipoprotein B, VLDL-cholesterol and triglycerides; while HDL-cholesterol and apolipoprotein A are elevated.

Pravafenix

The respective effects of pravastatin and fenofibrate are complementary. Pravastatin is more effective in reducing LDL-C and total cholesterol but presents only modest effects on TG and HDL-C while fenofibrate is very effective in decreasing TG and increasing HDL-C, but with few effects on LDL-C. Additionally, fibrates have the properties to modify the size and density of LDL-C particles to make them less atherogenic.

Fibrates and statins in combination have also been shown to synergistically increase the transcriptional activities of PPAR α receptors.

Clinical efficacy and safety

Four multicenter studies with either Pravafenix 40 mg/160 mg or Pravastatin 40 mg or Simvastatin 20 mg were conducted: 3 studies included a 12 week randomized, double-blind, active controlled period with an open-label extension phase and one was a 24-week open-label study.

In total, these studies enrolled 1,637 patients who have not had an adequate response to treatment with pravastatin 40 mg monotherapy or simvastatin 20 mg in Europe and in the USA.

In the pivotal European multicenter 64-week clinical trial including 12 week randomised, double-blind, double-dummy, 2-arm, parallel study period, 248 high vascular risk patients with mixed dyslipidaemia were randomised to one of the two treatment groups: Pravafenix 40 mg/160 mg or pravastatin 40 mg. Only patients who had not met their NCEP ATP III target LDL-C and Triglyceride goals (LDL >100 mg/dl and TG >150 mg/dl) after 8 weeks on pravastatin 40 mg (1 tablet, once daily) were randomized. Patients receiving Pravafenix 40 mg/160 mg were compared to those receiving pravastatin 40 mg: Pravafenix significantly lowered non-HDL-C, LDL-C, TG and significantly increased HDL-C to a greater extent than pravastatin 40 mg (table).

**Mean percent changes from baseline to week 12
for patients treated with Pravafenix 40 mg/160 mg or Pravastatin 40 mg once daily**

	Pravafenix 40 mg/160 mg N ^a = 120 Mean (%)± SE ^b	PRAVASTATIN 40 mg N ^a = 119 Mean (%)± SE ^b	Pravafenix versus PRAVASTATIN p-value ^c
Non-HDL-C (mg/dl)	-14.1 ± 1.78	-6.1 ± 1.79	0.0018
LDL-C (mg/dl)	-11.7 ± 1.75	-5.9 ± 1.76	0.019
HDL-C (mg/dl)	+6.5 ± 1.12	+2.3 ± 1.13	0.0089
TG (mg/dl)	-22.6 ± 4.37	-2.0 ± 4.39	0.0010
TC (mg/dl)	-9.9 ± 1.37	-4.4 ± 1.38	0.006
Apo A _I (g/L)	+5.5 ± 0.99	+2.8 ± 0.97	0.058
Apo B (g/L)	-12.6 ± 1.57	-3.8 ± 1.53	<0.0001
Apo B/Apo A _I	-16.3 ± 1.66	-6.0 ± 1.61	<0.0001
Fibrinogen (g/L)	-8.8 ± 1.80	+1.4 ± 1.75	<0.0001
Hs-CRP (mg/L)	-1.1 ± 0.61	+0.6 ± 0.70	0.003

^a Number of patients

^b Mean percent change (least square mean ± standard error) between baseline measured after 8 weeks on Pravastatin 40 mg and 12 additional weeks with Pravafenix 40 mg/160 mg or Pravastatin 40 mg

^c Pairwise p-value is significant if <0.05

The effects of Pravafenix 40 mg/160 mg were confirmed in a similar multicenter, 64-week trial including a 12 week randomized, double-blind phase in a study performed in the USA and comparing Pravafenix 40 mg/160 mg to Fenofibrate 160 mg monotherapy and Pravastatin 40 mg monotherapy in patients with mixed dyslipidaemia. The incremental benefit of Pravafenix 40 mg/160 mg on main lipid parameters versus Pravastatin 40 mg and Fenofibrate 160 mg monotherapy was also established.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Pravafenix in all subsets of the paediatric population in disorders of lipoprotein metabolism and other hyperlipidaemias (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

No clinically significant pharmacokinetic interaction was seen when fenofibrate was coadministered with pravastatin.

Absorption

Pravafenix is bioequivalent to coadministered fenofibrate and pravastatin in a single dose study. However in a multiple dose study, the results showed that the product is not bioequivalent because its bioavailability after multiple dosing is a 20% lower for the fenofibrate component of the combination. This is due to the fat content of the meal. Therefore the fixed dose combination (Pravafenix) could not be considered interchangeable with the free co-administration of fenofibrate and pravastatin mono-component drug products.

A pharmacokinetic study after a single dose administration of Pravafenix has been performed in fed and fasting condition. The results of this study show that food has effect on the rate and extent of absorption in the fixed dose combination. The bioavailability of fenofibric acid is lower in fasting conditions after a single dose administration of the Fenofibrate-Pravastatin 160/40 mg combination. The decreased in AUC_t, AUC_∞ and C_{max} of fenofibric acid (point estimate) is of 30.94%, 10.9% and 68.71% respectively.

The bioavailability of pravastatin is higher after a single dose administration of the test product Fenofibrate/Pravastatin 160/40 mg in fasting conditions than after a single dose of the product in fed conditions. The increase in AUC_{∞} , AUC_t , and C_{max} is of 111.88%, 114.06%, and 115.28% respectively. In line with several formulations for fenofibrate, the fixed combination is recommended to be taken with food because the bioavailability of fenofibrate is increased when administered with food and the lipid-lowering efficacy of pravastatin is not altered.

Pravastatin

Pravastatin is administered orally in the active form. It is rapidly absorbed; peak serum levels are achieved 1 to 1.5 hours after ingestion. On average, 34% of the orally administered dose is absorbed, with an absolute bioavailability of 17%.

The presence of food in the gastrointestinal tract leads to a reduction in the bioavailability, but the cholesterol-lowering effect of pravastatin is identical whether taken with or without food.

After absorption, 66% of pravastatin undergoes a first-pass extraction through the liver, which is the primary site of its action and the primary site of cholesterol synthesis and clearance of LDL-cholesterol. In vitro studies demonstrated that pravastatin is transported into hepatocytes and with substantially less intake in other cells. In view of this substantial first pass through the liver, plasma concentrations of pravastatin have only a limited value in predicting the lipid-lowering effect. The plasma concentrations are proportional to the doses administered.

Fenofibrate

Maximum plasma concentrations (C_{max}) occur within 4 to 5 hours after oral administration. Plasma concentrations are stable during continuous treatment in any given individual. The absorption of fenofibrate is increased when administered with food. The food effect increases with the fat content: the larger the lipid content the larger the bioavailability of fenofibrate.

Distribution

Pravastatin

About 50% of circulating pravastatin is bound to plasma proteins. The volume of distribution is about 0.5 l/kg. A small quantity of pravastatin passes into the human breast milk.

Fenofibrate

Fenofibric acid is strongly bound to plasma albumin (more than 99%).

Biotransformation and elimination

Pravastatin

Pravastatin is not significantly metabolised by cytochrome P450 nor does it appear to be a substrate or an inhibitor of P-glycoprotein but rather a substrate of other transport proteins.

Following oral administration, 20% of the initial dose is eliminated in the urine and 70% in the faeces. Plasma elimination half-life of oral pravastatin is 1.5 to 2 hours.

After intravenous administration, 47% of the dose is eliminated by the renal excretion and 53% by biliary excretion and biotransformation. The major degradation product of pravastatin is the 3- α -hydroxy isomeric metabolite. This metabolite has one-tenth to one-fortieth the HMG-CoA reductase inhibitor activity of the parent compound.

The systemic clearance of pravastatin is 0.81 l/h/kg and the renal clearance is 0.38 l/h/kg indicating tubular secretion.

Fenofibrate

No unchanged fenofibrate can be detected in the plasma where the principal metabolite is fenofibric acid. The drug is excreted mainly in the urine. Practically all the drug is eliminated within 6 days.

Fenofibrate is mainly excreted in the form of fenofibric acid and its glucuronide conjugate. In elderly patients, the fenofibric acid apparent total plasma clearance is not modified. The plasma elimination half-life of fenofibric acid is approximately 20 hours.

Kinetic studies following the administration of a single dose and continuous treatment have demonstrated that the drug does not accumulate. Fenofibric acid is not eliminated by haemodialysis.

5.3 Preclinical safety data

The safety of concomitant administration of pravastatin and fenofibrate was assessed in rats. Toxicological findings in these co-administration studies were consistent with those seen with pravastatin and fenofibrate administered individually.

Pravastatin

Based on conventional studies of safety pharmacology, repeated dose toxicity and toxicity on reproduction, there are no other risks for the patient than those expected due to the pharmacological mechanism of action.

Repeated dose studies indicate that pravastatin may induce varying degrees of hepatotoxicity and myopathy; in general, substantive effects on these tissues were only evident at doses 50 or more times the maximum human mg/kg dose. In vitro and in vivo genetic toxicology studies have shown no evidence of mutagenic potential. In mice, a 2-year carcinogenicity study with pravastatin demonstrates at doses of 250 and 500 mg/kg/day (> 310 times the maximum human mg/kg dose), statistically significant increases in the incidence of hepatocellular carcinomas in males and females, and lung adenomas in females only. In rats a 2-year carcinogenicity study demonstrates at a dose of 100 mg/kg/day (125 times the maximum human mg/kg/dose) a statistically significant increase in the incidence of hepatocellular carcinomas in males only.

Fenofibrate

Chronic toxicity studies have yielded no relevant information about specific toxicity of fenofibrate. Studies on mutagenicity of fenofibrate have been negative. In rats and mice, liver tumours have been found at high dosages, which are attributable to peroxisome proliferation. These changes are specific to small rodents and have not been observed in other animal species. This is of no relevance to therapeutic use in man.

Studies in mice, rats and rabbits did not reveal any teratogenic effect. Embryotoxic effects were observed at doses in the range of maternal toxicity. Prolongation of the gestation period and difficulties during delivery were observed at high doses. No sign of any effect on fertility has been detected.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Lactose monohydrate
Cellulose microcrystalline
Ascorbyl palmitate
Povidone K29-32
Sodium starch glycolate
Magnesium stearate
Talc
Triacetin
Sodium hydrogen carbonate
Lauroyl macrogolglycerides Type 1500
Hydroxypropylcellulose
Macrogol 20 000

Capsule shell

Gelatine

Indigo carmine

Black iron oxide

Titanium dioxide

Yellow iron oxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Polyamide-Aluminium-PVC/aluminium blister

2 years.

HDPE bottle

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polyamide-Aluminium-PVC/aluminium blister packs containing 30, 60 and 90 hard capsules.

Opaque white HDPE bottles containing 14, 30, 60 and 90 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Laboratoires SMB s.a.

Rue de la Pastorale, 26-28

B-1080 Brussels

Belgium

Tel. +32 (2) 411 48 28

Fax. +32 (2) 411 28 28

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/679/001-007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 April 2011

Date of latest renewal: 14 January 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release:

SMB Technology s.a.
rue du Parc Industriel 39
B-6900 Marche en Famenne
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Pravafenix 40 mg/160 mg hard capsules
pravastatin sodium/fenofibrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 40 mg of pravastatin sodium and 160 mg of fenofibrate

3. LIST OF EXCIPIENTS

Contains lactose monohydrate and sodium. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

30 hard capsules
60 hard capsules
90 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Laboratoires SMB s.a.
rue de la Pastorale, 26-28
B-1080 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/679/001 30 hard capsules
EU/1/11/679/002 60 hard capsules
EU/1/11/679/003 90 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pravafenix

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Pravafenix 40 mg/160 mg hard capsules
pravastatin sodium/fenofibrate

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

SMB

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BOTTLES

1. NAME OF THE MEDICINAL PRODUCT

Pravafenix 40 mg/160 mg hard capsules
pravastatin sodium/fenofibrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 40 mg of pravastatin sodium and 160 mg of fenofibrate.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate and sodium. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

14 hard capsules
30 hard capsules
60 hard capsules
90 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Laboratoires SMB s.a.
rue de la Pastorale, 26-28
B-1080 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/679/007 14 hard capsules
EU/1/11/679/004 30 hard capsules
EU/1/11/679/005 60 hard capsules
EU/1/11/679/006 90 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pravafenix

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE FOR 14 AND 30 HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Pravafenix 40 mg/160 mg hard capsules
pravastatin sodium/fenofibrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 40 mg of pravastatin sodium and 160 mg of fenofibrate.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate and sodium.

4. PHARMACEUTICAL FORM AND CONTENTS

14 hard capsules
30 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Laboratoires SMB s.a.
rue de la Pastorale, 26-28
B-1080 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/11/679/007 14 hard capsules
EU/1/11/679/004 30 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**BOTTLES FOR 60 AND 90 HARD CAPSULES****1. NAME OF THE MEDICINAL PRODUCT**

Pravafenix 40 mg/160 mg hard capsules
pravastatin sodium/fenofibrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 40 mg of pravastatin sodium and 160 mg of fenofibrate.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate and sodium. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules
90 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Laboratoires SMB s.a.
rue de la Pastorale, 26-28
B-1080 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/11/679/005 60 hard capsules
EU/1/11/679/006 90 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Pravafenix 40 mg/160 mg hard capsules pravastatin sodium/fenofibrate

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Pravafenix is and what it is used for
2. What you need to know before you take Pravafenix
3. How to take Pravafenix
4. Possible side effects
5. How to store Pravafenix
6. Contents of the pack and other information

1. What Pravafenix is and what it is used for

Pravafenix contains two active substances: pravastatin and fenofibrate. Both are cholesterol/lipid modifying medicines.

Pravafenix is used in addition to low fat diet in adults

- To lower the level of your 'bad' cholesterol (LDL cholesterol). It does this by lowering the level of total cholesterol, and fatty substances called triglycerides in the blood.
- To raise the level of your 'good' cholesterol (HDL cholesterol).

What should I know about cholesterol and triglycerides?

Cholesterol is one of several fats found in your blood. Your total cholesterol is made up mainly of LDL and HDL cholesterol.

LDL cholesterol is often called 'bad' cholesterol because it can build up in the walls of your arteries and form plaque. Over time, this plaque build-up can lead to a clogging of your arteries. This clogging can slow or block blood flow to vital organs such as the heart and brain. When the blood flow is blocked, the result can be a heart attack or stroke.

HDL cholesterol is often called 'good' cholesterol because it helps keep the 'bad' cholesterol from building up in the arteries and because it protects against heart disease.

Triglycerides are another fat in your blood. They may raise your risk of having heart problems.

In most people, there are no signs of cholesterol problems at first. Your doctor can measure your cholesterol with a simple blood test. Visit your doctor regularly to keep track of your cholesterol level.

Pravafenix is used if you are an adult with an elevated risk for heart disease and need to improve cholesterol and triglycerides fat levels in your blood when your 'bad' cholesterol levels are being adequately controlled with pravastatin alone (a statin, a cholesterol-lowering medicine).

2. What you need to know before you take Pravafenix

Do not take Pravafenix

- if you are allergic to fenofibrate, pravastatin, or any of the other ingredients of this medicine (listed in section 6).
- if you suffer from liver disease.
- if you are under 18 years old.
- if you suffer from kidney disease.
- if you have had photoallergy (allergic reaction caused by sunlight or exposure to UV light) or phototoxic reactions (damage to skin caused by exposure to sunlight or UV light) during treatment with fibrates (lipid-modifying medicines) or ketoprofen (an anti-inflammatory medicine that can be used orally or on the skin for muscle and bone disorders, and orally for gout or period pain)
- if you suffer from gallbladder disease.
- if you suffer from pancreatitis (inflammation of the pancreas leading to abdominal pain)
- if you are pregnant or breast-feeding.
- if you have a history of muscle problems (e.g. myopathy or rhabdomyolysis) during treatment with cholesterol-controlling medicines called 'statins' (such as simvastatin, atorvastatin, pravastatin or rosuvastatin) or fibrates (such as fenofibrate and bezafibrate).

Do not take Pravafenix if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking Pravafenix.

Warnings and precautions

Talk to your doctor or pharmacist before taking Pravafenix.

Before you take Pravafenix you should tell your doctor if you have or have had any medical problems.

- Tell your doctor about all your medical conditions including allergies.
- Tell your doctor if you drink large amounts of alcohol (if you drink more than the recommended daily amount; ask your doctor or pharmacist if you are unsure) or have ever had liver disease. See also below section "Taking Pravafenix with food and drink".
- Your doctor should do a blood test before you start taking Pravafenix. This is to check how well your liver and your kidneys are working.
- Your doctor may also want you to have blood tests to check how well your liver is working after you start taking Pravafenix.
- If you have or have had myasthenia (a disease with general muscle weakness including in some cases muscles used when breathing), or ocular myasthenia (a disease causing eye muscle weakness) as statins may sometimes aggravate the condition or lead to the occurrence of myasthenia (see section 4).

Contact your doctor immediately if you experience unexplained muscle pain, tenderness, or weakness. This is because, on rare occasions, muscle problems can be serious, including muscle breakdown resulting in kidney damage, and very rarely deaths have occurred.

Also tell your doctor or pharmacist if you have a muscle weakness that is constant. Additional tests and medicines may be needed to diagnose and treat this.

The risk of muscle breakdown is greater in certain patients. Tell your doctor if any of the following applies to you:

- Liver or kidney problems
- Thyroid problems
- You are more than 70 years old
- You have ever had muscle problems during a treatment with cholesterol-lowering medicines such as a statin or fibrate
- You are taking or have taken in the last 7 days a medicine called fusidic acid, (a medicine for bacterial infection) orally or by injection. The combination of fusidic acid and Pravafenix can lead to serious muscle problems (rhabdomyolysis).
- You or your close family members have a hereditary muscle disorder
- You have alcohol problems (regularly drinking large amounts of alcohol)

Check with your doctor or pharmacist before taking Pravafenix if you have severe respiratory failure, e.g. you have breathing problems including, persistent non-productive cough, deterioration in general health like fatigue (tiredness), weight loss and/or shortness of breath or fever.

If you feel any of these symptoms you should stop taking Pravafenix and inform your doctor.

While you are on this medicine your doctor will monitor you closely if you have diabetes or are at risk of developing diabetes. You are likely to be at risk of developing diabetes if you have high levels of sugars and fats in your blood, are overweight and have high blood pressure.

Children and adolescents

Do not take Pravafenix if you are under 18 years old

Other medicines and Pravafenix

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. It is important that you inform your doctor if you are already being treated with any of the following:

- Bile acid resins such as colestyramine/colestipol (a medicine for lowering cholesterol), because it affects the way Pravafenix works.
- Ciclosporin (a medicine often used in organ transplant patients).
- Medicines to prevent blood clots, such as warfarin, fluindione, phenprocoumon or acenocoumarol (anticoagulants)
- An antibiotic such as erythromycin, clarithromycin to treat infections caused by bacteria.
- Fusidic acid: If you need to take oral fusidic acid to treat a bacterial infection you will need to temporarily stop using this medicine. Your doctor will tell you when it is safe to restart Pravafenix. Taking Pravafenix with fusidic acid may rarely lead to muscle weakness, tenderness or pain (rhabdomyolysis). See more information regarding rhabdomyolysis in section 4.
- Glecaprevir/pibrentasvir (used to treat hepatitis C virus infection) because it can increase some adverse events including muscle problems.
- a particular class of medicines to treat diabetes (such as rosiglitazone, pioglitazone)

Pravafenix with food, drink and alcohol

- Always take Pravafenix with food as Pravafenix is less well absorbed from an empty stomach.
- You should always keep your alcohol intake to a minimum. If you are concerned about how much alcohol you can drink while you are taking this medicine, you should discuss this with your doctor.

If you are not sure about this, please follow your doctor's advice.

Pregnancy and breast-feeding

Do not take Pravafenix if you are pregnant or trying to get pregnant or think you may be pregnant. If you plan to become pregnant or become pregnant, inform your doctor immediately. The medicine must be discontinued because of the potential risk to the foetus.

Do not take Pravafenix if you are breast-feeding.

Driving and using machines

Pravafenix does not usually affect your ability to drive or use machines. If you experience any dizziness, blurred or double vision during treatment, make sure you are fit to drive and use machines before attempting to do so.

Pravafenix contains lactose and sodium

Pravafenix contains a sugar called lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product. This medicine contains 33.3 mg sodium (main component of cooking/table salt) in each capsule (excipients and active substance). This is equivalent to 1.7% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to take Pravafenix

Always take Pravafenix exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

- Before starting taking Pravafenix, you should be on a diet to lower your cholesterol.
- You should keep to this diet while taking Pravafenix

The usual dose is one capsule taken daily during the evening meal. Swallow the capsule with water. It is important to take the capsule with food, as it won't work as well if your stomach is empty.

When your doctor has prescribed Pravafenix along with colestyramine or any other bile acid binding resins (medicines for lowering cholesterol), take Pravafenix 1 hour before, or 4 to 6 hours after the resin. This is because colestyramine or other bile acid binding resins frequently reduce the absorption of medicines when taken too closely together and so may impede the absorption of Pravafenix. If you take indigestion remedies (used to neutralise acid in your stomach), take Pravafenix 1 hour after.

If you take more Pravafenix than you should

Please contact your doctor or pharmacist

If you forget to take Pravafenix

Do not take a double dose to make up for a forgotten dose, just take your normal amount of Pravafenix at the usual time the next day.

If you stop taking Pravafenix

Do not stop taking Pravafenix without first discussing it with your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following two side effects are important and will require immediate action.

Tell your doctor straight away if you have any unexplained muscular pain or cramps, tenderness, or weakness. This is because on very rare occasions (may affect up to 1 in 10,000 people), muscle problems can be serious, including muscle breakdown resulting in kidney damage, and very rarely deaths have occurred.

Sudden severe allergic reactions including swelling of the face, lip, tongue or wind pipe which can cause great difficulty in breathing. This is a very rare reaction which can be serious if it occurs. You should tell your doctor immediately if it happens.

Other Side effects

Common side effects (may affect up to 1 in 10 people)

- Digestive effects: gastric or intestinal disorders (abdominal pain, nausea, vomiting, diarrhoea and flatulence, constipation, dry mouth, upper abdominal pain with bloating (dyspepsia), burping (eructation)).
- Effects on liver: raised serum transaminases.

Uncommon side effects (may affect up to 1 in 100 people)

- Abnormal heartbeat (palpitations), formation of blood clots in veins (deep vein thrombosis) and blockage of the lung arteries by blood clots (pulmonary embolism)
- Rashes, skin rash, itching, hives or reactions to sunlight or exposure to UV light (photosensitivity reactions), scalp/hair abnormality (including hair loss)

- Effects on nervous system: dizziness (sensation of unsteadiness), headache, sleep disturbances (including difficulty sleeping and nightmares), pins and needles sensation (paresthesia).
- Muscle and joint pain (myalgia, arthralgia), back pain, alterations in some laboratory blood tests for muscle function.
- Problems with sight such as blurred or double vision.
- Kidney problems (increased or decreased levels of certain enzymes within the body seen in a test) bladder problems (painful or frequent urination, having to pass water at night), sexual dysfunction.
- Tiredness, weakness, influenza-like illness.
- Hypersensitivity.
- Increased blood cholesterol, increased blood triglycerides, increased LDL, increased gamma-glutamyl transferase (various liver enzymes), liver pain (upper right abdominal pain with or without pain in the back), increased weight.
- Obesity.
- Muscle inflammation (myositis), muscular cramps and weakness.

Rare side effects (may affect up to 1 in 1,000 people)

- Decrease in haemoglobin (oxygen-carrying pigment in blood) and leukocytes (white blood cells).

Very rare side effects (may affect up to 1 in 10,000 people)

- Inflammation of the liver (hepatitis), symptoms of which may be mild yellowing of the skin and whites of the eyes (jaundice), abdominal pain and itching.
- Muscle breakdown (rhabdomyolysis), some cases of tendon problems, sometimes complicated by rupture.
- A condition characterised by an inflammation of the muscles and the skin (dermatomyositis).
- Skin rash, possibly with pain in the joints (Erythematous lupus like syndrome).
- Tingling and numbness (peripheral polyneuropathy).

Side effects of unknown frequency (frequency cannot be estimated from the available data)

- Muscle weakness that is constant
- Muscle rupture
- Skin rash (lichenoid eruption)
- Myasthenia gravis (a disease causing general muscle weakness including in some cases muscles used when breathing).
- Ocular myasthenia (a disease causing eye muscle weakness).

Talk to your doctor if you experience weakness in your arms or legs that worsens after periods of activity, double vision or drooping of your eyelids, difficulty swallowing, or shortness of breath.

Possible side effects reported with some statins (same type of cholesterol-lowering medicines as pravastatin)

- Memory loss
- Depression
- Breathing problems including persistent cough/or shortness of breath or fever.
- Diabetes. This is more likely if you have high levels of sugars and fats in your blood, are overweight and have high blood pressure. Your doctor will monitor you while you are taking this medicine.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Pravafenix

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister/bottle after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Pravafenix contains

- The active substances are fenofibrate and pravastatin sodium. Each hard capsule contains 40 mg pravastatin sodium and 160 mg fenofibrate.
- The other ingredients are:
 - *capsule content*: lactose monohydrate, cellulose microcrystalline, ascorbyl palmitate, povidone, sodium starch glycolate, magnesium stearate, talc, triacetin, sodium hydrogen carbonate, lauroyl macroglycerides, hydroxypropylcellulose, macrogol 20 000.
 - *capsule shell*: gelatine, indigo carmine (E132), black iron oxide (E172), titanium dioxide (E171), yellow iron oxide (E172).

What Pravafenix looks like and contents of the pack

The capsules are hard gelatine capsule with olive cap and light green body containing a waxy white beige mass and a tablet. The capsules are supplied in Polyamide-Aluminium-PVC/aluminium blister packs containing 30, 60 or 90 capsules, and in opaque white plastic bottles containing either 14, 30, 60 or 90 capsules.

Not all pack sizes may be marketed.

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Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu/>.

ANNEX IV

**SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS
OF THE MARKETING AUTHORISATION(S)**

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for fenofibrate / pravastatin, the scientific conclusions of PRAC are as follows:

In view of available data on muscle rupture from the literature and spontaneous reports including in 62 cases a close temporal relationship, a positive de-challenge (14 cases) and/or re-challenge (2 cases) and in view of a plausible mechanism of action, the PRAC considers a causal relationship between pravastatin and muscle rupture is at least a reasonable possibility. The PRAC concluded that the product information of products containing fenofibrate/pravastatin should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for fenofibrate / pravastatin the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing fenofibrate / pravastatin is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.