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:
Each hard capsule contains 19 mg of lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Pravafenix is a 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 for the treatment of high coronary heart disease (CHD) -risk adult patients with mixed dyslipidaemia characterised by high triglycerides and low HDL-cholesterol levels whose 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**
No modification of posology should be necessary in patients with mild 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.)
**Hepatic impairment**  
No posology adjustment is required in patients with mild 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.).

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

**Method of administration**  
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.
- 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 upper limit of normal (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.).

**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 x 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).
**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 x 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 x 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.

**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 3xULN 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% 48/4900 patients) versus fenofibrate 1.4% (67/4895); 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.

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

4.5 Interactions 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.

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\text{max} (121%) of pravastatin was observed. In a similar study with clarithromycin a statistically significant increase in AUC (110%) and C\text{max} (127%) was observed. Although these changes were minor, caution should be exercised when associating pravastatin with erythromycin or clarithromycin.

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.

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

Overall adverse reactions with Pravafenix
Clinical adverse reactions reported by the investigators are listed below.

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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse reaction</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity reactions</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Diabetes mellitus aggravated, Obesity</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Sleep disturbance including insomnia and nightmares</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness, headache, paraesthesia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Palpitations</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal distension, abdominal pain, abdominal pain upper, constipation, diarrhoea, dry mouth, dyspepsia, eructation, flatulence, nausea, abdominal discomfort, vomiting.</td>
<td>Common</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Transaminases increased.</td>
<td>Common</td>
</tr>
<tr>
<td>Hepatic pain, gammaglutamyl transferase increased.</td>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Pruritus, urticaria</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Musculoskeletal, connective tissue and bone disorders</td>
<td>Arthralgia, back pain, blood creatine phosphokinase increased, muscle spasms, musculoskeletal pain, myalgia, pain in extremity</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Blood creatinine increased, creatinine renal clearance decreased, creatinine renal clearance increased, Renal failure</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>
General disorders and administration site conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthenia, fatigue, influenza like illness</td>
<td>Blood cholesterol increased, blood triglycerides increased, low-density lipoprotein increased, weight increased.</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

**Investigation**

<table>
<thead>
<tr>
<th>Description</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood cholesterol increased, blood triglycerides increased, low-density lipoprotein increased, weight increased.</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

**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 \(\geq 3\) X ULN, \(\leq 5\) X ULN) was 1.92% for patients treated with Pravafenix. Clinically important elevations in creatine phosphokinase (CK \(\geq 5\) X ULN, \(\leq 10\) X ULN without muscular symptoms) were seen in 0.38% of the patients treated with Pravafenix. Clinically important elevation (CK \(\geq 10\) X 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 \(\geq 3\) X ULN, \(\leq 5\) X ULN) was 0.83% for patients treated with Pravafenix. Clinically important elevations in serum transaminases (ALT and/or AST \(\geq 5\) X 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.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse reaction (fenofibrate)</th>
<th>Adverse reaction (Pravastatin)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Haemoglobin decreased, White blood cell count decreased</td>
<td></td>
<td>Rare</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Fatigue and vertigo</td>
<td></td>
<td>Rare</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Vision disturbance (including blurred vision and diplopia)</td>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Thromboembolism (pulmonary embolism, deep vein thrombosis)*</td>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Interstitial pneumopathies</td>
<td></td>
<td>Not known</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Cholelithiasis</td>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Jaundice, fulminant hepatic necrosis</td>
<td></td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Jaundice, complications of cholelithiasis (e.g cholecystitis, cholangitis, biliary colic, etc).</td>
<td></td>
<td>Not known</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>scalp/hair abnormality (including alopecia)</td>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Alopecia, photosensitivity</td>
<td></td>
<td>Rare</td>
</tr>
<tr>
<td>Reactions</td>
<td>Musculoskeletal, connective tissue and bone disorders</td>
<td>Muscle disorder (e.g. myositis, muscular weakness)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>------------------------------------------------------</td>
<td>---------------------------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rhabdomyolysis</td>
<td>Not known</td>
</tr>
<tr>
<td>Renal and urinary disorders:</td>
<td>Abnormal urination (including dysuria, frequency, nocturia)</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Reproductive system and breast disorders:</td>
<td>Sexual dysfunction</td>
<td>Sexual dysfunction</td>
<td>Uncommon</td>
</tr>
<tr>
<td>General disorders:</td>
<td>Blood urea increased</td>
<td>Fatigue</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td>Rare</td>
</tr>
</tbody>
</table>

*In the FIELD-study (fenofibrate study), a randomised placebo-controlled trial performed in 9795 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 % [48/4900 patients] versus fenofibrate 1.4% [67/4895 patients]; p = 0.074).

The following adverse events have been reported with some statins:
- Memory loss
- Depression
- Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4).

### 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 (PPARα). 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 (PPARα). 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 PPARα also induces an increase in the synthesis of Apoproteins A-I, A-II and of HDL cholesterol.

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 PPARα 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 1637 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

<table>
<thead>
<tr>
<th></th>
<th>Pravafenix 40 mg/160 mg</th>
<th>PRAVASTATIN 40 mg</th>
<th>Pravafenix versus PRAVASTATIN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 120</td>
<td>N = 119</td>
<td>p-value</td>
</tr>
<tr>
<td>Non-HDL-C (mg/dl)</td>
<td>-14.1 ± 1.78</td>
<td>-6.1 ± 1.79</td>
<td>0.0018</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>-11.7 ± 1.75</td>
<td>-5.9 ± 1.76</td>
<td>0.019</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>+6.5 ± 1.12</td>
<td>+2.3 ± 1.13</td>
<td>0.0089</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>-22.6 ± 4.37</td>
<td>-2.0 ± 4.39</td>
<td>0.0010</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>-9.9 ± 1.37</td>
<td>-4.4 ± 1.38</td>
<td>0.006</td>
</tr>
<tr>
<td>Apo A1 (g/L)</td>
<td>+5.5 ± 0.99</td>
<td>+2.8 ± 0.97</td>
<td>0.058</td>
</tr>
<tr>
<td>Apo B (g/L)</td>
<td>-12.6 ± 1.57</td>
<td>-3.8 ± 1.53</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Apo B/Apo A1</td>
<td>-16.3 ± 1.66</td>
<td>-6.0 ± 1.61</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>-8.8 ± 1.80</td>
<td>+1.4 ± 1.75</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hs-CRP (mg/L)</td>
<td>-1.1 ± 0.61</td>
<td>+0.6 ± 0.70</td>
<td>0.003</td>
</tr>
</tbody>
</table>

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 20% lower for the fenofibrate component of the combination. This is due to the fat content of the meal.
Therefore the FDC (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 FDC. 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 AUCt, AUC∞ and Cmax 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∞, AUCt, and Cmax 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 (Cmax) 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  

Cap  
Gelatine  
Indigo carmine (E132)  
Black iron oxide (E172)  
Titanium dioxide (E171)  
Yellow iron oxide (E172)  

6.2 Incompatibilities  
Not applicable  

6.3 Shelf life  
2 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 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)  

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
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.  MANUFACTURING AUTHORIZATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B.  CONDITIONS OF THE MARKETING AUTHORIZATION
A. MANUFACTURING AUTHORISATION HOLDER 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 OF THE MARKETING AUTHORISATION

- CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

Medicinal product subject to medical prescription.

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

Not applicable.

- OTHER CONDITIONS

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 0.6 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the Marketing Authorisation application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA
A. LABELLING
## PARTICULARS TO APPEAR ON THE OUTER PACKAGING

### CARTON FOR BLISTERS

<table>
<thead>
<tr>
<th><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravafenix 40 mg/160 mg hard capsules</td>
</tr>
<tr>
<td>Pravastatin/Fenofibrate</td>
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<table>
<thead>
<tr>
<th><strong>2. STATEMENT OF ACTIVE SUBSTANCE(S)</strong></th>
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<tbody>
<tr>
<td>Each capsule contains 40 mg of pravastatin sodium and 160 mg of fenofibrate</td>
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<table>
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<tr>
<th><strong>3. LIST OF EXCIPIENTS</strong></th>
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<tbody>
<tr>
<td>Contains lactose monohydrate. See leaflet for further information</td>
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<table>
<thead>
<tr>
<th><strong>4. PHARMACEUTICAL FORM AND CONTENTS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>30 hard capsules</td>
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<tr>
<td>60 hard capsules</td>
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<tr>
<td>90 hard capsules</td>
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<tr>
<th><strong>5. METHOD AND ROUTE(S) OF ADMINISTRATION</strong></th>
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<tbody>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
<tr>
<td>Oral use.</td>
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</table>

<table>
<thead>
<tr>
<th><strong>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</strong></th>
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<tbody>
<tr>
<td>Keep out of the reach and sight of children.</td>
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<tr>
<th><strong>7. OTHER SPECIAL WARNING(S), IF NECESSARY</strong></th>
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<th><strong>8. EXPIRY DATE</strong></th>
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<tr>
<th><strong>9. SPECIAL STORAGE CONDITIONS</strong></th>
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</table>
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/0/00/000/000 30 hard capsules
EU/0/00/000/000 60 hard capsules
EU/0/00/000/000 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
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

#### BLISTERS

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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</thead>
<tbody>
<tr>
<td>Pravafenix 40 mg/160 mg hard capsules</td>
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<tr>
<td>Pravastatin/Fenofibrate</td>
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</table>

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<th>4. BATCH NUMBER</th>
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<table>
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<tr>
<th>5. OTHER</th>
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</thead>
</table>
PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING CARTON FOR BOTTLES

1. NAME OF THE MEDICINAL PRODUCT

Pravafenix 40 mg/160 mg hard capsules
Pravastatin/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. 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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight 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/0/00/000/000 30 hard capsules
EU/0/00/000/000 60 hard capsules
EU/0/00/000/000 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
### PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

**BOTTLE FOR 30 HARD CAPSULES**

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<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
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<tr>
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<th>3. LIST OF EXCIPIENTS</th>
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<tr>
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<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
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<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
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<th>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</th>
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<th>INFORMATION IN BRAILLE</th>
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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/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. 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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight 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/0/00/000/000 60 hard capsules
EU/0/00/000/000 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
B. PACKAGE LEAFLET
1. WHAT PRAVAFENIX IS AND WHAT IT IS USED FOR

The name of your medicine is Pravafenix. It contains two active substances: pravastatin and fenofibrate. Both are cholesterol/lipid modifying medicines.

Pravafenix is used in addition to a 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 a patient 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. BEFORE YOU TAKE PRAVAFENIX
Do not take Pravafenix if
- You are allergic (hypersensitive) to fenofibrate, pravastatin, or any of the other ingredients of Pravafenix (see section 6: Further information).
- You suffer from liver disease.
- You are under 18 years old.
- You suffer from kidney disease.
- 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).
- You suffer from gallbladder disease.
- You suffer from pancreatitis (inflammation of the pancreas leading to abdominal pain).
- You are pregnant or breast-feeding.
- You have a history of muscle problems 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.

Children
Do not take Pravafenix if you are under 18 years old.

Take special care with 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 (see below section Taking Pravafenix with food and drink) or have ever had liver disease.
- 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.

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.

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 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.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. 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 or clarithromycin to treat infections caused by bacteria.

**Taking Pravafenix with food and drink**
- 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**
Ask your doctor or pharmacist for advice before taking any medicine.

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 should 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.

**Important information about some of the ingredients of Pravafenix**
Pravafenix contains a sugar called lactose. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicine.

### 3. HOW TO TAKE PRAVAFENIX

Always take Pravafenix exactly as your doctor has told you. You should 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 for adults 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, Pravafenix can cause side effects, although not everybody gets them. If the side-effects don’t go away after a few days, or you feel unwell in any other way, talk to your doctor before you take your next dose.

Tell your doctor straight away if you have any unexplained muscular pain or cramps, tenderness, or weakness. This is because on very rare occasions, 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.

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

Common side effects (affects 1 to 10 users in 100)
- 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 (affects 1 to 10 users in 1000)
- Abnormal heartbeat (palpitations), formation of blood clots in veins (deep vein thrombosis) and blockage of the lung arteries by blood clots (pulmonary embolism)
- Rashes, 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 (affects 1 to 10 users in 10 000)
- Decrease in haemoglobin (oxygen-carrying pigment in blood) and leukocytes (white blood cells).

Very rare side effects (affects less than 1 user in 10 000)
- 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.
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.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE PRAVAFENIX

Keep out of the reach and sight of children.

Do not use Pravafenix after the expiry date which is stated on the carton and the blister/bottle after EXP.

This medicine does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Pravafenix contains

- The active substances are fenofibrate and pravastatin. 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 macrogolglycerides, 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 30, 60 or 90 capsules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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Belgium

Manufacturer

SMB Technology s.a.
Rue du Parc Industriel 39
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This leaflet was last approved in
Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu/.