**PACKAGE INSERT**

## 1. NAME OF THE MEDICINAL PRODUCT

Pravafen 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.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Hard capsule.

Pravafen 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

Pravafen is indicated as an adjunct to diet to reduce triglyceride (TG) and increase HDL-C in high coronary heart disease (CHD) -risk adult patients with mixed dyslipidemia whose LDL-C levels are adequately controlled while on a treatment with pravastatin 40 mg monotherapy.

No incremental benefit of Pravafen on cardiovascular morbidity and mortality has been established over and above that demonstrated for statin monotherapy.

### 4.2 Posology and method of administration

Prior to initiating Pravafen, 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. 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 Pravafen should be decided after renal function has been evaluated (see section 4.4 Renal and urinary disorders). Limited safety data on Pravafen 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.
Pravafen 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. Pravafen 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 Pravafen 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, Pravafen 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 Pravafen 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 Pravafen (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 Pravafen 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 pravastatin 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 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, Pravafen 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 Pravafen 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 Pravafen 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
Pravafen 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, Pravafen 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. Pravafen 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.

Mortality and Coronary Heart Disease Morbidity
The effect of Pravafen on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established. The Action to Control Cardiovascular Risk in Diabetes Lipid (ACCORD Lipid) trial was a randomized placebo-controlled study of 5518 patients with type 2 diabetes mellitus on background statin therapy treated with fenofibrate. The mean duration of follow-up was 4.7 years. Fenofibrate plus statin combination therapy showed a non-significant 8% relative risk reduction in the primary outcome of major adverse cardiovascular events (MACE), a composite of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular disease death (hazard ratio [HR] 0.92, 95% CI 0.79-1.08) (p=0.32) as compared to statin monotherapy. In a gender subgroup analysis, the hazard ratio for MACE in men receiving combination therapy versus statin monotherapy was 0.82 (95% CI 0.69-0.99), and the hazard ratio for MACE in women receiving combination therapy versus statin monotherapy was 1.38 (95% CI 0.98-1.94) (interaction p=0.01). The clinical significance of this subgroup finding is unclear.

Cognitive side effects
There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Diabetes Mellitus
Some evidence suggests that statins as a class raise blood glucose as well as HbA1c 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>30kg/m 2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Concomitant use with glecaprevir/pibrentasvir
The use of Pravafen 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 thismedicine.

## 4.5 Interaction with other medicinal products and other forms of interaction

There have been no formal interaction studies for Pravafen. 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 $C_{max}$ (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 Pravafen 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 Pravafen is co-administered with a glitazone and to stop one of the two treatments if HDL-cholesterol is too low.

Food interaction
Pravafen 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 Pravafen 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 Pravafen is administered with food. (see sections 4.2 and 5.2).

## 4.6 Fertility, pregnancy and lactation

Pregnancy
*Pravafen*
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), Pravafen 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
*Pravafen*
No studies in lactating animals have been conducted with Pravafen. Therefore, taking into account the contra indication of pravastatin during lactation, Pravafen 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

Pravafen 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 Pravafen. Adverse reactions have usually been mild and transient.

Overall adverse reactions with Pravafen
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).

| 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 ≥ 3 X ULN, ≤ 5 X ULN) was 1.92% for patients treated with Pravafen. Clinically important elevations in creatine phosphokinase (CK ≥ 5 X ULN, ≤ 10 X ULN without muscular symptoms) were seen in 0.38% of the patients treated with Pravafen. Clinically important elevation (CK ≥ 10 X ULN without muscular symptoms) was seen in 0.06% of the patients treated with Pravafen. (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 X ULN, ≤ 5 X ULN) was 0.83% for patients treated with Pravafen. Clinically important elevations in serum transaminases (ALT and/or AST ≥ 5 X ULN) were seen in 0.38% of the patients treated with Pravafen. (see section 4.4).

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

Pravafen 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 Pravafen 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 |
| Eye disorders | | Vision disturbance (including blurred vision and diplopia) | Uncommon |

| | | | |
|---|---|---|---|
| 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 |
| | | 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 | | 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 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:
- Nightmares
- 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>30kg/$m^2$, raised triglycerides, history of hypertension).

**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

Pravafen 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 Pravafen.

*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.

*Pravafen*
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 Pravafen 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: Pravafen 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 Pravafen 40 mg/160 mg were compared to those receiving pravastatin 40 mg: Pravafen 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 Pravafen 40 mg/160 mg or Pravastatin 40 mg once daily**

| | Pravafen 40 mg/160 mg N[a] = 120 Mean (%)± SE[b] | PRAVASTATIN 40 mg N[a] = 119 Mean (%)± SE[b] | Pravafen 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 $A_1$ (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 $A_1$ | -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 Pravafen 40 mg/160 mg or Pravastatin 40 mg
[c] Pairwise p-value is significant if <0.05

The effects of Pravafen 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 Pravafen 40 mg/160 mg to Fenofibrate 160 mg monotherapy and Pravastatin 40 mg monotherapy in

patients with mixed dyslipidaemia. The incremental benefit of Pravafen 40 mg/160 mg on main lipid parameters versus Pravastatin 40 mg and Fenofibrate 160 mg monotherapy was also established.

## 5.2 Pharmacokinetic properties

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

Absorption

Pravafen 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 FDC (Pravafen) 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 Pravafen 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, $AUC_{\infty}$ 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 ($C_{max}$) 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 (E132)
Black iron oxide (E172)
Titanium dioxide (E171)
Yellow iron oxide (E172)

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Store below 30$^{o}$C.

### 6.5 Nature and contents of container

Opaque white HDPE bottles containing 30 hard capsules.

### 6.6 Special precautions for disposal

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

## 7. NAME AND ADDRESS OF MANUFACTURER

SMB Technology S.A.
Rue du Parc Industriel 39
B-6900 Marche en Famenne
Belgium

## 8. DATE OF REVISION OF THE TEXT

03/05/2021