Approved Professional Information for Medicines for Human Use:

PRAVAFEN

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PRAVAFEN 40 mg / 160 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 40 mg pravastatin sodium (equivalent to 38,03 mg pravastatin) and 160 mg fenofibrate.

Excipient(s) with known effect:

Contains sugar (lactose monohydrate: 19 mg per capsule). Contains sodium (33,3 mg per capsule).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PRAVAFEN is indicated as an adjunct to diet and other non-pharmacological treatment (e.g. exercise, weight reduction) for the treatment of mixed hyperlipidaemia in adult patients at high

cardiovascular risk to reduce triglycerides and increase HDL-C when LDL-C levels are adequately controlled while on a treatment with pravastatin 40 mg monotherapy.

4.2 Posology and method of administration

Prior to initiating 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. Rapid reduction of serum lipid levels usually follows PRAVAFEN 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 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

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

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

Hepatic impairment

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

Paediatric population (< 18 years old)

There is no relevant data on the use of PRAVAFEN in the paediatric population (< 18 years old) for the indication of mixed dyslipidaemia. Hence PRAVAFEN cannot be recommended for this group (see section 4.3).

Method of administration

Oral use.

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

4.3 Contraindications

- Hypersensitivity to fenofibrate or pravastatin, or to any of the excipients listed in section 6.1.
- Severe hepatic impairment including biliary cirrhosis or active liver disease including unexplained persistent elevations in liver function tests (including serum transaminase elevation) exceeding 3 fold the upper limit of normal (ULN) (see section 4.4).
- Children and adolescents (age below 18 years).
- Moderate to severe renal impairment (defined as an estimated creatinine clearance < 60 mL/min).
- Known photo allergy or photo toxic reaction during treatment with fibrates or ketoprofen.
- Gallbladder disease (see section 4.4).
- Chronic or acute pancreatitis with the exception of acute pancreatitis due to severe hypertriglyceridaemia (see section 4.4).
- Pregnancy and breastfeeding (see section 4.6).

- Personal history of myopathy and/or rhabdomyolysis with statins and/or fibrates or confirmed creatine phosphokinase (CK) elevation above 5 times the ULN under previous statin treatment (see section 4.4).
- PRAVAFEN should not be administered with fusidic acid (see section 4.4)

4.4 Special warnings and precautions for use

The pharmacokinetic properties of PRAVAFEN are not identical to the co-administration of the existing monotherapies when taken with fat-meal or in fasting state.

Musculoskeletal and connective tissue disorders

Pravastatin and fenofibrate have been associated with the onset of myalgia, myopathy and rhabdomyolysis with or without secondary renal insufficiency.

Rhabdomyolysis is an acute potentially fatal condition of skeletal muscle, which may develop at any time during treatment and is characterised by massive muscle destruction associated with major increase in CK (usually > 30 or 40 times the ULN) leading to myoglobinuria.

The risk of muscle toxicity is increased when a fibrate and a 3-hydroxy-3-methyl-glutaryl-Coenzyme A (HMG-CoA) reductase inhibitor, such as pravastatin, 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, 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).

Pravastatin, as in PRAVAFEN, must not be co-administered with fusidic acid (see section 4.3). There have been reports of rhabdomyolysis (including fatalities) in patients receiving this combination (see section 4.5). In patients where the use of fusidic acid is considered essential, PRAVAFEN should be discontinued throughout the duration of fusidic acid treatment. The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness.

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

Before treatment initiation

CK levels should be measured prior to initiation of therapy. The baseline CK levels may also be useful as a reference in the event of a later increase during the combination therapy. When measured, CK levels should be interpreted in the context of other potential factors that can cause transient muscle damage, such as strenuous exercise or muscle trauma and repeated if necessary. If CK levels are significantly elevated > 5 times the ULN at baseline, the test should be repeated after 5 – 7 days. If confirmed, the treatment should definitively not be initiated (see section 4.3).

During treatment

Routine monitoring of CK is recommended every 3 months during the first 12 months of treatment with PRAVAFEN and then at time intervals as determined by the treating medical practitioner but not less than annually.

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

If a markedly elevated (> 5 times the ULN) CK level is detected and confirmed, 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.

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

Hepatobiliary disorders

Increases in transaminase levels have been reported in patients treated with PRAVAFEN. 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 then at time intervals as determined by the treating medical practitioner beyond this period.

Special attention should be paid to patients who develop an increase in transaminase levels and PRAVAFEN should be discontinued if increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) exceed 3 times the ULN and persist for longer than 30 days.

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

Renal and urinary disorders

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

It is recommended to assess the estimated creatinine clearance at the initiation of the treatment and every 3 months during the first 12 months of the combination therapy and then at time intervals as determined by the treating medical practitioner but not less than annually.

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

Interstitial lung disease

Cases of interstitial lung disease have been reported with pravastatin as in PRAVAFEN, 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.

Pancreatitis

Pancreatitis has been reported in patients taking fenofibrate or pravastatin as in PRAVAFEN (see section 4.3). In the FIELD study (fenofibrate study), a randomised placebo-controlled trial performed in 9 795 patients with type 2 diabetes mellitus, a statistically significant increase in pancreatitis cases was observed in patients receiving fenofibrate versus patients receiving placebo (0,8 % versus 0,5 %; p = 0,031).

This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridaemia, a direct effect of the medicine, or a secondary phenomenon mediated through biliary tract stone or sludge formation, resulting in the obstruction of the common bile duct.

Venothromboembolic events

In the FIELD study (fenofibrate study), a statistically significant increase was reported in the incidence of pulmonary embolism (0,7 % in the placebo group versus 1,1 % in the fenofibrate group; p = 0,022) and a statistically non-significant increase in deep vein thromboses (placebo: 1,0 % [48/4 900 patients] versus fenofibrate 1,4 % [67/4 895 patients]; p = 0,074). Caution should be exercised in patients with history of pulmonary embolism.

Diabetes Mellitus

Statins such as pravastatin contained in PRAVAFEN may raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate.

Patients at risk (fasting glucose 5,6 to 6,9 mmol/L, BMI > 30 kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Excipient: Lactose

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

Excipient: Sodium

PRAVAFEN contains 33,3 mg sodium per capsule (excipients and active substance), equivalent to 1,7 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

The following statements reflect the information available on the individual active substances (fenofibrate and pravastatin).

Interactions relevant to pravastatin

Cholestyramine/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 cholestyramine 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.

Medicines metabolised by cytochrome P450

Pravastatin is not metabolised to a clinically significant extent by the cytochrome P450 system. The absence of a significant pharmacokinetic interaction with pravastatin has been specifically demonstrated for several medicines e.g. diltiazem, verapamil, itraconazole, ketoconazole, protease inhibitors, grapefruit juice and CYP2C9 inhibitors (e.g. fluconazole).

In a study 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. Caution should be exercised when co-administering pravastatin with erythromycin or clarithromycin or other macrolide antibiotics.

Fusidic acid

Interaction between pravastatin and fusidic acid can lead to an increased risk of rhabdomyolysis. The risk of myopathy including rhabdomyolysis is increased by the concomitant administration of systemic fusidic acid with statins, such as pravastatin. Co-administration of this combination may cause increased plasma concentrations of both medicines. 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 fusidic acid is necessary, pravastatin treatment should be discontinued throughout the duration of the fusidic acid treatment. Also see section 4.3 and 4.4.

Other medicines

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

Interactions relevant to fenofibrate

Bile acid resin

Cholestyramine or colestipol reduce the absorption of medicines and when cholestyramine or colestipol 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

Severe but reversible renal function impairment has 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 is contraindicated during pregnancy (see section 4.3).

Women of child-bearing potential must use highly effective contraception while taking PRAVAFEN. 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 medical practitioner has to be informed immediately and PRAVAFEN (pravastatin) should be discontinued because of the potential risk to the foetus (see section 4.3).

Breastfeeding

PRAVAFEN is contraindicated during breastfeeding (see section 4.3). Mothers on PRAVAFEN should not breastfeed their infants.

Pravastatin sodium

Pravastatin is excreted in human breast milk; therefore pravastatin is contraindicated for use in mothers who are breastfeeding their infants (see section 4.3).

Fenofibrate

Fenofibrate is excreted in milk and therefore, fenofibrate is contraindicated for use in mothers who are breastfeeding their infants (see section 4.3)

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

4.7 Effects on ability to drive and use machines

Dizziness and visual disturbances may occur during treatment which may impair the patient's ability to drive and operate machinery. Patients should be advised not to drive or operate machinery until they are aware of how PRAVAFEN affects them.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse drug reactions (ADRs) during PRAVAFEN therapy are increased transaminases and gastrointestinal disorders.

Tabulated list of adverse reactions

In clinical trials, over 1 566 patients received PRAVAFEN.

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	Aggravated diabetes mellitus, 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, upper abdominal pain, constipation, diarrhoea, dry mouth, dyspepsia, eructation, flatulence, nausea, abdominal discomfort, vomiting	Common
Hepato-biliary disorders	Increased transaminases	Common
	Hepatic pain, increased gammaglutamyl transferase	Uncommon
Skin and subcutaneous tissue disorders	Pruritus, urticaria	Uncommon
Musculoskeletal, connective tissue and bone disorders	Arthralgia, back pain, increased blood creatine phosphokinase, muscle spasms, musculoskeletal pain, myalgia, pain in extremity	Uncommon
Renal and urinary disorders	Increased blood creatinine, decreased creatinine renal clearance, increased creatinine renal clearance, renal failure	Uncommon
General disorders and administration site conditions	Asthenia, fatigue, influenza like illness	Uncommon
Investigations	Increased blood cholesterol, increased blood triglycerides, increased low-density lipoprotein, increased weight	Uncommon

Description of selected adverse reactions

Skeletal muscle: Marked and persistent increases of creatine phosphokinase (CK) have been reported. In clinical studies, the incidence of important elevations in creatine phosphokinase (CK ≥ 3 times the ULN, ≤ 5 times the ULN) was 1,92 % for patients treated with PRAVAFEN. Clinically important elevations in creatine phosphokinase (CK ≥ 5 times the ULN, ≤ 10 times the ULN without muscular symptoms) were seen in 0,38 % of the patients treated with PRAVAFEN. Clinically important elevation (CK ≥ 10 times the 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. In clinical studies, the incidence of important elevations in serum transaminases (ALT and/or AST ≥ 3 times the ULN, < 5 times the ULN) was 0,83 % for patients treated with PRAVAFEN. Clinically

important elevations in serum transaminases (ALT and/or AST ≥ 5 times the 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

Additional adverse reactions associated with the use of medicines containing pravastatin or fenofibrate are listed below.

System Organ Class	Adverse reaction (Fenofibrate)	Adverse reaction (Pravastatin)	Frequency
Blood and lymphatic system disorders	Decreased haemoglobin, decreased white blood cell count		Less frequent
Nervous system disorders	Fatigue and vertigo		Less frequent
		Peripheral polyneuropathy	Less frequent
Eye disorders		Vision disturbance (including blurred vision and diplopia)	Less frequent
Vascular disorders	Thromboembolism (pulmonary embolism, deep vein thrombosis)		Less frequent
Respiratory, thoracic and mediastinal disorders	Interstitial pneumopathies		Not known
Hepatobiliary disorders	Cholelithiasis		Less frequent
		Jaundice, fulminant hepatic necrosis	Less frequent
	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)	Less frequent
	Alopecia, photosensitivity reactions		Less frequent
Musculoskeletal, connective	Muscle disorder (e.g. myositis,		Less frequent

tissue and bone disorders	muscular weakness)		
		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	Less frequent
	Rhabdomyolysis	Immune-mediated necrotising myopathy (see section 4.4)	Not known
Renal and urinary disorders:		Abnormal urination (including dysuria, frequency, nocturia)	Less frequent
Reproductive system and breast disorders	Sexual dysfunction	Sexual dysfunction	Less frequent
General disorders:		Fatigue	Less frequent
Investigations	Increased blood urea		Less frequent

The following adverse events have been reported with some statins:

- Nightmares
- Memory loss
- Depression
- Cases of interstitial lung disease, especially with long term therapy (see section 4.4).
- Diabetes Mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5,6 mmol/L, BMI > 30 kg/m^2, raised triglycerides, history of hypertension).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicines. Healthcare professionals are

asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification/ Category and Class: A 7.5 Serum-cholesterol reducers

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. 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.

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.

Fenofibrate has a uricosuric effect, increasing urinary secretion of uric acid by two-fold.

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 VLD-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.

5.2 Pharmacokinetic properties

No clinically significant pharmacokinetic interaction was seen when fenofibrate was co-administered with pravastatin.

Absorption

In a multiple dose study, PRAVAFEN was shown not to be bioequivalent to co-administered fenofibrate and pravastatin because its bioavailability after multiple dosing was 20 % lower for the fenofibrate component of the combination. This is due to the fat content of the meal.
Therefore, the fixed dose combination (PRAVAFEN) cannot be considered interchangeable with the free co-administration of fenofibrate and pravastatin mono-component medicines.

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 an effect on the rate and extent of absorption in the fixed dose combination. The bioavailability of fenofibric acid is lower in fasting conditions after a single dose administration of the Fenofibrate-Pravastatin 160/40 mg combination. The decrease in AUCt, AUC_{∞} and C_{max} of fenofibric acid (point estimate) is of 30,94 %, 10,9 % and 68,71 % respectively.

The bioavailability of pravastatin is higher after a single dose administration of the test product Fenofibrate/Pravastatin 160/40 mg in fasting conditions than after a single dose of the product in fed conditions. The increase in AUC_{∞}, AUC_t, and C_{max} is of 111,88 %, 114,06 %, and 115,28 % respectively. PRAVAFEN 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

After oral administration, pravastatin is absorbed with peak serum levels at 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. 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 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 fenofibrate does not accumulate. Fenofibric acid is not eliminated by haemodialysis.

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

Polyamide-Aluminium-PVC/aluminium blister

3 years.

HDPE bottle

3 years.

6.4 Special precautions for storage

Store at or below 25 °C. Keep in the original packaging until required for use.

6.5 Nature and contents of container

PRAVAFEN capsules are packed in:

- An opaque white HDPE (High density polyethylene) container, with a white push-fit LDPP (Low density polypropylene) cap. Each container contains a silica gel dehydrating capsule. Each container contains 14, 30, 60, 90 or 100 capsules and is further packed into a printed carton.
- Polyamide-Aluminium-PVC/aluminium blister strips of 10 capsules which are further packed into printed cartons in pack sizes of 30, 60 and 90 capsules.

Not all pack sizes and/or pack types are neccesarily marketed.

6.6 Special precautions for disposal and other handling

Any unused medicine should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals Pty (Ltd)

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South Africa

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8. REGISTRATION NUMBER

PRAVAFEN 40 / 160 mg: 52/7.5/0769

9. DATE OF FIRST AUTHORISATION

PRAVAFEN 40 / 160 mg: 05 May 2020

10. DATE OF REVISION OF THE TEXT

12 January 2023