1. NAME OF THE MEDICINAL PRODUCT

Cholib® 145 mg/20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 145 mg of fenofibrate and 20 mg of simvastatin.

Excipient(s) with known effect:
One film-coated tablet contains 160.1 mg of lactose (as monohydrate), 145 mg of sucrose, 0.7 mg of lecithin (derived from soya bean (E322)) and 0.17 mg of sunset yellow FCF (E110).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Oval, biconvex, tan coloured, 19.3 x 9.3 mm film-coated tablet with bevelled edges and the inscription 145/20 on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cholib® is indicated as adjunctive therapy to diet and exercise in high cardiovascular risk adult patients with mixed dyslipidaemia to reduce triglycerides and increase HDL-C levels when LDL-C levels are adequately controlled with the corresponding dose of simvastatin monotherapy.

A beneficial effect of Cholib® on cardiovascular morbidity and mortality has not yet been demonstrated.

4.2 Posology and Method of Administration

Secondary causes of hyperlipidaemia, such as uncontrolled type 2 diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemia, obstructive liver disease, pharmacological treatment (like oral oestrogens), alcoholism should be adequately treated, before Cholib® therapy is considered 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 tablet per day. Grapefruit juice should be avoided (see section 4.5).

Response to therapy should be monitored by determination of serum lipid values (total cholesterol (TC), LDL-C, triglycerides (TG)).

Elderly patients (≥ 65 years old)
No dose adjustment is necessary. The usual dose is recommended, except for decreased renal function with estimated glomerular filtration rate < 60 mL/min/1.73 m^2 where Cholib® is contraindicated (see section 4.3).

Patients with renal impairment
Cholib® is contraindicated in patients with moderate to severe renal insufficiency whose estimated glomerular filtration rate is < 60 mL/min/1.73 m^2 (see section 4.3).

Cholib® should be used with caution in patients with mild renal insufficiency whose estimated glomerular filtration rate is 60 to 89 mL/min/1.73 m^2 (see section 4.4).

Patients with hepatic impairment

Cholib® has not been studied in patients with hepatic impairment and is therefore contraindicated in this population (see section 4.3).

Paediatric population

Cholib® is contraindicated in children and adolescents up to 18 years old. (see section 4.3).

Method of administration

Each tablet should be swallowed whole with a glass of water. The tablets should not be crushed or chewed. They may be taken with or without food (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substances, peanut, soya or to any of the excipients listed in section 6.1 (see also section 4.4)
- Known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen
- Active liver disease or unexplained persistent elevations of serum transaminases
- Known gallbladder disease
- Chronic or acute pancreatitis with the exception of acute pancreatitis due to severe hypertriglyceridaemia
- Moderate to severe renal insufficiency (estimated glomerular filtration rate < 60 mL/min/1.73 m2)
- Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone) (see section 4.5)
- Concomitant administration of gemfibrozil, ciclosporine, or danazol (see section 4.5)
- Concomitant administration of glecaprevir/ pibrentasvir (see section 4.5)
- Paediatric population (age below 18 years)
- Pregnancy and breast-feeding (see section 4.6)
- Personal history of myopathy and/or rhabdomyolysis with statins and/or fibrates or confirmed creatine phosphokinase 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

Muscle

Skeletal muscle toxicity, including rare cases of rhabdomyolysis with or without renal failure, has been reported with administration of lipid-lowering substances like fibrates and statins. The risk of myopathy with statins and fibrates is known to be related to the dose of each component and to the nature of the fibrate.

Cases of de novo or aggravated pre-existing myasthenia gravis or ocular myasthenia have been observed with statins (see section 4.8). Cholib® should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

Reduced function of transport proteins

Reduced function of hepatic OATP transport proteins can increase the systemic exposure of simvastatin and increase the risk of myopathy and rhabdomyolysis. Reduced function can occur as the result of inhibition by interacting medicines (eg ciclosporin) or in patients who are carriers of the SLCO1B1 c.521T>C genotype.

Patients carrying the SLCO1B1 gene allele (c.521T>C) coding for a less active OATP1B1 protein have an increased systemic exposure of simvastatin and increased risk of myopathy. The risk of high dose (80 mg) simvastatin related myopathy is about 1 % in general, without genetic testing. Based on the results of the SEARCH trial, homozygote C allele carriers (also called CC) treated with 80 mg have a 15% risk of

myopathy within one year, while the risk in heterozygote C allele carriers (CT) is 1.5%. The corresponding risk is 0.3% in patients having the most common genotype (TT) (See section 5.2).

Immune-mediated necrotizing myopathy (IMNM)

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

Measures to reduce the risk of myopathy caused by medicinal product interactions

The risk of muscle toxicity may be increased if Cholib® is administered with another fibrate, statin, niacin, fusidic acid or other specific concomitant substances (for specific interactions see section 4.5). Physicians contemplating combined therapy with Cholib® and lipid-modifying doses (≥ 1 g/day) of niacin (nicotinic acid) or medicinal products containing niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and when the dose of either medicinal product is increased.

The risk of myopathy and rhabdomyolysis is significantly increased by concomitant use of simvastatin with potent inhibitors of CYP 3A4 (see section 4.5).

Simvastatin is a substrate of the Breast Cancer Resistant Protein (BCRP) efflux transporter. Concomitant administration of products that are inhibitors of BCRP (e.g., elbasvir and grazoprevir) may lead to increased plasma concentrations of simvastatin and an increased risk of myopathy; therefore, a dose adjustment of simvastatin should be considered depending on the prescribed dose. Co-administration of elbasvir and grazoprevir with simvastatin has not been studied; however, the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with products containing elbasvir or grazoprevir (see section 4.5).

Cholib® must not be co-administered with fusidic acid. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving a statin in combination with fusidic acid (see section 4.5). In patients where the use of systemic fusidic acid is considered essential, statin treatment 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.

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 Cholib® and fusidic acid should only be considered on a case by case basis and under close medical supervision.

Creatine kinase measurement

Creatine Kinase should not be measured following strenuous exercise or in the presence of any plausible alternative cause of Creatine Kinase increase as this makes value interpretation difficult. If Creatine Kinase levels are significantly elevated at baseline (> 5 x ULN), levels should be re-measured within 5 to 7 days later to confirm the results.

Before the treatment

All patients starting therapy should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness.

Caution should be exercised in patients with pre-disposing factors for rhabdomyolysis. In order to establish a reference baseline value, a Creatine Kinase level should be measured before starting a treatment in the following situations:

- Elderly ≥ 65 years
- Female gender
- Renal impairment
- Uncontrolled hypothyroidism
- Hypoalbuminaemia
- Personal or familial history of hereditary muscular disorders

- Previous history of muscular toxicity with a statin or a fibrate
- Alcohol abuse

In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended.

In order to establish a reference baseline value, creatine phosphokinase levels should be measured and clinical monitoring is recommended.

If a patient has previously experienced a muscle disorder on a fibrate or a statin, treatment with a different member of the class should only be initiated with caution. If Creatine Kinase levels are significantly elevated at baseline (> 5 x ULN), treatment should not be started.

If myopathy is suspected for any other reason, treatment should be discontinued.

Therapy with Cholib® should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

Daptomycin:
Both daptomycin and HMG-CoA reductase inhibitors are independently associated with skeletal muscle effects. Reports of myopathy and/or rhabdomyolysis have been observed with simvastatin coadministered with daptomycin. Therefore, a temporary suspension of Cholib® should be considered in patients taking daptomycin particularly those with pre-disposing factors for myopathy or rhabdomyolysis.

Hepatic disorders
Increases in transaminase levels have been reported in some patients treated with simvastatin or fenofibrate. In the majority of cases these elevations were transient, minor and asymptomatic without the need for treatment discontinuation.

Transaminase levels have to be monitored before treatment begins, every 3 months during the first 12 months of treatment and thereafter periodically. Attention should be paid to patients who develop increase in transaminase levels and therapy should be discontinued if aspartate aminotransferase (AST) or also known as serum glutamic oxaloacetic transaminase (SGOT) and alanine aminotransferase (ALT) or also known as serum glutamic pyruvic transaminase (SGPT) levels increase to more than 3 times the upper limit of the normal range.

When symptoms indicative of hepatitis occur (e.g. jaundice, pruritus) and diagnosis is confirmed by laboratory testing, Cholib® therapy should be discontinued.

Cholib® should be used with caution in patients who consume substantial quantities of alcohol.

Pancreatitis
Pancreatitis has been reported in patients taking fenofibrate (see sections 4.3 and 4.8). This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridaemia, an induced pancreatic enzymes increase or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.

Renal function
Cholib® is contraindicated in moderate to severe renal impairment (see section 4.3).

Cholib® should be used with caution in patients with mild renal insufficiency whose estimated glomerular filtration rate is 60 to 89 mL/min/1.73 m^2 (see section 4.2).

Reversible elevations in serum creatinine have been reported in patients receiving fenofibrate monotherapy or co-administered with statins. Elevations in serum creatinine were generally stable over time with no evidence for continued increases in serum creatinine with long term therapy and tended to return to baseline following discontinuation of treatment.

During clinical trials, 10% of patients had a creatinine increase from baseline greater than 30 µmol/L with co-administered fenofibrate and simvastatin versus 4.4% with statin monotherapy. 0.3% of patients receiving co-administration had clinically relevant increases in creatinine to values > 200 µmol/L. Treatment should be interrupted when creatinine level is 50% above the upper limit of normal. It is recommended that creatinine is measured during the first 3 months after initiation of treatment and periodically thereafter.

Interstitial lung disease

Cases of interstitial lung disease have been reported with some statins and with fenofibrate, 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, Cholib® therapy should be discontinued.

Cognitive Impairment

There have been rare post-marketing 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 non-serious, 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 and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI>30 kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Veno-thromboembolic 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.

Excipients

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

As this medicinal product contains sucrose, patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

This medicinal product contains sunset yellow FCF (E110) that may cause allergic reactions

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

No interaction studies have been performed with Cholib®.

Interactions relevant to monotherapies

Inhibitors of CYP 3A4

Simvastatin is a substrate of cytochrome P450 3A4.

Potent inhibitors of cytochrome P450 3A4 increase the risk of myopathy and rhabdomyolysis by increasing the concentration of HMG-CoA reductase inhibitory activity in plasma during simvastatin therapy. Such inhibitors include itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors (e.g. nelfinavir), cobicistat and nefazodone. Combination with itraconazole, ketoconazole, posaconazole, HIV protease inhibitors (e.g. nelfinavir), cobicistat, erythromycin, clarithromycin, telithromycin and nefazodone is contraindicated (see section 4.3). If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with Cholib® must be suspended during the course of treatment. Caution should be exercised when combining Cholib® with certain other less potent CYP 3A4 inhibitors: fluconazole, verapamil, or diltiazem (see sections 4.3 and 4.4).

Danazol

The risk of myopathy and rhabdomyolysis is increased by concomitant administration of danazol with simvastatin. The dose of simvastatin should not exceed 10 mg daily in patients taking danazol. Therefore, the co-administration of Cholib® with danazol is contraindicated (see section 4.3).

Ciclosporin

The risk of myopathy/rhabdomyolysis is increased by concomitant administration of ciclosporin with simvastatin. Although the mechanism is not fully understood, ciclosporin has been shown to increase the plasma exposure (AUC) to simvastatin acid, presumably due in part to inhibition of CYP 3A4 and OATP-1B1 transporter. Because the dose of simvastatin should not exceed 10 mg daily in patients taking ciclosporin, the co-administration of Cholib® with ciclosporin is contraindicated (see section 4.3).

Amiodarone, amlodipine, diltiazem and verapamil

The risk of myopathy and rhabdomyolysis is increased by concomitant use of amiodarone, amlodipine, diltiazem or verapamil with simvastatin 40 mg per day.

In a clinical trial, myopathy was reported in 6% of patients receiving simvastatin 80 mg and amiodarone, versus 0.4% in patients on simvastatin 80 mg only.

Concomitant administration of amlodipine and simvastatin caused a 1.6-fold increase in exposure of simvastatin acid.

Concomitant administration of diltiazem and simvastatin caused a 2.7-fold increase in exposure of simvastatin acid, presumable due to inhibition of CYP 3A4.

Concomitant administration of verapamil and simvastatin resulted in a 2.3-fold increase in plasma exposure to simvastatin acid, presumably due, in part, to inhibition of CYP 3A4.

Therefore, the dose of Cholib® should not exceed 145 mg/20 mg daily in patients taking amiodarone, amlodipine, diltiazem or verapamil.

Inhibitors of Breast Cancer Resistant Protein (BCRP)
Concomitant administration of medicinal products that are inhibitors of BCRP, including products containing elbasvir or grazoprevir, may lead to increased plasma concentrations of simvastatin and an increased risk of myopathy (see section 4.4).

Other statins and fibrates
Gemfibrozil increases the AUC of simvastatin acid by 1.9-fold, possibly due to inhibition of the glucuronidation pathway. The risk of myopathy and rhabdomyolysis is significantly increased by concomitant use of gemfibrozil with simvastatin. The risk of rhabdomyolysis is also increased in patients concomitantly receiving other fibrates or statins. Therefore, the co-administration of Cholib® with gemfibrozil, other fibrates, or statins is contraindicated (see section 4.3).

Daptomycin
It should be considered to temporarily suspend Cholib® in patients taking daptomycin particularly those with pre-disposing factors for myopathy or rhabdomyolysis. The risk of myopathy or rhabdomyolysis may be increased by concomitant administration of HMG-CoA reductase inhibitors and daptomycin.

Niacin (nicotinic acid)
Cases of myopathy/rhabdomyolysis have been associated with concomitant administration of statins and niacin (nicotinic acid) at lipid-modifying doses (≥ 1 g/day), knowing that niacin and statins can cause myopathy when given alone.

Physicians contemplating combined therapy with Cholib® and lipid-modifying doses (≥ 1 g/day) of niacin (nicotinic acid) or medicinal products containing niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy.

Fusidic acid
The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. Co-administration of this combination may cause increased plasma concentrations of both agents. The mechanism of this interaction (whether it is pharmacodynamics 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, Cholib® treatment should be discontinued throughout the duration of the fusidic acid treatment. (Also see section 4.4).

Grapefruit juice
Grapefruit juice inhibits CYP 3A4. Concomitant intake of large quantities (over 1 liter daily) of grapefruit juice and simvastatin resulted in a 7-fold increase in plasma exposure to simvastatin acid. Intake of 240 mL of grapefruit juice in the morning and simvastatin in the evening also resulted in a 1.9-fold increase in plasma exposure to simvastatin acid. Intake of grapefruit juice during treatment with Cholib® should therefore be avoided.

Colchicine

There have been reports of myopathy and rhabdomyolysis with the concomitant administration of colchicine and simvastatin in patients with renal insufficiency. Therefore, close clinical monitoring of such patients taking colchicine and Cholib® is advised.

Vitamin K antagonists
Fenofibrate and simvastatin enhance effects of Vitamin K antagonists and may increase the risk of bleeding. It is recommended that the dose of those oral 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. INR should be determined before starting Cholib® and frequently enough during early therapy to ensure that no significant alteration of INR occurs. Once a stable INR has been documented, it can be monitored at the intervals usually recommended for patients on those oral anticoagulants. If the dose of Cholib® is discontinued, the same procedure should be repeated. Cholib® therapy has not been associated with bleeding in patients not taking anticoagulants.

Glitazones
Some cases of reversible paradoxical reduction of HDL-C have been reported during concomitant administration of fenofibrate and glitazones. Therefore it is recommended to monitor HDL-C if Cholib® is co-administered with a glitazone and stopping either therapy if HDL-C is too low.

Rifampicin
Because rifampicin is a potent CYP 3A4 inducer that interferes with simvastatin metabolism, patients undertaking long-term rifampicin therapy (e.g. treatment of tuberculosis) may experience loss of efficacy of simvastatin. In normal volunteers, the plasma exposure to simvastatin acid was decreased by 93% with concomitant administration of rifampicin.

Effects on the pharmacokinetics of other medicinal products
Fenofibrate and simvastatin are not CYP 3A4 inhibitors or inducers. Therefore, Cholib® is not expected to affect plasma concentrations of substances metabolised via CYP 3A4.

Fenofibrate and simvastatin are not inhibitors of CYP 2D6, CYP 2E1, or CYP 1A2. Fenofibrate is a mild to moderate inhibitor of CYP 2C9 and a weak inhibitor of CYP 2C19 and CYP 2A6.

Patients receiving co-administration of Cholib® and drugs metabolised by CYP 2C19, CYP 2A6, or especially CYP 2C9 with a narrow therapeutic index should be carefully monitored and, if necessary, dose adjustment of these drugs is recommended.

Interaction between simvastatin and fenofibrate
Effects of repeated administration of fenofibrate on the pharmacokinetics of single or multiple doses of simvastatin have been investigated in two small studies (n=12) followed by a larger one (n= 85) in healthy subjects.

In one study the AUC of the simvastatin acid (SVA), a major active metabolite of simvastatin, was reduced by 42% (90% CI 24%-56%) when a single dose of 40 mg simvastatin was combined with repeated administration of fenofibrate 160 mg. In the other study [Bergman et al, 2004] repeated co-administration of both simvastatin 80 mg and fenofibrate 160 mg led to a reduction in the AUC of the SVA of 36% (90% CI 30%-42%). In the larger study a reduction of 21% (90% CI 14%-27%) in AUC of SVA was observed after repeated co-administration of simvastatin 40 mg and fenofibrate 145 mg in the evening. This was not significantly different from the 29% (90% CI 22%-35%) reduction in AUC of SVA observed when co-administration was 12 hours apart: simvastatin 40 mg in the evening and fenofibrate 145 mg in the morning.

Whether fenofibrate had an effect on other active metabolites of simvastatin was not investigated. The exact mechanism of interaction is not known. In the available clinical data, the effect on LDL- C reduction was not considered to be significantly different to simvastatin monotherapy when LDL- C is controlled at the time of initiating treatment. The repeated administration of simvastatin 40 or 80 mg, the highest dose registered, did not affect the plasma levels of fenofibric acid at steady state.

Prescribing recommendations for interacting substances are summarised in the table below (see also sections 4.2 and 4.3).

Interacting substances	**Prescribing recommendations**
Potent CYP 3A4 inhibitors: e.g Itraconazole Ketoconazole Fluconazole Posaconazole Voriconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors (e.g. nelfinavir) Nefazodone Cobicistat Boceprevir Telaprevir	Contraindicated with Cholib®
Danazol Ciclosporin	Contraindicated with Cholib®
Gemfibrozil, Other statins and fibrates	Contraindicated with Cholib®
Amiodarone Verapamil Diltiazem Amlodipine	Do not exceed one Cholib® 145 mg/20 mg per day
Elbasvir Grazoprevir	Do not exceed one Cholib® 145 mg/20 mg per day
Glecaprevir Pibrentasvir	Contraindicated with Cholib®
Niacin (nicotinic acid) ≥ 1 g/day	Avoid with Cholib® unless clinical benefit outweigh the risk Monitor patients for any signs and symptoms of muscle pain, tenderness or weakness
Fusidic acid	Avoid taking Cholib®
Grapefruit juice	Avoid when taking Cholib®+
Vitamin K antagonists	Adjust the dose of these oral anticoagulants according to the INR monitoring
Glitazones	Monitor HDL-C and stop either therapy (glitazone or Cholib®) if HDL-C is too low

4.6 Fertility, Pregnancy and Lactation

Pregnancy

Cholib®

As simvastatin is contraindicated during pregnancy (see hereafter), Cholib® is contraindicated during pregnancy (see section 4.3).

Fenofibrate

There are no adequate data from the use of fenofibrate in pregnant women. Animal studies have shown embryo-toxic effects at doses in the range of maternal toxicity (see section 5.3). The potential risk for humans is unknown. Therefore, fenofibrate should only be used during pregnancy after a careful benefit/risk assessment.

Simvastatin

Simvastatin is contraindicated during pregnancy. Safety in pregnant women has not been established. Maternal treatment with simvastatin may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis. For these reasons, simvastatin must not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with simvastatin must be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant.

Breast-feeding

It is unknown whether fenofibrate, simvastatin and/or their metabolites are excreted in human milk. Therefore, Cholib® is contraindicated during breast-feeding (see section 4.3).

Fertility

Reversible effects on fertility have been observed in animals (see section 5.3). There are no clinical data on fertility from the use of Cholib®.

4.7 Effects on Ability to Drive and Use Machines

Fenofibrate has no or negligible influence on the ability to drive and use machines.

Dizziness has been reported rarely in post-marketing experience with simvastatin. This adverse reaction should be taken into account when driving vehicles or using machines under Cholib® therapy.

4.8 Undesirable Effects

Summary of the safety profile

The most commonly reported adverse drug reactions (ADRs) during Cholib® therapy are increased blood creatinine, upper respiratory tract infection, increased platelet count, gastroenteritis and increased alanine- aminotransferase.

Tabulated list of adverse reactions

Treatment emergent adverse reactions reported in patients receiving co-administration of fenofibrate and simvastatin occurring are listed below by system organ class and frequency.

The adverse reactions of Cholib® are in line with what is known from its two active substances: fenofibrate and simvastatin.

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) and not known (cannot be estimated from the available data).

Adverse reactions observed with the co-administration of fenofibrate and simvastatin (Cholib®)

System Organ Class	Adverse reactions	Frequency
Infections and infestations	Upper respiratory tract infection, Gastroenteritis	Common
Blood and lymphatic disorders	Platelet count increased	Common
Hepatobiliary disorders	Alanine- aminotransferase increased	Common
Skin and subcutaneous tissue disorders	Dermatitis and eczema	Uncommon
Investigations	Blood creatinine increased (see sections 4.3 and 4.4)	Very Common

Description of selected adverse reactions

Blood creatinine increased: 10% of patient had a creatinine increase from baseline greater than 30 µmol/L with co-administered fenofibrate and simvastatin versus 4.4% with statin monotherapy. 0.3% of patients receiving co-administration had clinically relevant increases in creatinine to values >200 µmol/l.

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

Additional adverse reactions associated with the use of medicinal products containing simvastatin or fenofibrate observed in clinical trials and postmarketing experience that may potentially occur with Cholib® are listed below.

System Organ Class	Adverse reactions (fenofibrate)	Adverse reactions (simvastatin)	Frequency
Blood and lymphatic system disorders	Haemoglobin decreased White blood cell count decreased		rare
		Anaemia	rare
Immune system disorders	Hypersensitivity		rare
Metabolism and nutrition disorders		Diabetes Mellitus****	not known

Psychiatric disorders		Insomnia	very rare
		Sleep disorder, including nightmares, depression	not known
Nervous system disorders	Headache		uncommon
		Paresthesia, dizziness, peripheral neuropathy	rare
		Memory impairment/ Memory loss	rare
		Myasthenia gravis	not known
Eye disorders		Vision blurred, Visual impairment	rare
		Ocular myasthenia	not known
Vascular disorders	Thromboembolism (pulmonary embolism, deep vein thrombosis) *		uncommon
Respiratory, thoracic and mediastinal disorders		Interstitial lung disease	not known

Gastrointestinal disorders	Gastrointestinal signs and symptoms (abdominal pain, nausea, vomiting, diarrhoea, flatulence)		common
	Pancreatitis*		uncommon
		Constipation, dyspepsia	rare
Hepatobiliary disorders	Transaminases increased		common
	Cholelithiasis		uncommon
	Complications of cholelithiasis (e.g. cholecystitis, cholangitis, biliary colic etc.)		not known
		Gamma-glutamyltransferase increase	rare
		Hepatitis/jaundice Hepatic failure	very rare
Skin and subcutaneous tissue disorders	Severe cutaneous reactions (e.g erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, etc.)		not known
	Cutaneous hypersensitivity (e.g. Rash, pruritus, urticaria)		uncommon
	Alopecia		rare
	Photosensitivity reactions		rare
		Hypersensitivity syndrome	rare
		Lichenoid drug reactions	very rare
Musculoskeletal, connective tissue disorders	Muscle disorders (e.g. myalgia, myositis, muscular spasms and weakness)		uncommon
	Rhabdomyolysis with or without renal failure		rare

	(see section 4.4),		
		Myopathy** Tendinopathy	rare unknown
		Immune-mediated necrotizing myopathy (see section 4.4)	
		Muscle rupture	very rare
Reproductive system and breast disorders	Sexual dysfunction		uncommon
		Erectile dysfunction	not known
		Gynecomastia	very rare
General disorders and administration site conditions		Asthenia	rare
Investigations	Blood homocysteine level increased (see section 4.4) *****		very common
	Blood urea increased		rare
		Blood alkaline phosphatase increased	rare
		Blood creatinine phosphokinase level increase	rare
		Glycosylated haemoglobin increased	not known
		Blood glucose increased	not known

There have been rare post-marketing 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 non-serious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks)

Description of selected adverse reactions

Pancreatitis

* In the FIELD 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).

Thromboembolism

* In the FIELD study, a statistically significant increase was reported in the incidence of pulmonary embolism (0.7% [32/4900 patients] in the placebo group versus 1.1% [53/4895 patients] 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).

Myopathy

** In a clinical trial, myopathy occurred commonly in patients treated with simvastatin 80 mg/day compared to patients treated with 20 mg/day (1.0% vs 0.02%, respectively).

Hypersensitivity syndrome
*** An apparent hypersensitivity syndrome has been reported rarely which has included some of the following features: angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, eosinophilia, erythrocyte sedimentation rate (ESR) increased, arthritis and arthralgia, urticaria, photosensitivity, fever, flushing, dyspnoea and malaise.

Diabetes mellitus
****Diabetes mellitus: 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.

Increased blood homocysteine level
***** In the FIELD study the average increase in blood homocysteine level in patients treated with fenofibrate was 6.5 µmol/L, and was reversible on discontinuation of fenofibrate treatment.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

Cholib®
No specific antidote is known. If an overdose is suspected, symptomatic treatment and appropriate supportive measures should be provided as required.

Fenofibrate
Only anecdotal cases of fenofibrate overdose have been received. In the majority of cases no overdose symptoms were reported. Fenofibrate cannot be eliminated by haemodialysis.

Simvastatin
A few cases of simvastatin overdose have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae. There is no specific treatment in the event of overdose. In this case, symptomatic and supportive measures should be adopted.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Lipid modifying substances, HMG-CoA reductase inhibitors in combination with other lipid modifying substances, ATC code: C10BA04

Mechanism of action

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).

Through activation of PPARα, fenofibrate activates lipoprotein lipase production and reduces production of apoprotein CIII. Activation of PPARα also induces an increase in the synthesis of apoproteins AI and AII.

Simvastatin
Simvastatin, which is an inactive lactone, is hydrolyzed in the liver to the corresponding active beta-hydroxy acid form which has a potent activity in inhibiting HMG-CoA reductase (3 hydroxy-3 methylglutaryl CoA reductase). This enzyme catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol.

Cholib®:
Cholib® contains fenofibrate and simvastatin, which have different modes of action as described above.

Pharmacodynamic effects

Fenofibrate
Studies with fenofibrate on lipoprotein fractions show decreases in levels of LDL and VLDL cholesterol (VLDL-C). HDL-C 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 also has a uricosuric effect leading to reduction in uric acid levels of approximately 25%.

Simvastatin
Simvastatin has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very-low-density protein (VLDL) and is catabolised predominantly by the high affinity LDL receptor. The mechanism of the LDL lowering effect of simvastatin may involve both reduction of VLDL-C concentration and induction of the LDL receptor, leading to reduced production and increased catabolism of LDL-C. Apolipoprotein B also falls substantially during treatment with simvastatin. In addition, simvastatin moderately increases HDL-C and reduces plasma TG. As a result of these changes the ratios of TC to HDL-C and LDL-C to HDL-C are reduced.

Cholib®

The respective effects of simvastatin and fenofibrate are complementary.

Clinical efficacy and safety

Cholib®

Four pivotal clinical studies were carried out in the clinical program. Overall, 8,174 subjects with mixed dyslipidemia entered a 6-week statin run-in period. Of these, 2,593 subjects were randomized for 12 to 24 weeks of treatment, 1,241 subjects received fenofibrate and simvastatin co- administration, 1,239 subjects received statin monotherapy and 113 received fenofibrate monotherapy, all administered in the evening.

Statin type and dose used:

		Week 0 to Week 12		Week 12 to Week 24	
Study	Statin 6 weeks run-in	Statin monotherapy	Fenofibrate/Simva-statin in combination	Statin monotherapy	Fenofibrate/Simvas-tatin in combination
0501	Simvastatin 20 mg	Simvastatin 40 mg	Simvastatin 20 mg	Simvastatin 40 mg	Simvastatin 40 mg
0503	Atorvastatin 10 mg	Atorvastatin 10 mg	Simvastatin 20 mg	Atorvastatin 20 mg	Simvastatin 40 mg
0504	Pravastatin 40 mg	Pravastatin 40 mg	Simvastatin 20 mg	Pravastatin 40 mg	Simvastatin 40 mg
13-377	Different statins	Simvastatin 20 mg	Simvastatin 20 mg	-	-

Cholib® 145/20

Study 0501 evaluated 2 different doses of fenofibrate-simvastatin combination compared to simvastatin 40 mg for a 24 week double-blind period. The primary efficacy criterion was superiority of the combination fenofibrate 145 and simvastatin 20 mg versus simvastatin 40 mg on TG decrease and HDL-C increase and non-inferiority for LDL-C decrease at 12 weeks.

Mean Percent Change from Baseline to 12 Weeks Full Analysis Subject Sample				
Parameter	**Feno 145+Simva 20 (N=493) Mean (SD)**	**Simva 40 (N=505) Mean (SD)**	**Treatment Comparison***	**P-value**
TG (mmol/L)	-28.20 (37.31)	-4.60 (40.92)	-26.47 (-30.0, -22.78)	<0.001
LDL-C (mmol/L)	-5.64 (23.03)	-10.51 (22.98)	4.75 (2.0, 7.51)	NA
HDL-C (mmol/L)	7.32 (15.84)	1.64 (15.76)	5.76 (3.88, 7.65)	<0.001
TC (mmol/L)	-6.00 (15.98)	-7.56 (15.77)	1.49 (-0.41, 3.38)	0.123
Non-HDL-C (mmol/L)	-9.79 (21.32)	-9.79 (20.14)	-0.11 (-2.61,2.39)	0.931
Apo AI (g/L)	3.97 (13.15)	0.94 (13.03)	2.98 (1.42,4.55)	<0.001
Apo B (g/L)	-6.52 (21.12)	-7.97 (17.98)	1.22 (-1.19,3.63)	0.320
Apo B/Apo AI	-8.49 (24.42)	-7.94 (18.96)	-0.73 (-3.44,1.97)	0.595
Fibrinogen (g/L)	-0.31 (0.70)	-0.02 (0.70)	-0.32 (-0.40, -0.24)	< 0.001

*Treatment Comparison: difference between the LS Means % change for Feno 145 + Simva 20 and Simva 40, as well as the associated 95% confidence interval

After the first 12 weeks of treatment, the combination of fenofibrate 145 mg and simvastatin 20 mg showed superiority over simvastatin 40 mg for TG reduction and HDL-C increase but did not meet the criteria for non-inferiority on LDL-C. The combination of fenofibrate 145 mg with simvastatin 20 mg demonstrated statistically significant superiority on apoA1 increase and fibrinogen decrease compared to simvastatin 40 mg.

Study M13-377 evaluated 2 different fixed dose combinations of fenofibrate-and simvastatin compared to the same simvastatin dose for a 12-week double-blind period. The primary efficacy criterion was superiority of the combination fenofibrate 145 and simvastatin 20 mg versus simvastatin 20 mg on TG decrease and HDL-C increase. The combination of fenofibrate 145 mg with simvastatin 20 mg demonstrated statistically significant superiority over simvastatin 20 mg on TG and HDL-C (both p<0.001)

Mean Actual Change from Baseline to 12 Weeks Full Analysis Subject Sample				
Parameter	**Feno 145/Simva 20 (N=109) Mean (SD)**	**Simva 20 (N=114) Mean (SD)**	**Treatment Comparison***	**P-value**
TG (mmol/L)	-30.56 (25.79)	10.70 (48.79)	-40.3 (-49.34, -31.16)	<0.001
LDL-C (mmol/L)	1.87 (25.40)	-1.97 (24.79)		
HDL-C (mmol/L)	9.02 (16.82)	0.28 (12.10)	8.37 (4.47, 12.27)	<0.001
TC (mmol/L)	-3.92 (15.92)	0.01 (18.27)		
Non-HDL-C (mmol/L)	-7.94 (21.03)	0.38 (24.73)		
ApoA1 (g/L	3.59 (15.15)	2.83 (13.66)		
Apo B (g/L)	-7.27 (22.51)	-1.07 (23.11)		

*Treatment Comparison: difference between the LS Means percent change for Feno 145/ Simva 20 and Simva 20, as well as the associated 95% confidence interval

Supportive study

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid trial was a randomized placebo-controlled study of 5,518 patients with type 2 diabetes mellitus treated with fenofibrate in addition to simvastatin. Fenofibrate plus simvastatin therapy did not show any significant differences compared to simvastatin monotherapy in the composite primary outcome of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death (hazard ratio [HR] 0.92, 95% CI 0.79-1.08,p = 0.32; absolute risk reduction: 0.74%). In the pre- specified subgroup of dyslipidaemic patients, defined as those in the lowest tertile of HDL-C (≤ 34 mg/dl or 0.88 mmol/L) and highest tertile of TG (≥ 204 mg/dl or 2.3 mmol/L) at baseline, fenofibrate plus simvastatin therapy demonstrated a 31% relative reduction compared to simvastatin monotherapy for the composite primary outcome (hazard ratio [HR] 0.69, 95% CI 0.49-0.97, p=0.03; absolute risk reduction: 4.95%). Another prespecified subgroup analysis identified a statistically significant treatment-by-gender interaction (p=0.01) indicating a possible treatment benefit of combination therapy in men (p=0.037) but a potentially higher risk for the primary outcome in women treated with combination therapy compared to simvastatin monotherapy (p=0.069). This was not observed in the aforementioned subgroup of patients with dyslipidaemia but there was also no clear evidence of benefit in dyslipidaemic women treated with fenofibrate plus simvastatin, and a possible harmful effect in this subgroup could not be excluded.

5.2 Pharmacokinetic Properties

Absorption

Maximum plasma concentrations (C_{max}) of fenofibrate occur within 2 to 4 hours after oral administration. Plasma concentrations are stable during continuous treatment in any given individual.

Fenofibrate is water-insoluble and must be taken with food to facilitate absorption. The use of micronised fenofibrate and NanoCrystal® technology for the formulation of the fenofibrate 145mg tablet enhances its absorption.

Contrarily to previous fenofibrate formulations, the maximum plasma concentration and overall exposure of this formulation is independent from food intake.

A food-effect study involving administration of this formulation of fenofibrate 145 mg tablets to healthy male and female subjects under fasting conditions and with a high fat meal indicated that exposure (AUC and C_{max}) to fenofibric acid is not affected by food.

Therefore, fenofibrate in Cholib® may be taken without regard to meals.

Kinetic studies following the administration of a single dose and continuous treatment have demonstrated that the drug does not accumulate.

Simvastatin is an inactive lactone which is readily hydrolyzed in vivo to the corresponding beta-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Hydrolysis takes place mainly in the liver; the rate of hydrolysis in human plasma is very slow.

Simvastatin is well absorbed and undergoes extensive hepatic first-pass extraction. The extraction in the liver is dependent on the hepatic blood flow. The liver is the primary site of action of the active form. The availability of the beta-hydroxyacid to the systemic circulation following an oral dose of simvastatin was found to be less than 5% of the dose. Maximum plasma concentration of active inhibitors is reached approximately 1-2 hours after administration of simvastatin. Concomitant food intake does not affect the absorption.

The pharmacokinetics of single and multiple doses of simvastatin showed that no accumulation of medicinal product occurred after multiple dosing.

Distribution
Fenofibric acid is strongly bound to plasma albumin (more than 99%).
The protein binding of simvastatin and its active metabolite is > 95%.

Biotransformation and Elimination
After oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite fenofibric acid. No unchanged fenofibrate can be detected in the plasma. Fenofibrate is not a substrate for CYP 3A4. No hepatic microsomal metabolism is involved.

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.

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 hemodialysis.

Mean plasma half-life: the plasma elimination half-life of fenofibric acid is approximately 20 hours.

Simvastatin is a substrate of CYP 3A4 and of the efflux transporter BCRP. Simvastatin is taken up actively into the hepatocytes by the transporter OATP1B1. The major metabolites of simvastatin present in human plasma are the beta-hydroxyacid and four additional active metabolites. Following an oral dose of radioactive simvastatin to man, 13% of the radioactivity was excreted in the urine and 60% in the faeces within 96 hours. The amount recovered in the faeces represents absorbed medicinal product-equivalents excreted in bile as well as unabsorbed medicinal product. Following an intravenous injection of the beta-hydroxyacid metabolite, its half-life averaged 1.9 hours. An average of only 0.3% of the intravenous dose was excreted in urine as inhibitors.

Effects of repeated administration of fenofibrate on the pharmacokinetics of single or multiple doses of simvastatin have been investigated in two small studies (n=12) followed by a larger one (n=85) in healthy subjects.

In one study the AUC of the simvastatin acid (SVA), a major active metabolite of simvastatin, was reduced by 42% (90% CI 24%-56%) when a single dose of 40 mg simvastatin was combined with repeated administration of fenofibrate 160 mg. In the other study [Bergman et al, 2004] repeated co-administration of both simvastatin 80 mg and fenofibrate 160 mg led to a reduction in the AUC of the SVA of 36% (90% CI 30%-42%). In the larger study a reduction of 21% (90% CI 14%-27%) in AUC of SVA was observed after repeated co-administration of simvastatin 40 mg and fenofibrate 145 mg in the evening. This was not significantly different from the 29% (90% CI 22%-35%) reduction in AUC of SVA observed when co-administration was 12

hours apart: simvastatin 40 mg in the evening and fenofibrate 145 mg in the morning.

Whether fenofibrate had an effect on other active metabolites of simvastatin was not investigated. The exact mechanism of interaction is not known. In the available clinical data, the effect on LDL-C reduction was not considered to be significantly different to simvastatin monotherapy when LDL-C is controlled at the time of initiating treatment.

The repeated administration of simvastatin 40 or 80 mg, the highest dose registered, did not affect the plasma levels of fenofibric acid at steady state.

Special populations

Carriers of the SLCO1B1 gene c.521T>C allele have lower OATP1B1 activity. The mean exposure (AUC) of the main active metabolite, simvastatin acid is 120% in heterozygote carriers (CT) of the C allele and 221% in homozygote (CC) carriers relative to that of patients who have the most common genotype (TT). The C allele has a frequency of 18% in the European population. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of simvastatin, which may lead to an increased risk of rhabdomyolysis (see section 4.4).

5.3 Preclinical Safety Data

No preclinical studies have been performed with the fixed dose combination Cholib®.

Fenofibrate

Acute toxicity studies have yielded no relevant information about specific toxicity of fenofibrate.

In a three-month oral nonclinical study in the rat species with fenofibric acid, the active metabolite of fenofibrate, toxicity for the skeletal muscles (particularly those rich in type I-slow oxidative-myofibres) and cardiac degeneration, anemia and decreased body weight were seen at exposure levels ≥50-fold the human exposure for the skeletal toxicity and >15 fold for the cardiomyotoxicity.

Reversible ulcers and erosions in the gastro-intestinal tract occurred in dogs treated during 3 months at exposures approximately 7-fold the clinical AUC.

Studies on mutagenicity of fenofibrate have been negative.

In rats and mice, liver tumours have been found in carcinogenicity studies, which are attributable to peroxisome proliferation. These changes are specific to rodents and have not been observed in other species at comparable dose levels. 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 effects on fertility were detected in non-clinical reproductive toxicity studies conducted with fenofibrate. However reversible hypospermia and testicular vacuolation and immaturity of the ovaries were observed in a repeat-dose toxicity study with fenofibric acid in young dogs.

Simvastatin

Based on conventional animal studies regarding pharmacodynamics, repeated dose toxicity, genotoxicity and carcinogenicity, there are no other risks for the patient than may be expected on account of the pharmacological mechanism. At maximally tolerated doses in both the rat and the rabbit, simvastatin produced no fetal malformations, and had no effects on fertility, reproductive function or neonatal development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablet core:

Butylhydroxyanisole (E320)
Lactose monohydrate
Sodium laurilsulfate
Starch, pregelatinised (maize)
Docusate sodium
Sucrose
Citric acid monohydrate (E330)
Hypromellose (E464)
Crospovidone (E1202)
Magnesium stearate (E572)
Silicified microcrystalline cellulose (comprised of cellulose, microcrystalline and silica, colloidal anhydrous)
Ascorbic acid (E300)

Film-coating:

Poly (vinyl alcohol), partially hydrolysed (E1203)
Titanium dioxide (E171)
Talc (E553b)
Lecithin (derived from soya bean (E322))
Xanthan gum (E415)
Iron oxide red (E172)
Iron oxide yellow (E172)
Sunset yellow FCF (E110)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

Please refer to the product carton for expiry.

6.4 Special Precautions for Storage

Store below 30°C.

6.5 Nature and Contents of Container

Alu/Alu blisters
Pack sizes: 10, 30 and 90 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special Precautions for Disposal and Other Handling

Any unused medicinal product or waste material should be disposed of in accordance

with local requirements.

7 PRODUCT OWNER

Abbott Products Operations AG
Hegenheimermattweg 127,
4123 Allschwil, Switzerland

8 DATE OF LAST REVISION OF THE TEXT

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