ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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, film-coated tablet, with bevelled edges and 145/20 on one side. The diameter dimensions are 19.3 x 9.3 mm approximately and the tablet weight is about 734 mg.

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.

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).

Concomitant therapy
In patients taking products containing elbasvir or grazoprevir concomitantly with Cholib the dose of simvastatin should not exceed 20 mg/day. (See sections 4.4 and 4.5.)

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 (agents that increase AUC approximately 5 fold or greater) (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone, and medicinal products containing cobicistat) (see sections 4.4 and 4.5)
- Concomitant administration of gemfibrozil, ciclosporin, or danazol (see sections 4.4 and 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.

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 rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; positive anti-HMG CoA reductase antibody; muscle biopsy showing necrotizing myopathy; and improvement with immunosuppressive agents. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required. Consider risk of IMNM carefully prior to initiation of another statin. If therapy is initiated with another statin, monitor for signs and symptoms of IMNM.

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 sections 4.3 and 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).

The risk of myopathy is increased by high levels of HMG CoA reductase inhibitory activity in plasma (i.e., elevated simvastatin and simvastatin acid plasma levels), which may be due, in part, to interacting drugs that interfere with simvastatin metabolism and/or transporter pathways (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, or whose dose of simvastatin is being increased, 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.

<u>Hepatic disorders</u>
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.

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.

Myasthenia gravis
In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia (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.

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 medicine contains less than 1 mmol sodium (23 mg) per one tablet, that is to say essentially 'sodium-free'.

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.

Multiple mechanisms may contribute to potential interactions with HMG Co-A reductase inhibitors. Drugs or herbal products that inhibit certain enzymes (e.g. CYP3A4) and/or transporter (e.g. OATP1B) pathways may increase simvastatin and simvastatin acid plasma concentrations and may lead to an increased risk of myopathy/rhabdomyolysis.

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).

Consult the prescribing information of all concomitantly used drugs to obtain further information about their potential interactions with simvastatin and/or the potential for enzyme or transporter alterations and possible adjustments to dose and regimens.

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 sections 4.2 and 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).

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 and when the dose of either medicinal product is increased.

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 changed or 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: Itraconazole Ketoconazole Fluconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors (e.g. nelfinavir) Nefazodone Cobicistat	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, unless clinical benefit outweigh the risk
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	Patients should be closely monitored. Temporary suspension of Cholib treatment may be considered
Grapefruit juice	Avoid when taking Cholib
Vitamin K antagonists	Adjust the dose of these oral anticoagulants according to 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
During four double blind clinical trials of 24-week duration 1,237 patients have received treatment with co-administered fenofibrate and simvastatin. In a pooled analysis of these four trials, the rate of discontinuation due to treatment emergent adverse reactions was 5.0% (51 subjects on 1012) after 12 weeks of treatment with fenofibrate and simvastatin 145 mg/20 mg per day and 1.8% (4 subjects on 225) after 12 weeks of treatment with fenofibrate and simvastatin 145 mg/40 mg per day.

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. Frequency categories are based on information available from simvastatin and fenofibrate Summary of Product Characteristics available in the EU.

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
		Anaphylaxis	very 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

System Organ Class	Adverse reactions (fenofibrate)	Adverse reactions (simvastatin)	Frequency
	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, Ste vens-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 eruptions	very rare
Musculoskeletal, connective tissue disorders	Muscle disorders (e.g. myalgia, myositis, muscular spasms and weakness)		uncommon
	Rhabdomyolysis with or without renal failure (see section 4.4),		rare
		Myopathy** Immune-mediated necrotizing myopathy (see section 4.4) Tendinopathy	rare unkown
		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

System Organ Class	Adverse reactions (fenofibrate)	Adverse reactions (simvastatin)	Frequency
		Blood creatine phosphokinase level increase	rare
		Glycosylated haemoglobin increased	not known
		Blood glucose increased	not known

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 via the national reporting system listed in Appendix V.

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-hydroxyacid 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, 7,583 subjects with mixed dyslipidemia entered a 6 week statin run-in period. Of these, 2,474 subjects were randomized for 24 weeks treatment, 1,237 subjects received fenofibrate and simvastatin co-administration and 1,230 subjects received statin 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/ Simvastatin in combination	Statin monotherapy	Fenofibrate/ Simvastatin in combination
0501	simvastatin 20 mg	simvastatin 40 mg	simvastatin 20 mg	simvastatin 40 mg	simvastatin 40 mg
0502	simvastatin 40 mg	simvastatin 40 mg	simvastatin 40 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

Cholib 145/40
Study 0502 was evaluated a constant dose of fenofibrate-simvastatin combination and statin comparator throughout the 24 week double-blind period. The primary efficacy criterion was superiority of the combination fenofibrate 145 and simvastatin 40 mg versus simvastatin 40 mg on TG and LDL-C decrease and HDL-C increase at 12 weeks.

At 12 weeks and 24 weeks the combination of fenofibrate 145 mg and simvastatin 40 mg (F145/S40) showed superiority over simvastatin 40 mg (S40) for TG reduction and HDL-C increase.

The combination F145/S40 showed superiority over S40 for LDL-C reduction only at 24 weeks from a non-significant additional 1.2% reduction of LDL-C at 12 weeks to a statistically significant 7.2% reduction at 24 weeks.

TG, LDL-C and HDL-C Percent Change from Baseline to 12 and 24 Weeks Full Analysis Subject Sample				
Lipid parameter (mmol/L)	**Feno 145+Simva 40 (N=221)**	**Simva 40 (N=219)**	**Treatment Comparison***	**P-value**
After 12 weeks	**% Change Mean (SD)**			
TG	-27.18 (36.18)	-0.74 (39.54)	-28.19 (-32.91, -23.13)	<0.001
LDL-C	-6.34 (23.53)	-5.21 (22.01)	-1.24 (-5.22, 2.7)	0.539
HDL-C	5.77 (15.97)	-0.75 (12.98)	6.46 (3.83, 9.09)	<0.001
After 24 weeks	**% Change Mean (SD)**			
TG	-22.66 (43.87)	1.81 (36.64)	-27.56 (-32.90, -21.80)	<0.001
LDL-C	-3.98 (24.16)	3.07 (30.01)	-7.21 (-12.20, -2.21)	0.005
HDL-C	5.08 (16.10)	0.62 (13.21)	4.65 (1.88, 7.42)	0.001

*Treatment Comparison consists of the difference between the LS-means for Feno 145 + Simva 40 an d Simva 40, as well as the corresponding 95% CI.

The results on the biological parameters of interest at 24 weeks are presented in the table below. F145/S40 demonstrated statistically significant superiority on all parameters except on ApoA1 increase.

ANCOVA (analysis of covariance) of Percent Change in TC, non-HDL-C, ApoAI, ApoB, ApoB/ApoAI and fibrinogen from Baseline to 24 Weeks – Full Analysis Subject Sample					
Parameter	**Treatment Group**	**N**	**Means (SD)**	**Treatment Comparison***	**P-value**
TC (mmol/L)	Feno 145 + Simva 40 Simva 40	213 203	-4.95 (18.59) 1.69 (20.45)	-6.76 (-10.31, -3.20)	<0.001
Non-HDL-C (mmol/L)	Feno 145 + Simva 40 Simva 40	213 203	-7.62 (23.94) 2.52 (26.42)	-10.33 (-14.94, -5.72)	<0.001
Apo AI (g/L)	Feno 145 + Simva 40 Simva 40	204 194	5.79 (15.96) 4.02 (13.37)	2.34 (-0.32, 4.99)	0.084
Apo B (g/L)	Feno 145 + Simva 40 Simva 40	204 194	-2.95 (21.88) 6.04 (26.29)	-9.26 (-13.70, -4.82)	<0.001
Apo B/Apo AI	Feno 145 + Simva 40 Simva 40	204 194	-4.93 (41.66) 3.08 (26.85)	-8.29 (-15.18, -1.39)	0.019
Fibrinogen* (g/L)	Feno 145 + Simva 40 Simva 40	202 192	-29 (0.04) 0.01 (0.05)	-0.30 (-0.41, -0.19)	<0.001

*Treatment Comparison consists of the difference between the LS-means for Feno 145 + Simva 40 an d Simva 40, as well as the corresponding 95% CI. LS (less square mean) SD (standard deviation)

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 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.

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.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Cholib in all subsets of the paediatric population in combined dyslipidaemia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The geometric mean ratios and 90% CIs for the comparison of AUC, AUC(0-t) and C_{max} of the active metabolites, fenofibric acid and simvastatin acid, of the fixed dose combination Cholib 145 mg/20 mg tablet and the co-administration of the separate 145 mg fenofibrate and 20 mg simvastatin tablets as used in the clinical program, were all within the 80-125% bioequivalence interval.

The geomean maximum plasma level (C_{max}) of the inactive parent simvastatin was 2.7 ng/mL for the fixed dose combination Cholib 145 mg/20 mg tablet and 3.9 ng/mL for the co-administration of the separate 145 mg fenofibrate and 20 mg simvastatin tablets as used in the clinical program.

The geometric mean ratios and 90% CIs for the comparison of plasma exposure (AUC and AUC(0-t)) to simvastatin after administration of the fixed dose combination Cholib 145 mg/20 mg tablet and after co-administration of the separate 145 mg fenofibrate and 20 mg simvastatin tablets as used in the clinical program, were within the 80-125% bioequivalence interval.

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 145 mg 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

2 years.

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

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

7. MARKETING AUTHORISATION HOLDER

Viatris Healthcare Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
Dublin
Ireland

8. MARKETING AUTHORISATION NUMBERS

EU/1/13/866/001-002
EU/1/13/866/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 August 2013
Date of latest renewal: 16 May 2018

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Cholib 145 mg/40 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 145 mg of fenofibrate and 40 mg of simvastatin.

Excipient(s) with known effect:
One film-coated tablet contains, 194.7 mg of lactose (as monohydrate), 145 mg of sucrose and 0.8 mg of lecithin (derived from soya bean (E322)).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Oval, biconvex, brick red coloured, film-coated tablet, with bevelled edges and 145/40 on one side. The diameter dimensions are 19.3 x 9.3 mm approximately and the tablet weight is about 840 mg.

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.

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).

Concomitant therapy
In patients taking products containing elbasvir or grazoprevir concomitantly with Cholib the dose of simvastatin should not exceed 20 mg/day. (See sections 4.4 and 4.5.)

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 (agents that increase AUC approximately 5 fold or greater) (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone, and medicinal products containing cobicistat) (see sections 4.4 and 4.5)
- Concomitant administration of gemfibrozil, ciclosporin, or danazol (see sections 4.4 and 4.5)
- Concomitant administration of glecaprevir, pibrentasvir, elbasvir or grazoprevir (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)

Concomitant administration of amiodarone, verapamil, amlodipine or diltiazem (see section 4.5)

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.

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 rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; positive anti-HMG CoA reductase antibody; muscle biopsy showing necrotizing myopathy; and improvement with immunosuppressive agents. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required. Consider risk of IMNM carefully prior to initiation of another statin. If therapy is initiated with another statin, monitor for signs and symptoms of IMNM.

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 sections 4.3 and 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).

The risk of myopathy is increased by high levels of HMG CoA reductase inhibitory activity in plasma (i.e., elevated simvastatin and simvastatin acid plasma levels), which may be due, in part, to interacting drugs that interfere with simvastatin metabolism and/or transporter pathways (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, or whose dose of simvastatin is being increased, 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.

<u>Hepatic disorders</u>
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.

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.

Myasthenia gravis
In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia (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.

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 medicine contains less than 1 mmol sodium (23 mg) per one tablet, that is to say essentially 'sodium-free'.

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.

Multiple mechanisms may contribute to potential interactions with HMG Co-A reductase inhibitors. Drugs or herbal products that inhibit certain enzymes (e.g. CYP3A4) and/or transporter (e.g. OATP1B) pathways may increase simvastatin and simvastatin acid plasma concentrations and may lead to an increased risk of myopathy/rhabdomyolysis.

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).

Consult the prescribing information of all concomitantly used drugs to obtain further information about their potential interactions with simvastatin and/or the potential for enzyme or transporter alterations and possible adjustments to dose and regimens.

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 sections 4.2 and 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).

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 and when the dose of either medicinal product is increased.

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 changed or 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: Itraconazole Ketoconazole Fluconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors (e.g. nelfinavir) Nefazodone Cobicistat	Contraindicated with Cholib
Danazol Ciclosporin	Contraindicated with Cholib
Gemfibrozil, Other statins and fibrates	Contraindicated with Cholib
Amiodarone Verapamil Diltiazem Amlodipine	Contraindicated with Cholib 145 mg/40 mg
Elbasvir Grazoprevir	Contraindicated with Cholib 145 mg/40 mg
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	Patients should be closely monitored. Temporary suspension of Cholib treatment may be considered
Grapefruit juice	Avoid when taking Cholib
Vitamin K antagonists	Adjust the dose of these oral anticoagulants according to 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
During four double blind clinical trials of 24-week duration 1,237 patients have received treatment with co-administered fenofibrate and simvastatin. In a pooled analysis of these four trials, the rate of discontinuation due to treatment emergent adverse reactions was 5.0% (51 subjects on 1012) after 12 weeks of treatment with fenofibrate and simvastatin 145 mg/20 mg per day and 1.8% (4 subjects on 225) after 12 weeks of treatment with fenofibrate and simvastatin 145 mg/40 mg per day.

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. Frequency categories are based on information available from simvastatin and fenofibrate Summary of Product Characteristics available in the EU.

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
		Anaphylaxis	very 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		common

System Organ Class	Adverse reactions (fenofibrate)	Adverse reactions (simvastatin)	Frequency
	pain, nausea, vomiting, diarrhoea, flatulence)		
	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, Ste vens-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 eruptions	very rare
Musculoskeletal, connective tissue disorders	Muscle disorders (e.g. myalgia, myositis, muscular spasms and weakness)		uncommon
	Rhabdomyolysis with or without renal failure (see section 4.4),		rare
		Myopathy** Immune-mediated necrotizing myopathy (see section 4.4) Tendinopathy	rare unkown
		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

System Organ Class	Adverse reactions (fenofibrate)	Adverse reactions (simvastatin)	Frequency
	Blood urea increased		rare
		Blood alkaline phosphatase increased	rare
		Blood creatine phosphokinase level increase	rare
		Glycosylated haemoglobin increased	not known
		Blood glucose increased	not known

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 via the national reporting system listed in Appendix V.

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-hydroxyacid 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, 7,583 subjects with mixed dyslipidemia entered a 6 week statin run-in period. Of these, 2,474 subjects were randomized for 24 weeks treatment, 1,237 subjects received fenofibrate and simvastatin co-administration and 1,230 subjects received statin 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/ Simvastatin in combination	Statin monotherapy	Fenofibrate/ Simvastatin in combination
0501	simvastatin 20 mg	simvastatin 40 mg	simvastatin 20 mg	simvastatin 40 mg	simvastatin 40 mg
0502	simvastatin 40 mg	simvastatin 40 mg	simvastatin 40 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

Cholib 145/40
Study 0502 was evaluated a constant dose of fenofibrate-simvastatin combination and statin comparator throughout the 24 week double-blind period. The primary efficacy criterion was superiority of the combination fenofibrate 145 and simvastatin 40 mg versus simvastatin 40 mg on TG and LDL-C decrease and HDL-C increase at 12 weeks.

At 12 weeks and 24 weeks the combination of fenofibrate 145 mg and simvastatin 40 mg (F145/S40) showed superiority over simvastatin 40 mg (S40) for TG reduction and HDL-C increase.

The combination F145/S40 showed superiority over S40 for LDL-C reduction only at 24 weeks from a non-significant additional 1.2% reduction of LDL-C at 12 weeks to a statistically significant 7.2% reduction at 24 weeks.

TG, LDL-C and HDL-C Percent Change from Baseline to 12 and 24 Weeks Full Analysis Subject Sample				
Lipid parameter (mmol/L)	**Feno 145+Simva 40 (N=221)**	**Simva 40 (N=219)**	**Treatment Comparison***	**P-value**
After 12 weeks	**% Change Mean (SD)**			
TG	-27.18 (36.18)	-0.74 (39.54)	-28.19 (-32.91, -23.13)	<0.001
LDL-C	-6.34 (23.53)	-5.21 (22.01)	-1.24 (-5.22, 2.7)	0.539
HDL-C	5.77 (15.97)	-0.75 (12.98)	6.46 (3.83, 9.09)	<0.001
After 24 weeks	**% Change Mean (SD)**			
TG	-22.66 (43.87)	1.81 (36.64)	-27.56 (-32.90, -21.80)	<0.001
LDL-C	-3.98 (24.16)	3.07 (30.01)	-7.21 (-12.20, -2.21)	0.005
HDL-C	5.08 (16.10)	0.62 (13.21)	4.65 (1.88, 7.42)	0.001

*Treatment Comparison consists of the difference between the LS-means for Feno 145 + Simva 40 an d Simva 40, as well as the corresponding 95% CI.

The results on the biological parameters of interest at 24 weeks are presented in the table below. F145/S40 demonstrated statistically significant superiority on all parameters except on ApoA1 increase.

ANCOVA (analysis of covariance) of Percent Change in TC, non-HDL-C, ApoAI, ApoB, ApoB/ApoAI and fibrinogen from Baseline to 24 Weeks – Full Analysis Subject Sample					
Parameter	**Treatment Group**	**N**	**Means (SD)**	**Treatment Comparison***	**P-value**
TC (mmol/L)	Feno 145 + Simva 40 Simva 40	213 203	-4.95 (18.59) 1.69 (20.45)	-6.76 (-10.31, -3.20)	<0.001
Non-HDL-C (mmol/L)	Feno 145 + Simva 40 Simva 40	213 203	-7.62 (23.94) 2.52 (26.42)	-10.33 (-14.94, -5.72)	<0.001
Apo AI (g/L)	Feno 145 + Simva 40 Simva 40	204 194	5.79 (15.96) 4.02 (13.37)	2.34 (-0.32, 4.99)	0.084
Apo B (g/L)	Feno 145 + Simva 40 Simva 40	204 194	-2.95 (21.88) 6.04 (26.29)	-9.26 (-13.70, -4.82)	<0.001
Apo B/Apo AI	Feno 145 + Simva 40 Simva 40	204 194	-4.93 (41.66) 3.08 (26.85)	-8.29 (-15.18, -1.39)	0.019
Fibrinogen* (g/L)	Feno 145 + Simva 40 Simva 40	202 192	-29 (0.04) 0.01 (0.05)	-0.30 (-0.41, -0.19)	<0.001

*Treatment Comparison consists of the difference between the LS-means for Feno 145 + Simva 40 an d Simva 40, as well as the corresponding 95% CI. LS (less square mean) SD (standard deviation)

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 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.

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.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Cholib in all subsets of the paediatric population in combined dyslipidaemia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The geometric mean ratios and 90% CIs for the comparison of AUC, AUC(0-t) and C_{max} for fenofibric acid, simvastatin and simvastatin acid of the fixed dose combination Cholib 145 mg/40 mg tablet and the co-administration of the separate 145 mg fenofibrate and 40 mg simvastatin tablets as used in the clinical program, were all within the 80-125% bioequivalence interval.

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 145 mg 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)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

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

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

7. MARKETING AUTHORISATION HOLDER

Viatris Healthcare Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
Dublin
Ireland

8. MARKETING AUTHORISATION NUMBERS

EU/1/13/866/003-004
EU/1/13/866/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 August 2013
Date of latest renewal: 16 May 2018

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Mylan Laboratories SAS
Route de Belleville - Lieu-dit Maillard
01400 Châtillon-sur-Chalaronne
France

Mylan Hungary Kft.
Mylan utca 1.
Komárom, 2900
Hungary

Astrea Fontaine,
Site De Fontaine, Rue Des Pres Potets,
Fontaine Les Dijon, 21121
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within six months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk management plan (RMP)**

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

An updated RMP should be submitted:

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

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Cholib 145 mg/20 mg film-coated tablets
fenofibrate/simvastatin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 145 mg of fenofibrate and 20 mg of simvastatin

3. LIST OF EXCIPIENTS

Contains: lactose, sucrose, lecithin (derived from soya bean (E322)), sunset yellow FCF (E110).

4. PHARMACEUTICAL FORM AND CONTENTS

10 film-coated tablets
30 film-coated tablets
90 film coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

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

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Healthcare Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
Dublin
Ireland

12. MARKETING AUTHORISATION NUMBERS

EU/1/13/866/001 10 film-coated tablets
EU/1/13/866/002 30 film-coated tablets
EU/1/13/866/005 90 film coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cholib 145 mg/20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

< PC: {number} [product code]
SN: {number} [serial number]
NN: {number} [national reimbursement number or other national number identifying the medicinal product]>

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Cholib 145 mg/20 mg tablets
fenofibrate/simvastatin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Viatris

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Cholib 145 mg/40 mg film-coated tablets
fenofibrate/simvastatin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 145 mg of fenofibrate and 40 mg of simvastatin

3. LIST OF EXCIPIENTS

Contains: lactose, sucrose, lecithin (derived from soya bean (E322))

4. PHARMACEUTICAL FORM AND CONTENTS

10 film-coated tablets
30 film-coated tablets
90 film coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Healthcare Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
Dublin
Ireland

12. MARKETING AUTHORISATION NUMBERS

EU/1/13/866/003 10 film-coated tablets
EU/1/13/866/004 30 film-coated tablets
EU/1/13/866/006 90 film coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cholib 145 mg/40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

< PC: {number} [product code]
SN: {number} [serial number]
NN: {number} [national reimbursement number or other national number identifying the medicinal product]>

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Cholib 145 mg/40 mg tablets
fenofibrate/simvastatin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Viatris

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Cholib 145 mg/20 mg film-coated tablets

fenofibrate/simvastatin

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

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

What is in this leaflet

1. What Cholib is and what it is used for

Cholib contains two different active substances: fenofibrate (belongs to the group called ‘fibrates’) and simvastatin (belongs to the group called ‘statins’). They are both used to lower levels of total cholesterol, “bad” cholesterol (LDL cholesterol), and fatty substances called triglycerides in the blood. In addition, they both raise levels of “good” cholesterol (HDL cholesterol).

What should I know about cholesterol and triglycerides?

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

LDL cholesterol is often called ‘bad’ cholesterol because it can build up in the walls of your arteries and form plaque. Over time, this plaque build-up can lead to a clogging of your arteries.

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

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

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

Cholib is used in adults at high risk of problems like heart attack and stroke who have high blood levels of 2 types of fats (triglycerides and LDL cholesterol). It is given to lower triglycerides and increase the good cholesterol (HDL cholesterol) in patients whose bad cholesterol (LDL cholesterol) is already controlled with simvastatin alone in a dose of 20 mg.

You must continue a low fat diet or other measures (e.g. exercise, weight reduction) during treatment with Cholib.

2. What you need to know before you take use Cholib

Do not take Cholib:

- If you are allergic to fenofibrate or simvastatin or any of the other ingredients of Cholib (listed in section 6)
- If you are allergic to peanut, arachis oil, soya lecithin or related substances
- If while taking other medicines, you have had an allergic reaction or skin damage from sunlight or UV light (these medicines include other fibrates and an anti-inflammatory medicine called "ketoprofen")
- If you have liver or gallbladder problems
- If you have pancreatitis (inflamed pancreas which causes abdominal pain), which is not caused by high levels of fats in the blood
- If you have moderate or severe kidney problems
- If you have a history of muscle problems during treatment to lower the level of fats in the blood with either of the active substances in this medicine, or with other statins (such as atorvastatin, pravastatin or rosuvastatin) or fibrates (such as bezafibrate or gemfibrozil)
- If you are already taking the following medicines:
  - danazol (a man-made hormone used to treat endometriosis)
  - ciclosporin (a medicine often used in organ transplant patients)
  - itraconazole, ketoconazole, fluconazole or posaconazole (medicines for fungal infections)
  - HIV protease inhibitors such as indinavir, nelfinavir, ritonavir and saquinavir (medicines used for HIV infection and AIDS)
  - Cobicistat (medicine used for HIV infection)
  - glecaprevir or pibrentasvir (used to treat hepatitis C virus infection)
  - erythromycin, clarithromycin, or telithromycin (medicines for bacterial infections)
  - nefazodone (a medicine for depression)
- If you are already being treated and will continue your treatment with:
  - a fibrate (e.g. gemfibrozil)
  - a statin (medicines to lower the levels of fats in the blood, e.g. simvastatin, atorvastatin)
- If you are under 18 years of age
- If you are pregnant or breast-feeding

Do not take Cholib if any of the above applies to you. Check with your doctor or pharmacist if you are not sure.

Warnings and precautions:

Talk to your doctor or pharmacist before taking Cholib if:

- you have an underactive thyroid gland (hypothyroidism)
- you are due to have an operation. You may need to stop taking Cholib for a short time.
- you drink large amounts of alcohol (more than 21 units (210 mL) a week of pure alcohol)
- you have chest pain and are feeling breathless. These may be signs of a blood clot in the lung (pulmonary embolism)
- you have severe lung disease
- you have kidney disease
- you or a close family member have a muscle problem which runs in the family
- you are taking or, in the last 7 days, have taken or been given a medicine called fusidic acid (a medicine for bacterial infection)
- you are taking hepatitis C antiviral agents such as elbasvir or grazoprevir (used to treat hepatitis C virus infection)

- you have or have had myasthenia (a disease with general muscle weakness including in some cases muscles used when breathing), or ocular myasthenia (a disease causing eye muscle weakness) as statins may sometimes aggravate the condition or lead to the occurrence of myasthenia (see section 4).

If any of the above applies to you, talk to your doctor or pharmacist before taking Cholib. Check with your doctor or pharmacist if you are not sure.

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

Your doctor should do a blood test before you start taking Cholib. This is to check how well your liver is working.

Your doctor may also want you to have blood tests to check how well your liver is working after you start taking Cholib.

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

Your doctor may do a blood test to check your muscles before and after starting treatment.

Children and adolescents

Cholib must not be given to children and adolescents (age below 18 years).

Other medicines and Cholib:

It is particularly important to tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This also concerns medicines obtained without a prescription including herbal medicines.

Tell your doctor or pharmacist if you are taking any of the following medicines:

- danazol (a man-made hormone used to treat endometriosis)
- ciclosporin (a medicine often used in organ transplant patients)
- itraconazole, ketoconazole, fluconazole or posaconazole (medicines for fungal infections)
- HIV protease inhibitors such as indinavir, nelfinavir, ritonavir and saquinavir (medicines used for HIV infection and AIDS)
- Cobicistat (medicine used for HIV infection)
- glecaprevir or pibrentasvir (used to treat hepatitis C virus infection)
- erythromycin, clarithromycin, or telithromycin (medicines for bacterial infections)
- nefazodone (a medicine for depression)
- a fibrate (e.g. fenofibrate, gemfibrozil)
- a statin (e.g. simvastatin, atorvastatin)

Do not take Cholib if any of the above applies to you. Check with your doctor or pharmacist if you are not sure.

In particular tell your doctor or pharmacist if you are taking any of the following medicines (taking Cholib with any of these medicines can increase the risk of muscle problems):

- high doses of at least 1 gram per day of niacin (nicotinic acid) or a treatment containing niacin (medicine for lowering fat levels in the blood)
- colchicine (a medicine used to treat gout)

Do not take fusidic acid (a medicine for bacterial infections) while using this medicine.

As well as the medicines listed previously, tell your doctor or pharmacist if you are taking, have recently taken or might take any of the following medicines:

- anticoagulants such as warfarin, fluindione, phenprocoumone or acenocoumarol (medicines to prevent blood clots)
- pioglitazone (a particular class of medicines to treat diabetes)
- rifampicin (a medicine used to treat tuberculosis)
- elbasvir or grazoprevir (used to treat hepatitis C virus infection)

If any of the above applies to you, talk to your doctor or pharmacist before taking Cholib. Check with your doctor or pharmacist if you are not sure.

Cholib with food and drink

Grapefruit juice contains one or more components that alter how the body uses Cholib. Do not consume grapefruit juice with Cholib as it may increase your risk of muscle problems.

Pregnancy and breast-feeding

- Do not take Cholib if you are pregnant, trying to get pregnant or think you may be pregnant. If you get pregnant while taking Cholib, stop taking it immediately and contact your doctor.
- Do not take Cholib if you are breast-feeding or plan to breast-feed your baby, because it is not known if the medicine passes into breast milk.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

Cholib is not expected to affect you being able to drive or use tools or machines. However, it should be taken into account that some people get dizzy after taking Cholib.

Important information about some of the ingredients of Cholib

Cholib contains types of sugars called lactose and sucrose. If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.

Cholib contains soya lecithin. If you are allergic to peanut, soya or arachis oil do not use Cholib.

Cholib contains sunset yellow FCF (E110) that may cause allergic reactions.

3. How to take Cholib

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

Your doctor will determine the appropriate strength for you, depending on your condition, your current treatment and your personal risk status.
The usual dose is one tablet per day.
You can take Cholib with or without food.
Swallow the tablet with a glass of water.
Do not crush or chew the tablet.

You should continue a low-fat diet or other measures (e.g. exercise, weight reduction) whilst taking Cholib.

If you take more Cholib than you should

If you have taken more Cholib than you should or if someone else has taken your medicine, tell your doctor or pharmacist or contact your nearest hospital

If you forget to take Cholib

Do not take a double dose to make up for a forgotten tablet. Take the next tablet at your regular time on the next day. If you are worried about this, talk to your doctor or pharmacist.

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

4. Possible side effects

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

- Unexplained muscle pain, tenderness, or weakness may be sign of muscle break down. Therefore please contact your doctor immediately if you experience these symptoms. This is because on rare occasions, there have been cases of serious muscle problems including muscle breakdown resulting in kidney damage; and very rare deaths have occurred. Compared to a fibrate or a statin alone, the risk of muscle breakdown is increased when you take these 2 medicines together, as in Cholib. It is higher in female patients or in patients 65 years or older.

<u>Some patients have experienced the following serious side effects whilst taking fenofibrate or simvastatin (both active substances in Cholib):</u>

- hypersensitivity (allergic) reactions including swelling of the face, tongue and throat which may cause difficulty in breathing (angioedema) (rare)
- a serious allergic reaction which causes difficulty in breathing or dizziness (anaphylaxis) (very rare)
- Hypersensitivity reaction to Cholib with symptoms like: pain or inflammation of the joints, inflammation of blood vessels, unusual bruising, skin eruptions and swelling, hives, skin sensitivity to the sun, fever, flushing, shortness of breath and feeling unwell, lupus-like disease picture (including rash, joint disorders, and effects on white blood cells)
- cramps or painful, tender or weak muscles, muscle rupture - these may be signs of muscle inflammation or breakdown, which can cause kidney damage or even death
- stomach pain - this may be a sign that your pancreas is inflamed (pancreatitis)
- chest pain and feeling breathless - these may be signs of a blood clot in the lung (pulmonary embolism)
- pain, redness or swelling in the legs - these may be signs of a blood clot in the leg (deep vein thrombosis)
- yellowing of the skin and whites of the eyes (jaundice), or an increase in liver enzymes - these may be signs of an inflamed liver (hepatitis and hepatic failure)
- increased sensitivity of your skin to sunlight, sun lamps and sunbeds
- rash that may occur on the skin or sores in the mouth (lichenoid drug eruptions)

If any of the previously listed serious side effects happen, stop taking Cholib and tell your doctor immediately or go to the emergency room at your nearest hospital - you may need urgent medical treatment.

Some patients have experienced the following side effects whilst taking Cholib, fenofibrate or simvastatin:

Very common side effects (may affect more than 1 in 10 people):

- Increase in the blood level of “creatinine” (substance excreted by the kidneys)
- Increase in blood levels of “homocysteine” (too much of this amino acid in the blood is related to a higher risk of coronary heart disease, stroke and peripheral vascular disease, although a causal link has not been established)

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

- increase in blood platelets count
- elevations in blood tests of liver function (transaminases)
- digestive disturbances (stomach pain, nausea, vomiting, diarrhoea and flatulence)
- infection of the upper respiratory tract

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

- muscle problems
- gallstones
- rashes, itching, red patches on the skin
- headache
- sexual difficulties

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

- low red blood cell count (anaemia)
- numbness or weakness of the arms and legs
- confusion
- feeling dizzy
- feeling exhausted (astenia)
- increase in “urea” - produced by the kidneys - shown in tests
- increase in “gamma-glutamyltransferase” - produced by the liver - shown in tests
- increase in “alkaline phosphatase” - produced by the bile system - shown in tests
- increase in “creatine phosphokinase” - produced by the muscle - shown in tests
- drop in haemoglobin (that carries oxygen in blood) and white blood cells- shown in tests
- trouble sleeping
- poor memory or memory loss
- hair loss
- constipation
- dyspepsia
- blurred vision; impaired vision

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

- gynecomastia (breast enlargement in men)

The following side effects have also been reported but the frequency cannot be estimated from the available information (frequency not known):

- severe allergic skin rash with blisters
- complications of gall stones such as colic because of stones in bile duct, infection of the bile ducts or gall bladder
- diabetes mellitus

- erectile dysfunction
- feeling depressed
- sleep disturbances including nightmares
- specific lung disease with difficulties breathing (called interstitial lung disease)
- muscle weakness that is constant
- increase in “glycosylated haemoglobin” and blood glucose levels - markers for blood glucose control in diabetes mellitus - shown in tests
- myasthenia gravis (a disease causing general muscle weakness including in some cases muscles used when breathing). Ocular myasthenia (a disease causing eye muscle weakness). Talk to your doctor if you experience weakness in your arms or legs that worsens after periods of activity, double vision or drooping of your eyelids, difficulty swallowing, or shortness of breath.

Reporting of side effects

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

5. How to store Cholib

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

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

Store below 30°C.

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

6. Contents of the pack and other information

What Cholib contains

The active substances are fenofibrate and simvastatin. Each tablet contains 145 mg of fenofibrate and 20 mg of simvastatin.

This medicine contains less than 1 mmol sodium (23 mg) per one tablet, that is to say essentially ‘sodium-free’.

The other ingredients are:

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-coat:
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).

What Cholib looks like and contents of the pack

Oval, biconvex, tan coloured, film-coated tablet, with bevelled edges and 145/20 on one side. The diameter dimensions are 19.3 x 9.3 mm approximately and the tablet weight is about 734 mg.

The tablets are provided in carton boxes with blisters containing 10, 30 or 90 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Viatris Healthcare Limited, Damastown Industrial Park, Mulhuddart, Dublin 15, Dublin, Ireland

Manufacturer:
Mylan Laboratories SAS, Route de Belleville - Lieu-dit Maillard, 01400 Châtillon-sur-Chalaronne - France.
Mylan Hungary Kft., Mylan utca 1, Komárom 2900, Hungary
Astrea Fontaine, Site De Fontaine, Rue Des Pres Potets, Fontaine Les Dijon, 21121, France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in <{MM/YYYY}>:

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Package leaflet: Information for the user

Cholib 145 mg/40 mg film-coated tablets

fenofibrate/simvastatin

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

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

What is in this leaflet

1. What Cholib is and what it is used for

Cholib contains two different active substances: fenofibrate (belongs to the group called 'fibrates') and simvastatin (belongs to the group called 'statins'). They are both used to lower levels of total cholesterol, "bad" cholesterol (LDL cholesterol), and fatty substances called triglycerides in the blood. In addition, they both raise levels of "good" cholesterol (HDL cholesterol).

What should I know about cholesterol and triglycerides?
Cholesterol is one of several fats found in your blood. Your total cholesterol is made up mainly of LDL and HDL cholesterol.
LDL cholesterol is often called 'bad' cholesterol because it can build up in the walls of your arteries and form plaque. Over time, this plaque build-up can lead to a clogging of your arteries.
HDL cholesterol is often called 'good' cholesterol because it helps keep the 'bad' cholesterol from building up in the arteries and because it protects against heart disease.
Triglycerides are another fat in your blood. They may raise your risk of having heart problems.
In most people, there are no signs of cholesterol or triglycerides problems at first. Your doctor can measure your lipids with a simple blood test. Visit your doctor regularly to keep track of your lipids level.

Cholib is used in adults at high risk of problems like heart attack and stroke who have high blood levels of 2 types of fats (triglycerides and LDL cholesterol). It is given to lower triglycerides and increase the good cholesterol (HDL cholesterol) in patients whose bad cholesterol (LDL cholesterol) is already controlled with simvastatin alone in a dose of 40 mg.

You must continue a low fat diet or other measures (e.g. exercise, weight reduction) during treatment with Cholib.

2. What you need to know before you take use Cholib

Do not take Cholib:

- If you are allergic to fenofibrate or simvastatin or any of the other ingredients of Cholib (listed in section 6)
- If you are allergic to peanut, arachis oil, soya lecithin or related substances
- If while taking other medicines, you have had an allergic reaction or skin damage from sunlight or UV light (these medicines include other fibrates and an anti-inflammatory medicine called "ketoprofen")
- If you have liver or gallbladder problems
- If you have pancreatitis (inflamed pancreas which causes abdominal pain), which is not caused by high levels of fats in the blood
- If you have moderate or severe kidney problems
- If you have a history of muscle problems during treatment to lower the level of fats in the blood either of the active substances in this medicine, or with other statins (such as atorvastatin, pravastatin or rosuvastatin) or fibrates (such as bezafibrate or gemfibrozil)
- If you are already taking the following medicines:
  - danazol (a man-made hormone used to treat endometriosis)
  - ciclosporin (a medicine often used in organ transplant patients)
  - itraconazole, ketoconazole, fluconazole or posaconazole (medicines for fungal infections)
  - HIV protease inhibitors such as indinavir, nelfinavir, ritonavir and saquinavir (medicines used for HIV infection and AIDS)
  - Cobicistat (medicine used for HIV infection)
  - erythromycin, clarithromycin, or telithromycin (medicines for bacterial infections)
  - nefazodone (a medicine for depression)
  - amiodarone (a medicine for an irregular heartbeat) or verapamil (a medicine for high blood pressure, chest pain associated with heart disease, or other heart conditions)
  - hepatitis C antiviral agents such as elbasvir, grazoprevir, glecaprevir or pibrentasvir (used to treat hepatitis C virus infection)
- If you are already being treated and will continue your treatment with:
  - a fibrate (e.g. gemfibrozil)
- a statin (medicines to lower the levels of fats in the blood, e.g. simvastatin, atorvastatin)If you are under 18 years of age
- If you are pregnant or breast-feeding

Do not take Cholib if any of the above applies to you. Check with your doctor or pharmacist if you are not sure.

Warnings and precautions:

Talk to your doctor or pharmacist before taking Cholib if:

- you have an underactive thyroid gland (hypothyroidism)
- you are due to have an operation. You may need to stop taking Cholib for a short time
- you drink large amounts of alcohol (more than 21 units (210 mL) a week of pure alcohol)
- you have chest pain and are feeling breathless. These may be signs of a blood clot in the lung (pulmonary embolism)
- you have severe lung disease
- you have kidney disease
- you or a close family member have a muscle problem which runs in the family
- you are taking or, in the last 7 days, have taken or been given a medicine called fusidic acid (a medicine for bacterial infection)
- you are taking hepatitis C antiviral agents such as elbasvir or grazoprevir (used to treat hepatitis C virus infection
- you have or have had myasthenia (a disease with general muscle weakness including in some cases muscles used when breathing), or ocular myasthenia (a disease causing eye muscle

weakness) as statins may sometimes aggravate the condition or lead to the occurrence of myasthenia (see section 4).

If any of the above applies to you, talk to your doctor or pharmacist before taking Cholib. Check with your doctor or pharmacist if you are not sure.

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

Your doctor should do a blood test before you start taking Cholib. This is to check how well your liver is working.

Your doctor may also want you to have blood tests to check how well your liver is working after you start taking Cholib.

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

Your doctor may do a blood test to check your muscles before and after starting treatment.

Children and adolescents

Cholib must not be given to children and adolescents (age below 18 years).

Other medicines and Cholib:

It is particularly important to tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This also concerns medicines obtained without a prescription including herbal medicines.

Tell your doctor or pharmacist if you are taking any of the following medicines:
- danazol (a man-made hormone used to treat endometriosis)
- ciclosporin (a medicine often used in organ transplant patients)
- itraconazole, ketoconazole, fluconazole or posaconazole (medicines for fungal infections)
- HIV protease inhibitors such as indinavir, nelfinavir, ritonavir and saquinavir (medicines used for HIV infection and AIDS)
- Cobicistat (medicine used for HIV infection)
- elbasvir, grazoprevir, glecaprevir or pibrentasvir (used to treat hepatitis C virus infection)erythromycin, clarithromycin, or telithromycin (medicines for bacterial infections)
- nefazodone (a medicine for depression)
- amiodarone (a medicine for an irregular heartbeat) or verapamil (a medicine for high blood pressure, chest pain associated with heart disease, or other heart conditions)
- a fibrate (e.g. fenofibrate, gemfibrozil)
- a statin (e.g. simvastatin, atorvastatin)

Do not take Cholib if any of above applies to you. Check with your doctor or pharmacist if you are not sure.

In particular tell your doctor or pharmacist if you are taking any of the following medicines (taking Cholib with any of these medicines can increase the risk of muscle problems):
- high doses of at least 1 gram per day of niacin (nicotinic acid) or a treatment containing niacin (medicine for lowering fat levels in the blood)
- colchicine (a medicine used to treat gout).

Do not take fusidic acid (a medicine for bacterial infections) while using this medicine.

As well as the medicines listed previously, tell your doctor or pharmacist if you are taking, have recently taken or might take any of the following medicines:

- anticoagulants such as warfarin, fluindione, phenprocoumone or acenocoumarol (medicines to prevent blood clots)
- pioglitazone (a particular class of medicines to treat diabetes)
- rifampicin (a medicine used to treat tuberculosis).

If any of the above applies to you, talk to your doctor or pharmacist before taking Cholib. Check with your doctor or pharmacist if you are not sure.

Cholib with food and drink

Grapefruit juice contains one or more components that alter how the body uses Cholib. Do not consume grapefruit juice with Cholib as it may increase your risk of muscle problems.

Pregnancy and breast-feeding

- Do not take Cholib if you are pregnant, trying to get pregnant or think you may be pregnant. If you get pregnant while taking Cholib, stop taking it immediately and contact your doctor.
- Do not take Cholib if you are breast-feeding or plan to breast-feed your baby, because it is not known if the medicine passes into breast milk.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

Cholib is not expected to affect you being able to drive or use tools or machines. However, it should be taken into account that some people get dizzy after taking Cholib.

Important information about some of the ingredients of Cholib

Cholib contains types of sugars called lactose and sucrose. If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.

Cholib contains soya lecithin. If you are allergic to peanut, soya or arachis oil do not use Cholib.

3. How to take Cholib

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

Your doctor will determine the appropriate strength for you, depending on your condition, your current treatment and your personal risk status.
The usual dose is one tablet per day.
You can take Cholib with or without food.
Swallow the tablet with a glass of water.
Do not crush or chew the tablet.

You should continue a low-fat diet or other measures (e.g. exercise, weight reduction) whilst taking Cholib.

If you take more Cholib than you should

If you have taken more Cholib than you should or if someone else has taken your medicine, tell your doctor or pharmacist or contact your nearest hospital

If you forget to take Cholib

Do not take a double dose to make up for a forgotten tablet. Take the next tablet at your regular time on the next day. If you are worried about this, talk to your doctor or pharmacist.

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

4. Possible side effects

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

- Unexplained muscle pain, tenderness, or weakness may be sign of muscle break down. Therefore please contact your doctor immediately if you experience these symptoms. This is because on rare occasions, there have been cases of serious muscle problems including muscle breakdown resulting in kidney damage; and very rare deaths have occurred. Compared to a fibrate or a statin alone, the risk of muscle breakdown is increased when you take these 2 medicines together, as in Cholib. It is higher in female patients or in patients 65 years or older.

Some patients have experienced the following serious side effects whilst taking fenofibrate or simvastatin (both active substances in Cholib):

- hypersensitivity (allergic) reactions including swelling of the face, tongue and throat which may cause difficulty in breathing (angioedema) (rare)
- a serious allergic reaction which causes difficulty in breathing or dizziness (anaphylaxis) (very rare)
- Hypersensitivity reaction to Cholib with symptoms like: pain or inflammation of the joints, inflammation of blood vessels, unusual bruising, skin eruptions and swelling, hives, skin sensitivity to the sun, fever, flushing, shortness of breath and feeling unwell, lupus-like disease picture (including rash, joint disorders, and effects on white blood cells)
- cramps or painful, tender or weak muscles, muscle rupture - these may be signs of muscle inflammation or breakdown, which can cause kidney damage or even death
- stomach pain - this may be a sign that your pancreas is inflamed (pancreatitis)
- chest pain and feeling breathless - these may be signs of a blood clot in the lung (pulmonary embolism)
- pain, redness or swelling in the legs - these may be signs of a blood clot in the leg (deep vein thrombosis)
- yellowing of the skin and whites of the eyes (jaundice), or an increase in liver enzymes - these may be signs of an inflamed liver (hepatitis and hepatic failure).
- increased sensitivity of your skin to sunlight, sun lamps and sunbeds
- rash that may occur on the skin or sores in the mouth (lichenoid drug eruptions)

If any of the previously listed serious side effects happen, stop taking Cholib and tell your doctor immediately or go to the emergency room at your nearest hospital - you may need urgent medical treatment.

Some patients have experienced the following side effects whilst taking Cholib, fenofibrate or simvastatin:

Very common side effects (may affect more than 1 in 10 people):

- Increase in the blood level of “creatinine” (substance excreted by the kidneys)
- Increase in blood levels of “homocysteine” (too much of this amino acid in the blood is related to a higher risk of coronary heart disease, stroke and peripheral vascular disease, although a causal link has not been established)

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

- increase in blood platelets count
- elevations in blood tests of liver function (transaminases)
- digestive disturbances (stomach pain, nausea, vomiting, diarrhoea and flatulence)
- infection of the upper respiratory tract

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

- muscle problems
- gallstones
- rashes, itching, red patches on the skin.
- headache
- sexual difficulties

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

- low red blood cell count (anaemia)
- numbness or weakness of the arms and legs
- confusion
- feeling dizzy
- feeling exhausted (astenia)
- increase in “urea” - produced by the kidneys - shown in tests
- increase in “gamma-glutamyltransferase” - produced by the liver - shown in tests
- increase in “alkaline phosphatase” - produced by the bile system - shown in tests
- increase in “creatine phosphokinase” - produced by the muscle - shown in tests
- drop in haemoglobin (that carries oxygen in blood) and white blood cells- shown in tests.
- trouble sleeping
- poor memory or memory loss
- hair loss
- constipation
- dyspepsia
- blurred vision; impaired vision

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

- gynecomastia (breast enlargement in men)

The following side effects have also been reported but the frequency cannot be estimated from the available information (frequency not known):

- severe allergic skin rash with blisters
- complications of gall stones such as colic because of stones in bile duct, infection of the bile ducts or gall bladder
- diabetes mellitus
- erectile dysfunction
- feeling depressed
- sleep disturbances including nightmares

- specific lung disease with difficulties breathing (called interstitial lung disease)
- muscle weakness that is constant
- increase in “glycosylated haemoglobin” and blood glucose levels - (markers for blood glucose control in diabetes mellitus - shown in tests
- myasthenia gravis (a disease causing general muscle weakness including in some cases muscles used when breathing). Ocular myasthenia (a disease causing eye muscle weakness). Talk to your doctor if you experience weakness in your arms or legs that worsens after periods of activity, double vision or drooping of your eyelids, difficulty swallowing, or shortness of breath.

Reporting of side effects

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

5. How to store Cholib

Keep this medicine out of the sight and reach of children.
Do not use Cholib after the expiry date which is stated on the carton and the blister after EXP.
The expiry date refers to the last day of that month.

Store below 30°C.

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

6. Contents of the pack and other information

What Cholib contains

The active substances are fenofibrate and simvastatin. Each tablet contains 145 mg of fenofibrate and 40 mg of simvastatin.

This medicine contains less than 1 mmol sodium (23 mg) per one tablet, that is to say essentially ‘sodium-free’.

The other ingredients are:

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-coat:
Poly (vinyl alcohol), partially hydrolysed (E1203), titanium dioxide (E171), talc (E553b), lecithin (derived from soya bean (E322)), xanthan gum (E415), iron oxide red (E172).

What Cholib looks like and contents of the pack

Oval, biconvex, brick red coloured, film-coated tablet, with bevelled edges and 145/40 on one side. The diameter dimensions are 19.3 x 9.3 mm approximately and the tablet weight is about 840 mg.

The tablets are provided in carton boxes with blisters containing 10,30 or 90 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Viatris Healthcare Limited, Damastown Industrial Park, Mulhuddart, Dublin 15, Dublin, Ireland

Manufacturer:
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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.