Trilipix® 135 mg
Trilipix® 45 mg
modified release capsules

135 mg fenofibric acid
45 mg fenofibric acid

Trilipix 135mg modified-release capsules are hard gelatin capsules with a blue cap and a yellow body for oral administration. Each capsule contains choline fenofibrate as the active medical ingredient, which is equivalent to 135 mg of the corresponding fenofibric acid.

Trilipix 45mg modified-release capsules are hard gelatin capsules with a reddish brown cap and a yellow body for oral administration. Each capsule contains choline fenofibrate as the active medical ingredient, which is equivalent to 45 mg of the corresponding fenofibric acid.

Trilipix 135mg Excipients (non medicinal ingredients):
Capsule content: Hypromellose, povidone, hydroxypropyl cellulose, colloidal silicon dioxide, sodium stearyl fumarate, methacrylic acid copolymer, talc, triethyl citrate (E1505).
Capsule shell Trilipix 135mg: Yellow iron oxide (E172), titanium dioxide (E171), FD&C Blue number 2, gelatin.

Trilipix 45mg Excipients (non medicinal ingredients):
Capsule content: Hypromellose, povidone, hydroxypropyl cellulose, colloidal silicon dioxide, sodium stearyl fumarate, methacrylic acid copolymer, talc, triethyl citrate (E1505).
Capsule shell Trilipix 45mg: Yellow iron oxide (E172), titanium dioxide (E171), black iron oxide (E172), red iron oxide (E172), gelatin.

Indications

1. Co-administration Therapy with Statins for the Treatment of Mixed Dyslipdemia

Trilipix is indicated as an adjunct to diet in combination with a statin to reduce triglyceride (TG) and increase HDL-C in patients with mixed dyslipidemia and coronary heart disease (CHD) or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal.

CHD risk equivalents comprise:
- Other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic anueurysm, and symptomatic carotid artery disease);
- Diabetes;
- Multiple risk factors that confer a 10-year risk for CHD > 20%.

2. Treatment of Severe Hypertriglyceridemia

Trilipix is indicated as adjunctive therapy to diet to reduce TG in patients with severe hypertriglyceridemia. Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually obviate the need for pharmacological intervention. Markedly elevated levels of serum triglycerides (e.g. >2,000 mg/dL) may increase the risk of developing pancreatitis. The effect of Trilipix therapy on reducing this risk has not been adequately studied.

3. Treatment of Primary Hyperlipidemia or Mixed Dyslipidemia

Trilipix is indicated as adjunctive therapy to diet to reduce elevated LDL-C levels, total-cholesterol, TG and Apo B, and to increase HDL-C in patients with primary hyperlipidemia or mixed dyslipidemia.

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

Fenofibrate at a dose equivalent to 135 mg of Trilipix was not shown to reduce coronary heart disease morbidity and mortality in a large, randomized controlled trial of patients with type 2 diabetes mellitus.

Posology and method of administration
Patients should be placed on an appropriate lipid-lowering diet before receiving Trilipix as monotherapy or co-administered with a statin, and should continue this diet during treatment.
Trilipix modified release capsules can be taken without regard to meals.
Serum lipids should be monitored periodically.
The maximum dose is 135 mg once daily.

Adults
- Co-administration therapy with statins for the treatment of mixed dyslipidemia:
Trilipix 135 mg may be co-administered with an HMG-CoA reductase inhibitor (statin) in patients with mixed dyslipidemia. For convenience, the daily dose of Trilipix may be taken at the same time as a statin, according to the dosing recommendations for each medication. Co-administration with the maximum dose of a statin has not been evaluated in clinical studies and should be avoided unless the benefits are expected to outweigh the risks.

- Severe Hypertriglyceridemia
The initial dose of Trilipix is 45 to 135 mg once daily. Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at 4 to 8 week intervals. The maximum dose is 135 mg once daily.

- Primary Hyperlipidemia or Mixed Dyslipidemia
The dose of Trilipix is 135 mg once daily.

Elderly
Dose selection for the elderly should be made on the basis of renal function

Renal impairment
Treatment with Trilipix should be initiated at a dose of 45 mg once daily in patients with mild to moderate renal impairment (creatinine clearance 30-80ml/min) and should only be increased after evaluation of the effects on renal function and lipid levels at this dose. The use of Trilipix should be avoided in patients with severely impaired renal function.

Hepatic impairment
Patients with hepatic disease have not been studied.

Children
Trilipix is not recommended for use in children below age 18 due to a lack of data on safety and efficacy.

General Considerations for Treatment
Fenofibrate at a dose equivalent to 135mg of Trilipix was not shown to reduce coronary heart disease morbidity and mortality in a large, randomized controlled trial of patients with type 2 diabetes mellitus.

Laboratory studies should be performed to establish that lipid levels are abnormal before instituting Trilipix therapy.

Every reasonable attempt should be made to control serum lipids with non-drug methods including appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that may be contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides,

estrogens) should be discontinued or changed if possible, and excessive alcohol intake should be addressed before triglyceride-lowering drug therapy is considered. If the decision is made to use lipid-altering drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

Drug therapy is not indicated for patients who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of VLDL.

Contraindications
Trilipix is contraindicated in:
- patients witth severe renal insufficiency (creatinine clearance < 30 ml/min), including those receiving dialysis.
- patients with active live disease, including those with primary biliary cirrhosis and unexplained persistent liver function abnormalities.
- patients with preexisting gallbladder disease
- Nursing mothers
- patients with hypersensitivity to fenofibric acid, choline fenofibrate or fenofibrate .(see Warnings and precautions for use)

When Trilipix is co-administered with a statin, refer to the Contraindications section of the respective statin labeling.

Warnings and precautions for use
Skeletal muscles:
Fibrate and statin monotherapy increase the risk of myositis or myopathy, and have been associated with rhabdomyolysis. Data from observational studies suggest that the risk of rhabdomyolysis is increased when fibrates are co-administered with a statin (with a significantly higher rate observed for gemfibrozil). Refer to the respective statin labeling for important drug-drug interactions that increase statin levels and could increase this risk. The risk for serious muscle toxicity appears to be increased in elderly patients and in patients with diabetes, renal failure, or hypothyroidism.

Myalgia was reported in 3.3% of patients treated with Trilipix monotherapy and 3.1% to 3.5% of patients treated with Trilipix co-administered with statins compared to 4.7% to 6.1% of patients treated with statin monotherapy. Increases in creatine phosphokinase (CPK) to > 5 times upper limit of normal occurred in no patients treated with Trilipix monotherapy and 0.2% to 1.2% of patients treated with Trilipix co-administered with statins compared to 0.4% to 1.3% of patients treated with statin monotherapy.

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of CPK levels. Patients should promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and Trilipix and statin therapy should be discontinued if markedly elevated CPK levels occur or myopathy or myositis is diagnosed.

Renal Function:
Reversible elevations in serum creatinine have been reported in patients receiving Trilipix as monotherapy or co-administered with statins as well as patients receiving fenofibrate. In the pooled analysis of three double-blind controlled studies of Trilipix administered as monotherapy or in combination with statins, increases in creatinine to > 2 mg/dL occurred in 0.8% of patients treated with Trilipix monotherapy and 1.1% to 1.3% of patients treated with Trilipix co-administered with statins compared to 0% to 0.4% of patients treated with statin monotherapy. 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. The clinical significance of these observations is unknown.

Monitoring renal function in patients with renal impairment taking Trilipix is suggested. Renal monitoring should be considered for patients at risk for renal insufficiency, such as the elderly and those with diabetes.

Liver function
Trilipix at a dose of 135 mg once daily administered as monotherapy or co-administered with low to moderate doses of statins has been associated with increases in serum transaminases [AST (SGOT) or ALT (SGPT)]. Hepatocellular, chronic active and cholestatic hepatitis observed with fenofibrate therapy have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic active hepatitis.
Regular monitoring of liver function, including serum ALT (SGPT) and AST (SGPT) should be performed periodically for the duration of therapy with Trilipix, and therapy discontinued if enzyme levels persist above 3 times the upper limit of normal.

Pancreatitis
Pancreatitis has been reported in patients taking drugs of the fibrate class, including Trilipix. This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.

Mortality and Coronary Heart Disease Morbidity
The effect of Trilipix on CHD morbidity and mortality and non-cardiovascular mortality has not been established. Because of similarities between Trilipix and fenofibrate, clofibrate and gemfibrozil, the findings in the following large randomized, placebo-controlled clinical studies with these fibrate drugs may also apply to Trilipix.

The ACCORD trial was a randomized placebo-controlled study of 5518 patients with T2DM on background statin therapy treated with fenofibrate. The mean duration of follow-up was 4.7yrs. Fenofibrate plus statin combination therapy showed non-significant 8% RR reduction in MACE, a composite of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular disease death (hazard ratio [HR] 0.92, 95% CI 0.79-1.08) (p=0.32) as compared to statin monotherapy. In a gender subgroup analysis, HR for MACE in men receiving combination therapy vs. statin monotherapy was 0.82 (95% CI 0.69-0.99), and HR for MACE in women receiving combination therapy vs. statin alone was 1.38 (95% CI 0.98-1.94) (p=0.01). The clinical significance of this subgroup finding is unclear.

Interaction with other medicinal products and other forms of interaction
Oral Anticoagulants
Caution should be exercised when Trilipix is given in conjunction with oral coumarin anticoagulants. Trilipix may potentiate the anticoagulant effects of these agents resulting in prolongation of the prothrombin time/INR. Frequent monitoring of prothrombin time/INR and dose adjustment of the oral anticoagulant are recommended until the prothrombin time/INR has stabilized in order to prevent bleeding complications.

Cyclosporine
Because cyclosporine can produce nephrotoxicity with decreases in creatinine clearance and rises in serum creatinine, and because renal excretion is the primary elimination route of drugs of the fibrate class including Trilipix, there is a risk that an interaction will lead to decline of renal function. The benefits and risks of using Trilipix with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed.

Statins: The risk of serious muscle toxicity may be increased if fenofibrate or fenofibric acid is used concomitantly with HMG-CoA reductase inhibitors. Such combination therapy should be used with caution and patients monitored closely for signs of muscle toxicity (See section 4.4.). Specific studies in healthy volunteers have demonstrated the absence of clinically relevant pharmacokinetic interaction with lipid lowering agents such as HMG-CoA reductase inhibitors

(atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin) and ezetimibe, however a pharmacodynamic interaction cannot be excluded. No dosing adjustment is then required for Trilipix or the co-administered drugs.

Oral hypoglycaemic agents: In healthy volunteers, no clinically relevant pharmacokinetic interactions have been shown between fenofibrate or fenofibric acid and rosiglitazone, metformin or glimepiride, No dosing adjustment is required for Trilipix or the co-administered drugs.

Gastrointestinal agents: In healthy volunteers, no clinically relevant pharmacokinetic interactions have been shown between fenofibrate or fenofibric acid and omeprazole.

In vitro studies using human liver microsomes indicate that fenofibric acid is not an inhibitor of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. It is a weak inhibitor of CYP2C8, CYP2C19, and CYP2A6, and mild-to-moderate inhibitor of CYP2C9 at therapeutic concentrations.

Comparison of atorvastatin exposures when atorvastatin (80mg QD for 10 days) is given in combination with fenofibric acid (Trilipix 135mg QD for 10 days) and ezetimibe (10mg QD for 10 days) versus when atorvastatin is given in combination with ezetimibe only (ezetimibe 10mg QD and atorvastatin, 80mg QD for 10 days): The C_{max} decreased by 1% for atorvastatin and ortho-hydroxy-atorvastatin and increased by 2% for para-hydroxy-atorvastatin. The AUC decreased 6% and 9% for atorvastatin and ortho-hydroxy-atorvastatin, respectively, and did not change for para-hydroxy-atorvastatin.

Comparison of ezetimibe exposures when ezetimibe (10mg QD for 10 days) is given in combination with fenofibric acid (Trilipix 135mg QD for 10 days) and atorvastatin (80mg QD for 10 days) versus when ezetimibe is given in combination with atorvastatin only (ezetimibe 10mg QD and atorvastatin, 80mg QD for 10 days): The C_{max} increased by 26% and 7% for total and free ezetimibe, respectively. The AUC increased by 27% and 12% for total and free ezetimibe, respectively.

Table 1. Effects of Co-Administered Drugs on Fenofibric Acid Systemic Exposure from Trilipix or Fenofibrate Administration

Co-Administered Drug	Dosage Regimen of Co-Administered Drug	Dosage Regimen of Trilipix or Fenofibrate	Changes in Fenofibric Acid Exposure	
			AUC	C_{max}
Lipid-lowering agents				
Rosuvastatin	40mg QD for 10 days	Trilipix 135mg QD for 10 days	↓ 2%	↓ 2%
Atorvastatin	20mg QD for 10 days	Fenofibrate 160mg[1] QD for 10 days	↓ 2%	↓ 4%
Atorvastatin + ezetimibe	Atorvastatin, 80mg QD and ezetimibe, 10mg QD for 10 days	Trilipix 135mg QD for 10 days	↑ 5%	↑ 5%
Pravastatin	40mg as a single dose	Fenofibrate 3 x 67mg[2] as a single dose	↓ 1%	↓ 2%
Fluvastatin	40mg as a single dose	Fenofibrate 160mg[1] as a single dose	↓ 2%	↓ 10%
Simvastatin	80mg QD for 7 days	Fenofibrate 160mg[1] QD for 7 days	↓ 5%	↓ 11%
Anti-diabetic agents				
Glimepiride	1mg as a single dose	Fenofibrate 145mg[1] QD for 10 days	↑ 1%	↓ 1%
Metformin	850mg TID for 10	Fenofibrate 54mg[1]	↓ 9%	↓ 6%

	days	TID for 10 days		
Rosiglitazone	8mg QD for 5 days	Fenofibrate 145mg[1] QD for 14 days	↑ 10%	↑ 3%
Gastrointestinal agents				
Omeprazole	40mg QD for 5 days	Trilipix 135mg as a single dose fasting	↑ 6%	↑ 17%
Omeprazole	40mg QD for 5 days	Trilipix 135mg as a single dose with food	↑ 4%	↓ 2%

[1] TriCor (fenofibrate) oral tablet
[2] TriCor (fenofibrate) oral micronized capsule

Table 2. Effects of Trilipix of Fenofibrate Co-Administration on Systemic Exposure of Other Drugs

Dosage Regimen of Trilipix or Fenofibrate	Dosage Regimen of Co-Administered Drug	Changes in Co-Administered Drug Exposure		
		Analyte	AUC	C_{max}
Lipid-lowering agents				
Trilipix 135mg QD for 10 days	Rosuvastatin, 40mg QD for 10 days	Rosuvastatin	↑ 6%	↑ 20%
Fenofibrate 160mg[1] QD for 10 days	Atorvastatin, 20mg QD for 10 days	Atorvastatin	↓ 17%	0%
Fenofibrate 3 x 67mg[2]	Pravastatin, 40mg as a single dose	Pravastatin	↑ 13%	↑ 13%
		3α Hydroxyliso-pravastatin	↑ 26%	↑ 29%
Fenofibrate 160mg[1] as a single dose	Fluvastatin, 40mg as a single dose	(+) -3R,5S-Fluvastatin	↑ 15%	↑ 16%
Fenofibrate 160mg[1] QD for 7 days	Simvastatin, 80mg QD for 7 days	Simvastatin Acid	↓ 36%	↓ 11%
		Simvastatin	↓ 11%	↓ 17%
		Active HMG-CoA Inhibitors	↓ 12%	↓ 1%
		Total HMG-CoA Inhibitors	↓ 8%	↓ 10%
Anti-diabetic agents				
Fenofibrate 145mg[1] QD for 10 days	Glimepiride, 1mg as a single dose	Glimepiride	↑ 36%	↑ 18%
Fenofibrate 54mg[1] TID for 10 days	Metformin, 850mg TID for 10 days	Metformin	↑ 3%	↑ 6%
Fenofibrate 145mg[1] QD for 14 days	Rosiglitazone, 8mg QD for 5 days	Rosiglitazone	↑ 6%	↓ 1%

[1] TriCor (fenofibrate) oral tablet
[2] TriCor (fenofibrate) oral micronized capsule

Pregnancy and Lactation
Pregnancy Category: C
The safety of Trilipix in pregnant women has not been established.There are no adequate and well controlled studies of Trilipix in pregnant women. Trilipix should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When Trilipix is administered with a statin in a woman of childbearing potential, refer to pregnancy category and product labeling for the statin. All statins are contraindicated in pregnant women.

In pregnant rats given oral dietary doses of 14, 127, and 361 mg/kg/day from gestation day 6-15 during the period of organogenesis, adverse developmental findings were not observed at

14mg/kg/day (less than 1 times the maximum recommended human dose [MRHD], based on body surface area comparisons; mg/m^2). At higher multiples of human doses evidence of maternal toxicity was observed.

In pregnant rabbits given oral gavage doses of 15, 150, and 300mg/kg/day from gestation day 6-18 during the period of organogenisis and allowed to deliver, aborted litters were observed at 150mg/kg/day (10 times the MRHD, based on body surface area comparisons; mg/m^2). No developmental findings were observed at 15mg/kg/day (at less than 1 times the MRHD, based on body surface area comparison; mg/m^2).

In pregnany rats given oral dietary doses of 15, 75, and 300mg/kg/day from gestation day 15 through lactation day 21 (weaning), maternal toxicity was observed at less than 1 times the MRHD, based on body surface area comparisons; mg/m^2.

Nursing Mothers
Trilipix should not be used in nursing mothers. A decision should be made whether to discontinue nursing or to discontinue the drug.

It is unknown whether fenofibric acid is excreted in human breast milk. The excretion of Fenofibric acid in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Trilipix should be made taking into account the benefit of breast-feeding to the child and the benefit of Trilipix therapy to the woman.

Effects on ability to drive and use machines
Trilipix has no or negligible influence on the ability to drive and use machines

Adverse Reactions

Clinical Studies Experience
Because clinical studies are conducted under widely varying conditions, adverse event rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug.

Trilipix ® (fenofibric acid)
Monotherapy
Treatment-emergent adverse events reported in 3% or more of patients treated with Trilipix during the randomized controlled trials are listed in Table 3 below.

Co-Administration Therapy with Statins (Double-blind Controlled Trials)
Treatment-emergent adverse events reported in 3% or more of patients treated with Trilipix co¬administered with statins during the randomized controlled trials are listed in Table 3 below.

Table 3: Treatment-Emergent Adverse Events Reported in ≥ 3% of Patients Receiving Trilipix or Trilipix Co-Administered with a Statin During Double-Blind Controlled Studies [Number (%)]

Adverse event	Trilipix (n=490)	Low dose statin* (n=493)	Trilipix + low dose statin* (n=490)	Moderate dose statin (n=491)**	Trilipix + moderate dose statin** (n=489)	High dose statin*** (n=245)
Gastrointestinal disorders						
Constipation	16 (3.3)	11 (2.2)	16 (3.3)	13 (2.6)	15 (3.1)	6 (2.4)
Diarrhea	19 (3.9)	16 (3.2)	15 (3.1)	24 (4.9)	18 (3.7)	17 (6.9)
Dyspepsia	18 (3.7)	13 (2.6)	13 (2.7)	17 (3.5)	23 (4.7)	6 (2.4)

Nausea	21 (4.3)	18 (3.7)	17 (3.5)	22 (4.5)	27 (5.5)	10 4.1)
General disorders and administration site conditions						
Fatigue	10 (2.0)	13 (2.6)	13 (2.7)	13 (2.6)	16 (3.3)	5 (2.0)
Pain	17 (3.5)	9 (1.8)	16 (3.3)	8 (1.6)	7 (1.4)	8 (3.3)
Infections and infestations						
Nasopharyngitis	17 (3.5)	29 (5.9)	23 (4.7)	16 (3.3)	21 (4.3)	9 (3.7)
Sinusitis	16 (3.3)	4 (0.8)	14 (2.9)	8 (1.6)	17 (3.5)	4 (1.6)
Upper respiratory tact infection	26 (5.3)	13 (2.6)	18 (3.7)	23 (4.7)	23 (4.7)	7 (2.9)
Investigations						
ALT increased	6 (1.2)	2 (0.4)	15 (3.1)	2 (0.4)	12 (2.5)	4 (1.6)
Musculoskeletal and connective tissue disorders						
Arthralgia	19 (3.9)	22 (4.5)	21 (4.3)	21 (4.3)	17 (3.5)	12 (4.9)
Back pain	31 (6.3)	31 (6.3)	30 (6.1)	32 (6.5)	20 (4.1)	8 (3.3)
Muscle spams	8 (1.6)	18 (3.7)	12 (2.4)	24 (4.9)	15 (3.1)	6 (2.4)
Myalgia	16 (3.3)	24 (4.9)	17 (3.5)	23 (4.7)	15 (3.1)	15 (6.1)
Pain in extremity	22 (4.5)	24 (4.9)	14 (2.9)	21 (4.3)	13 (2.7)	9 (3.7)
Nervous system disorders						
Dizziness	20 (4.1)	8 (1.6)	19 (3.9)	11 (2.2)	16 (3.3)	2 (0.8)
Headache	62 (12.7)	64 (13.0)	64 (13.1)	82 (16.1)	58 (11.9)	32 (13.1)

*Low dose statin: rosuvastatin 10 mg, simvastatin 20 mg, or atorvastatin 20 mg
**Moderatedose statin: rosuvastatin 20 mg, simvastatin 40 mg, or atorvastatin 40 mg
***High dose statin: rosuvastatin 40 mg, simvastatin 80 mg, or atorvastatin 80 mg

Co-Administration Therapy with Statins (Long-Term Exposure for up to 64 Weeks)
Patients successfully completing any one of the three double-blind, controlled studies were eligible to participate in a 52-week long-term extension study where they received Trilipix co-administered with the moderate dose statin. A total of 2201 patients received at least one dose of Trilipix co-administered with a statin in the double-blind controlled study or the long-term extension study for up to a total of 64 weeks of treatment. Additional treatment-emergent adverse events (not listed in Table 3 above) reported in 3% or more of patients receiving Trilipix co-administered with a statin in either the double-blind controlled studies or the long-term extension study are provided below.

Infections and Infestations: Bronchitis, influenza, and urinary tract infection.
Investigations: AST increased, blood CPK increased, and hepatic enzyme increased.
Musculoskeletal and Connective Tissue Disorders: Musculoskeletal pain.
Psychiatric disorders: Insomnia.
Respiratory, Thoracic, and Mediastinal Disorders: Cough and pharyngolaryngeal pain.
Vascular Disorders: Hypertension.

Fenofibrate
Fenofibric acid is the active metabolite of fenofibrate. The following undesirable effects have been observed during placebo-controlled clinical trials using fenofibrate (n=2344) with the below indicated frequencies:

MedDra system organ class	Very Common (≥1/10)	Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100);	Rare (≥1/10,000, <1/1,000)	Very rare (<1/10,000), including isolated reports
Blood and lymphatic system disorders				Haemoglobin decreased White blood cell count decreased	
Immune System disorder				Hypersensitivity	
Nervous system disorders			Headache		
Vascular disorders			Thromboembolism (pulmonary embolism, deep vein thrombosis)**		
Gastrointestinal disorders		Gastrointestinal signs and symptoms (abdominal pain, nausea, vomiting, diarrhoea, flatulence)	Pancreatitis*		
Hepatobiliary disorders		Transaminases increased (see section 4.4)	Cholelithiasis (see section 4.4)	Hepatitis	
Skin and subcutaneous tissue disorders			Cutaneous hypersensitivity (e.g. rashes, pruritus, urticaria)	Alopecia Photosensitivity reactions	
Musculoskeletal connective tissue and bone disorders			Muscle disorders (e.g myalgia, myositis, muscular spasms and weakness)		
Reproductive system and breast disorders			Sexual dysfunction		
Investigations	Blood Homocysteine level increased***		Blood creatinine increased	Blood urea increased	

* In the FIELD-study, a randomized placebo-controlled trial performed in 9795 patients with type 2 diabetes mellitus, a statistically significant increase in pancreatitis cases was observed in patients receiving fenofibrate versus patients receiving placebo (0.8% versus 0.5%; p = 0.031).

** In the same study, a statistically significant increase was reported in the incidence of pulmonary embolism (0.7% in the placebo group versus 1.1% in the fenofibrate group; p = 0.022)

and a statistically non-significant increase in deep vein thromboses (placebo: 1.0 % [48/4900 patients] versus fenofibrate 1.4% [67/4895 patients]; p=0.074)

*** the average increase in blood homocysteine level in patients treated with fenofibrate was 6.5 µmol/L, and was reversible on discontinuation of fenofibrate treatment. The increased risk of venous thrombotic events may be related to the increased homocysteine level. The clinical significance of this is not clear.

In addition to those events reported during clinical trials, the following side effects have been reported spontaneously during postmarketing use of fenofibrate. A precise frequency cannot be estimated from the available data and is therefore classified as “not known”.
- **Respiratory, thoracic and mediastinal disorders**: Interstitial lung disease
- **Musculoskeletal, connective tissue and bone disorders**: Rhabdomyolysis
- **Hepatobiliary disorders**: jaundice, complications of cholelithiasis (e.g. cholecystitis, cholangitis, biliary colic).
- **Skin and Subcutaneous Tissue Disorders**: severe cutaneous reactions (e.g. erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis)
- **Nervous system disorders**: Fatigue

Overdose
There is no specific treatment for overdose with Trilipix. General supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status, should an overdose occur. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Because Trilipix is highly bound to plasma proteins, hemodialysis should not be considered.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: Serum Lipid Reducing Agents / Cholesterol and Triglycerides Reducers / Fibrates.
ATC code: C10AB

The active moiety of Trilipix is fenofibric acid. The pharmacological effects of fenofibric acid in both animals and humans have been extensively studied through oral administration of fenofibrate.
The lipid-modifying effects of fenofibric acid seen in clinical practice have been explained in vivo in transgenic mice and in vitro in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor α (PPARα). Through this mechanism, fenofibric acid increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of Apo CIII (an inhibitor of lipoprotein lipase activity).

The resulting decrease in TG produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPARα also induces an increase in the synthesis of HDL-C and Apo AI and AII.

Elevated levels of Total-C, LDL-C, and Apo B, and decreased levels of HDL-C and its transport complex, Apo AI and Apo AII, are risk factors for human atherosclerosis. Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the levels of Total-C, LDL-C, and TG, and inversely with the level of HDL-C. The independent effect of raising HDL-C or lowering TG on the risk of cardiovascular morbidity and mortality has not been determined.

Pharmacokinetic properties

Trilipix contains fenofibric acid, which is the only circulating pharmacologically active moiety in plasma after oral administration of Trilipix. Fenofibric acid is also the circulating pharmacologically active moiety in plasma after oral administration of fenofibrate, the ester of fenofibric acid.

Plasma concentrations of fenofibric acid after administration of one 135 mg Trilipix delayed release capsule are equivalent to those after one 200 mg capsule of micronized fenofibrate administered under fed conditions.

Absorption: Fenofibric acid is well absorbed throughout the gastrointestinal tract. The absolute bioavailability of fenofibric acid is approximately 81%.

Peak plasma levels of fenofibric acid occur within 4 to 5 hours after a single dose administration of Trilipix capsule under fasting conditions.

Fenofibric acid exposure in plasma, as measured by Cmax and AUC, is not significantly different when a single 135 mg dose of Trilipix is administered under fasting or nonfasting conditions.

Distribution: Upon multiple dosing of Trilipix, fenofibric acid levels reach steady state within 8 days. Plasma concentrations of fenofibric acid at steady state are approximately slightly more than double those following a single dose. Serum protein binding is approximately 99% in normal and dyslipidemic subjects.

Metabolism: Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine.

In vivo metabolism data after fenofibrate administration indicate that fenofibric acid does not undergo oxidative metabolism (e.g. cytochrome P450) to a significant extent.

Excretion: After absorption, Trilipix is primarily excreted in the urine in the form of fenofibric acid and fenofibric acid glucuronide.

Fenofibric acid is eliminated with a half-life of approximately 20 hours, allowing once daily administration of Trilipix.

Specific Populations:
Geriatrics: In five elderly volunteers 77 to 87 years of age, the oral clearance of fenofibric acid following a single oral dose of fenofibrate was 1.2 L/h, which compares to 1.1 L/h in young adults. This indicates that an equivalent dose of Trilipix can be used in elderly subjects with normal renal function, without increasing accumulation of the drug or metabolites

Renal Impairment: The pharmacokinetics of fenofibric acid was examined in patients with mild, moderate, and severe renal impairment. Patients with severe renal impairment (creatinine clearance [CrCl] < 30 mL/min showed a 2.7-fold increase in exposure for fenofibric acid and increased accumulation of fenofibric acid during chronic dosing compared to that of healthy subjects. Patients with mild to moderate renal impairment (CrCl 30-80 mL/min) had similar exposure but an increase in the half-life for fenofibric acid compared to that of healthy subjects. Based on these findings, the use of Trilipix should be avoided in patients who have severe renal impairment and dose reduction is required in patients having mild to moderate renal impairment.

Preclinical safety data
Fenofibric acid
Because fenofibrate is rapidly converted to its active metabolite, fenofibric acid, either during or immediately following absorption both in animals and humans, studies conducted with fenofibrate are relevant for the assessment of the toxicity profile of fenofibric acid. The systemic toxicity of fenofibrate and fenofibric acid in animal studies is comparable.

Fenofibrate
Chronic toxicity studies have yielded no relevant information about specific toxicity of fenofibrate.
Studies on mutagenicity of fenofibrate have been negative.
In rats and mice, liver tumours have been found at high dosages, which are attributable to peroxisome proliferation. These changes are specific to small rodents and have not been observed in other animal species. This is of no relevance to therapeutic use in man.
Studies in mice, rats and rabbits did not reveal any teratogenic effect. Embryotoxic effects were observed at doses in the range of maternal toxicity. Prolongation of the gestation period and difficulties during delivery were observed at high doses. No sign of any effect on fertility has been detected.

Incompatibilities
Not applicable.

Shelf life and storage conditions
Store in the original package at a temperature below 30°C.
Do not use the medicine after the expiry date stated on the carton.
Store in the original package.
Keep this medicine out of the sight and reach of children.

Pack sizes
Trilipix 135 mg comes in carton boxes with blister strips containing 30 capsules
Trilipix 45 mg comes in carton boxes with blister strips containing 30 capsules
The blisters in the carton boxes are made of aluminium with aluminium lidding foil,

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

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Manufactured by:
Fournier Laboratories Ireland Ltd.,
Anngrove, Carrigtwohill, Co. Cork, Ireland

Packaged and released by:
Mylan Laboratories SAS
Route de Belleville
Lieu-dit Maillard
01400 Châtillon-sur-Chalaronne – FRANCE