TRILIPIX®

Choline fenofibrate 135 mg delayed release capsule

1. NAME OF THE MEDICINAL PRODUCT

Trilipix® 45 mg delayed release capsule
Trilipix® 135 mg delayed release capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each delayed release capsule contains choline fenofibrate equivalent to 45 or 135 mg of fenofibric acid.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard, delayed release capsule, with 45 mg and 135 mg choline fenofibrate, respectively.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Trilipix® is indicated for mixed dyslipidemia in addition to lifestyle modification and statin, in patients with high cardiovascular risk dyslipidemia (Frederickson type IIb): Triglyceride ≥ 150 mg/dL (≥1.69 mmol/L), High Density Lipoprotein-C < 40 mg/dL (< 1.02 mmol/L) in males or < 50 mg/dL (< 1.28 mmol/L) in females, and Low Density Lipoprotein-C ≥130 mg/dL (≥ 3.37 mmol/L); obesity (BMI > 25 kg/m^2), diabetes mellitus, coronary heart disease) when triglyceride is not adequately controlled.

4.2 Posology and method of administration

Patients should be placed on an appropriate lipid-lowering diet before receiving Trilipix® as co-administered with a statin, and should continue this diet during treatment. Trilipix® delayed release capsule 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.

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.

4.3 Contraindications

- Patients with severe renal impairment (creatinine clearance < 30 ml/min), including those receiving dialysis
- Liver disease (including biliary cirrhosis and unexplained persistent liver function abnormality), and hepatic insufficiency,
- Gallbladder disease,
- Chronic or acute pancreatitis with the exception of acute pancreatitis due to severe hypertriglyceridemia,
- Known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen
- Hypersensitivity to the active substance (fenofibric acid, choline fenofibrate), fenofibrate or to any of the excipients,
- Nursing mothers.

As Trilipix® is co-administered with statins, refer to the Contraindications section of the respective statin labeling.

4.4 Special 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. 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.

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 (level exceeding 5 times the upper limit of the normal range) occur or myopathy or myositis is diagnosed.

Renal Function

Reversible elevations in serum creatinine have been reported in patients receiving Trilipix® as co-administered with statins as well as patients receiving fenofibrate. 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 recommended. Renal monitoring should be considered for patients at risk for renal insufficiency, such as the elderly and those with diabetes. Treatment should be interrupted in case of an increase in creatinine levels > 50% of upper limit of normal. It is recommended that creatinine is measured during the first 3 months after initiation of treatment and thereafter periodically.

Liver Function

Trilipix® at a dose of 135 mg once daily, 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 coronary heart disease 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 Action to Control Cardiovascular Risk in Diabetes Lipid (ACCORD Lipid) trial was a randomized placebo-controlled study of 5518 patients with type 2 diabetes mellitus on background statin therapy treated with fenofibrate. The mean duration of follow-up was 4.7 years. Fenofibrate plus statin combination therapy showed a non-significant 8% relative risk reduction in the primary outcome of major adverse cardiovascular events (MACE), a composite of non- fatal myocardial infarction, non-fatal stroke, and cardiovascular disease death (hazard ratio [HR] 0.92, 95% CI 0.79-1.08) (p = 0.32) as compared to statin monotherapy. In a gender subgroup analysis, the hazard ratio for MACE in men receiving combination therapy versus statin monotherapy was 0.82 (95% CI 0.69-0.99), and the hazard ratio for MACE in women receiving combination therapy versus statin monotherapy was 1.38 (95% CI 0.98-1.94) (interaction p = 0.01). The clinical significance of this subgroup finding is unclear.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was a 5-year randomized, placebo-controlled study of 9795 patients with type 2 diabetes mellitus treated with fenofibrate. Fenofibrate demonstrated a non-significant 11% relative reduction in the primary outcome of coronary heart disease events (hazard ratio [HR] 0.89, 95% CI 0.75-1.05, p = 0.16) and a significant 11% reduction in the secondary outcome of total cardiovascular disease events (HR 0.89 [0.80-0.99], p = 0.04). There was a non-significant 11% (HR 1.11 [0.95, 1.29], p = 0.18) and 19% (HR 1.19 (0.90, 1.57], p = 0.22) increase in total and coronary heart disease mortality, respectively, with

fenofibrate as compared to placebo.

In the Coronary Drug Project, a large study of post-myocardial infarction patients treated for 5 years with clofibrate, there was no difference in mortality seen between the clofibrate group and the placebo group. There was, however, a difference in the rate of cholelithiasis and cholecystitis requiring surgery between the two groups (3.0% vs.1.8%).

In a study conducted by the World Health Organization (WHO), 5000 subjects without known coronary artery disease were treated with placebo or clofibrate for 5 years and followed for an additional one year. There was a statistically significant, higher age-adjusted all-cause mortality in the clofibrate group compared with the placebo group (5.70% vs. 3.96%, p = < 0.01). Excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy, postcholecystectomy complications, and pancreatitis. This appeared to confirm the higher risk of gallbladder disease seen in clofibrate-treated patients studied in the Coronary Drug Project.

The Helsinki Heart Study was a large (N = 4081) study of middle-aged men without a history of coronary artery disease. Subjects received either placebo or gemfibrozil for 5 years, with a 3.5 year open extension afterward. Total mortality was numerically higher in the gemfibrozil randomization group but did not achieve statistical significance (p = 0.19, 95% confidence interval for relative risk G:P = 0.91-1.64). Although cancer deaths trended higher in the gemfibrozil group (p = 0.11), cancers (excluding basal cell carcinoma) were diagnosed with equal frequency in both study groups. Due to the limited size of the study, the relative risk of death from any cause was not shown to be different than that seen in the 9 year follow-up data from WHO study (RR = l.29). A secondary prevention component of the Helsinki Heart Study enrolled middle-aged men excluded from the primary prevention study because of known or suspected coronary heart disease. Subjects received gemfibrozil or placebo for 5 years. Although cardiac deaths trended higher in the gemfibrozil group, this was not statistically significant (hazard ratio 2.2, 95% confidence interval: 0.94-5.05).

Serum Creatinine

Reversible elevations in serum creatinine have been reported in patients receiving Trilipix® as well as patients receiving fenofibrate. In the pooled analysis of three 12-week, double-blind, controlled studies of Trilipix®, increases in creatinine to > 2 mg/dL occurred in 0.8% of patients treated with Trilipix® without other lipid-altering drugs. 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.

Cholelithiasis

Trilipix®, like fenofibrate, clofibrate, and gemfibrozil, may increase cholesterol excretion into the bile, potentially leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Trilipix® therapy should be discontinued if gallstones are found.

Coumarin 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/International Normalized Ratio (PT/INR). Frequent monitoring of PT/INR and dose adjustment of the oral anticoagulant are recommended until the PT/INR has stabilized in order to prevent bleeding complications.

Hematological Changes

Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of Trilipix® and fenofibrate therapy. However, these levels stabilize during long-term administration. Thrombocytopenia and agranulocytosis have been reported in individuals treated with fenofibrates. Periodic monitoring of red and white blood cell counts are recommended during the first 12 months of Trilipix® administration.

Hypersensitivity Reactions

- Acute Hypersensitivity
  Anaphylaxis and angioedema have been reported post-marketing with fenofibrate. In some cases, reactions were life-threatening and required emergency treatment. If a patient develops signs or symptoms of an acute hypersensitivity reaction, advise them to seek immediate medical attention and discontinue fenofibrate.
- Delayed Hypersensitivity
  Severe cutaneous adverse drug reactions (SCAR), including Stevens-Johnson syndrome, toxic epidermal necrolysis, and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), have been reported post-marketing, occurring days to weeks after initiation of fenofibrate. The cases of DRESS were associated with cutaneous reactions (such as rash or exfoliative dermatitis) and a combination of eosinophilia, fever, systemic organ involvement (renal, hepatic, or respiratory). Discontinue fenofibrate and treat patients appropriately if SCAR is suspected.

Venothromboembolic Disease

In the FIELD trial, pulmonary embolus (PE) and deep vein thrombosis (DVT) were observed at higher rates in the fenofibrate-than the placebo-treated group. Of 9795 patients enrolled in FIELD, there were 4900 in the placebo group and 4895 in the fenofibrate group. For DVT, there were 48 events (1 %) in the placebo group and 67 (1%) in the fenofibrate group ($p = 0.074$); and for PE, there were 32 (0.7%) events in the placebo group and 53 (1%) in the fenofibrate group ($p = 0.022$).
In the Coronary Drug Project, a higher proportion of the clofibrate group experienced definite or suspected fatal or nonfatal PE or thrombophlebitis than the placebo group (5.2% vs. 3.3% at five years; $p < 0.01$).

Paradoxical Decreases in HDL Cholesterol Levels

There have been post-rnarketing and clinical trial reports of severe decreases in HDL cholesterol levels (as low as 2 mg/dL) occurring in diabetic and non-diabetic patients initiated on fibrate therapy. The decrease in HDL-C is mirrored by a decrease in apolipoprotein Al. This decrease has been reported to occur within 2 weeks to years after initiation of fibrate therapy. The HDL-C levels remain depressed until fibrate therapy has been withdrawn; the response to withdrawal of fibrate therapy is rapid and sustained. The clinical significance of this decrease in HDL-C is unknown. It is recommended that HDL-C levels be checked within the first few months after initiation of fibrate therapy. If a severely depressed HDL-C level is detected, fibrate therapy should be withdrawn, and the HDL-C level monitored until it has returned to baseline, and fibrate therapy should not be re-initiated.

4.5 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.

Immunosuppressants

Immunosuppressants such as cyclosporine and tacrolimus 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 deterioration 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.

Glitazones:

Some cases of reversible paradoxical reduction of HDL-cholesterol have been reported during concomitant administration of fenofibrate and glitazones. Therefore, it is recommended to monitor HDL-cholesterol if one of these components is added to the other and stopping of either therapy if HDL-cholesterol is too low.

Gastrointestinal agents

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

Cytochrome P450 enzyme system:

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.

Bile Acid Binding Resins

Since bile acid binding resins may bind other drugs given concurrently, patients should take Trilipix® at least 1 hour before or 4 to 6 hours after a bile acid resin to avoid impeding its absorption.

Colchicine

Cases of myopathy, including rhabdomyolysis, have been reported with fenofibrates co- administered with colchicine, and caution should be exercised when prescribing fenofibrate with colchicine.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of Trilipix® in pregnant women. Animal studies have not demonstrated any teratogenic effects. Embryotoxic effects have been shown at doses in the range of maternal toxicity (see section 5.3 Preclinical safety data). The potential risk for humans is unknown. Therefore, Trilipix® should only be used during pregnancy after a careful benefit/risk assessment.

Lactation

It is unknown whether choline fenofibrate and/or its metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Therefore, fenofibrate should not be used during breast-feeding.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical Studies Experience with Trilipix® (fenofibric acid)

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 1 below.

Table 1: 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 tract 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 1 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 incl. isolated reports

Blood and lymphatic system disorders				Decreased in haemoglobin Decreased white blood cell count	
Immune system				Hypersensitivity	
Nervous system disorders			Headache		
Vascular disorders			Thrombo-embolism (pulmonary embolism, deep vein thrombosis)*		
Gastrointestinal disorders		Gastrointestinal signs and symptoms (abdominal pain, nausea, vomiting, diarrhoea, flatulence)	Pancreatitis*		
Hepatobiliary disorders		Increased transaminases	Cholelithiasis	Hepatitis	
Skin and subcutaneous tissue disorders			Cutaneous hypersensitivity (e.g. Rashes, pruritus, urticaria)	Alopecia, photosensitivity reactions	
Musculoskeletal, connective tissue and bone disorders			Muscle disorder (e.g. myalgia, myositis, muscular spasms and weakness)		
Reproductive system and breast disorders			Sexual dysfunction		
Investigations	Blood homocysteine level increased***		Increased blood creatinine	Increased blood urea	

* 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).

**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 µ mol/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 post-marketing 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

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Serum Lipid Reducing Agents/Cholesterol and Triglycerides Reducers/Fibrates.

ATC code: C10AB11

Properties of the active moiety

The active moiety of Trilipix® is fenofibric acid. The pharmacological effects of fenofibric acid in both animals and humans have been studied through oral administration of fenofibrate.

Mechanism of action

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.

Clinical efficacy

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.

There is evidence that treatment with fibrates may reduce coronary heart disease events but they have not been shown to decrease all cause mortality in the primary or secondary prevention of cardiovascular disease.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid trial was a randomized placebo-controlled study of 5518 patients with type 2 diabetes mellitus treated with fenofibrate in addition to simvastatin. Fenofibrate plus simvastatin therapy did not show any significant differences compared to simvastatin monotherapy in the composite primary outcome of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death (hazard ratio [HR] 0.92, 95% CI 0.79-1.08, p = 0.32; absolute risk reduction: 0.74%). In the pre-specified subgroup of dyslipidaemic patients, defined as those in the lowest tertile of HDL-C (≤ 34 mg/dl or 0.88 mmol/L) and highest tertile of TG (≥ 204 mg/dl or 2.3 mmol/L) at baseline, fenofibrate plus simvastatin therapy demonstrated a 31% relative reduction compared to simvastatin monotherapy for the composite primary outcome (hazard ratio [HR] 0.69, 95% CI 0.49-0.97, p = 0.03; absolute risk reduction: 4.95%). Another prespecified subgroup analysis identified a statistically significant treatment-by-gender interaction (p = 0.01) indicating a possible treatment benefit of combination therapy in men (p = 0.037) but a potentially higher risk for the primary outcome in women treated with combination therapy compared to simvastatin monotherapy (p=0.069). This was not observed in the aforementioned subgroup of patients with dyslipidaemia but there was also no clear evidence of benefit in dyslipidaemic women treated with fenofibrate plus simvastatin, and a possible harmful effect in this subgroup could not be excluded.

5.2 Pharmacokinetic properties

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 Trilipix® 135 mg 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%.
Maximum plasma levels of fenofibric acid occur within 4 to 5 hours after a single dose administration of Trilipix® delayed release 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.

Pediatrics: The pharmacokinetics of Trilipix® has not been studied in pediatric populations.

Gender: No pharmacokinetic difference between males and females has been observed for Trilipix®.

Race: The influence of race on the pharmacokinetics of Trilipix® has not been studied; however, fenofibric acid is not metabolized by enzymes known for exhibiting inter-ethnic variability.

Hepatic Impairment: No pharmacokinetic studies have been conducted in patients with hepatic impairment.

5.3 Preclinical safety data

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.

Acute toxicity studies have yielded no relevant information about specific toxicity of fenofibric acid. 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 and increased postnatal losses were observed at high doses showing clear maternal toxicity.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Delayed release capsule content:
Hypromellose
Povidone
Hydroxypropyl cellulose
Silica, colloidal anhydrous
Sodium stearyl fumarate
Methacrylic acid copolymer
Talc
Triethyl citrate

Capsule shell Trilipix® 45 mg:
Yellow iron oxide
Titanium dioxide
Black iron oxide
Red iron oxide
Gelatin

Capsule shell Trilipix® 135 mg:
Yellow iron oxide
Titanium dioxide
FD&C Blue #2
Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life : The expiry date is indicated on the packaging

6.4 Special precautions for storage

Store in the original container. Store below 30°C.

6.5 Nature and contents of container

Trilipix® 45 mg: Box of 30 delayed release capsules in blisters each with 10 delayed release capsules.

Trilipix® 135 mg: Box of 30 delayed release capsules in blisters each with 10 delayed release capsules.
The blisters are made of aluminium.

6.6 Special precautions for disposal and other handling
Delayed release capsules of Trilipix® 45 mg with a reddish brown cap and a yellow body.
Delayed release capsules of Trilipix® 135 mg with a blue cap and a yellow body.

HARUS DENGAN RESEP DOKTER
Reg No:
Trilipix 45 mg : DKI1927000703A1
Trilipix 135 mg : DKI1927000703B1

Manufactured by:
Fournier Laboratories Ireland Limited, Carrigtwohill, Co. Cork, Ireland

Packed and release by:
Mylan Laboratories SAS, Chatillon sur Chalaronne, France

Imported by:
PT Abbott Indonesia
Jl. Raya Jakarta- Bogor Km. 37,
Depok, Indonesia

Refer to CCDS SOLID 1000305087 v5.0
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L004/10/20

INFORMASI PRODUK UNTUK PASIEN

TRILIPIX®

Choline fenofibrate Kapsul Pelepasan Terkontrol

Bacalah seluruh brosur ini dengan seksama sebelum Anda memulai meminum obat ini karena brosur ini mengandung informasi penting untuk Anda.

- Simpanlah brosur ini, mungkin suatu saat Anda perlu membacanya lagi.
- Jika Anda mempunyai pertanyaan lebih lanjut, tanyakan kepada dokter atau apoteker Anda.
- Obat ini hanya diresepkan untuk Anda saja. Jangan menyerahkannya kepada orang lain, karena mungkin dapat membahayakan mereka, meskipun tanda-tanda penyakit mereka sama dengan penyakit Anda.
- Jika Anda mengalami efek samping, bicarakan dengan dokter atau apoteker Anda. Ini meliputi efek samping yang tidak tercantum dalam brosur ini. Lihat bagian 4.

Apa saja yang ada di brosur ini?

1. Obat apa Trilipix® itu dan digunakan untuk apa?

Trilipix® mengandung kandungan obat golongan yang umumnya dikenal sebagai 'fibrat'. Obat-obatan ini digunakan untuk menurunkan tingkat lemak (lipid) dalam darah. Misalnya lemak yang dikenal sebagai 'trigliserida'.

Trilipix® digunakan bersamaan dengan gaya hidup sehat (diet rendah lemak dan perawatan nonmedis lainnya seperti olahraga dan penurunan berat badan) dan bersama dengan obat lain yang disebut statin untuk menurunkan kadar lemak dalam darah pada pasien dengan risiko kardiovaskular tinggi dengan kadar trigleserida yang tidak terkontrol.

Ingat bahwa Anda harus terus mengikuti diet rendah lemak selama pengobatan dengan Trilipix®.

2. Apa yang perlu Anda ketahui sebelum meminum Trilipix®?

Anda tidak boleh menggunakan Trilipix® dalam kasus berikut:

- Jika Anda memiliki penyakit hati, ginjal, atau kandung empedu yang parah.
- Jika Anda menderita pankreatitis kronis atau akut (radang pankreas, menyebabkan sakit perut) yang tidak disebabkan oleh tingginya tingkat lemak dalam darah (trigliserida darah yang berlebihan).
- Jika Anda sedang menyusui.
- Jika Anda pemah memiliki reaksi alergi atau kerusakan pada kulit karena sinar matahari atau sinar UV pada saat menggunakan fibrat atau ketoprofen (obat antiinflamasi).
- Jika Anda alergi (hipersensitif) terbadap asam fenofibric (fenofobric acid), fenofibrate atau bahan lainnya dari Trilipix®.
- Jangan menggunakan Trilipix® jika salah satu di atas berlaku untuk Anda.
- Jika Anda tidak yakin, bicaralah dengan dokter atau apoteker Anda sebelum menggunakan Trilipix®

Peringatan dan Perhatian

Mengemudi dan menggunakan mesin
Obat ini tidak akan mempengaruhi kemampuan Anda untuk mengemudi atau menggunakan alat atau mesin.

Beritahukan kepada dokter Anda, jika Anda memiliki kondisi sebagai berikut:
- Gangguan hati
- Gangguan ginjal
- Gangguan kandung empedu
- Gangguan tiroid
- Menderita pankreatitis (radang pankreas, menyebabkan sakit perut)
- Anda atau keluarga Anda pemah mengalami gangguan otot pada saat menggunakan obat penurun lipid statin (misalnya atorvastatin, fluvastatin, pravastatin, simvastatin, atau rosuvastatin) atau fibrat (misalnya fenofibrate, bezafibrate, atau gemfibrozil)

Efek pada otot
Berhenti menggunakan Trilipix® dan segera beritahukan kepada dokter Anda jika Anda mengalami nyeri otot yang menyakitkan pada saat menggunakan obat ini, terutama jika gejala ini disertai demam, merasa tidak sehat, atau urin berwama gelap.
Risiko rhabdomyolysis (penyakit yang ditandai dengan penghancuran serat otot) meningkat pada kasus penggunaan fibrat dengan statin.
Dokter Anda dapat melakukan tes darah, jika perlu, sebelum memula pengobatan untuk memeriksa status dari otot Anda.
Dokter Anda akan menyarankan untuk melakukan pemeriksaan laboratori um secara berkala untuk melihat fungsi ginjal dan hati Anda

Obat-obatan lain
Anda harus memberitahu dokter Anda jika Anda menggunakan salah satu obat berikut:
- Obat antikoagulan yang digunakan untuk mengencerkan darah (misalnya, warfarin)
- Siklosporin, takrolimus (immunosuppressant)
- Obat-obatan lain untuk mengontrol kadar lemak dalam darah (seperti statin atau fibrat). Menggunakan statin pada saat yang sama sebagai Trilipix® dapat meningkatkan risiko masalah otot
- Colchicine (obat untuk asam urat)
- Obat untuk gangguan kandung empedu (misalnya, kolestiramin, kolestipol)

Beritahu dokter atauapoteker Anda jika Anda memiliki penyakit lain, memiliki alergi, atau sedang/baru saja mengkonsumsi obat-obatan lain, termasuk obat-obatan yang bisa didapat tanpa resep dokter

Kehamilan dan Menyusui
Silahkan mencari saran dari dokter atau apoteker sebelum menggunakan obat ini.
Tidak ada data penggunaan Trilipix® pada wanita hamil, sehingga belum diketahui risikonya pada manusia. Trilipix tidak dianjurkan untuk digunakan selama kehamilan kecuali benar-benar diperlukan. Jika Anda sedang hamil atau berencana untuk hamil, beritahukan kepada dokter Anda.
Anda tidak boleh mengkonsumsi Trilipix® jika Anda sedang menyusui. Beritahukan kepada dokter Anda

jika Anda sedang menyusui.

3. Cara penggunaan Trilipix®

Selalu minum obat ini sesuai instruksi yang diberikan oleh dokter atau apoteker Anda. Anda harus memastikan dengan dokter atau apoteker Anda jika Anda tidak yakin.
Trilipix® digunakan bersama dengan obat statin. Anda dapat menggunakan statin dan Trilipix® pada waktu yang sama.
Dosis maksimal setiap hari adalah 135 mg. Dokter Anda akan memutuskan apakah Anda akan diberikan dosis 45 mg atau 135 mg.
Jika Anda memiliki masalah ginjal, dokter mungkin mulai pengobatan Anda dengan Trilipix® 45 mg sekali sehari.
Anda dapat menggunakan Trilipix® dengan atau tanpa makanan.
Kapsul harus ditelan utuh dengan air. Jangan membuka kapsul atau menggerus isi kapsul.

Berapa lama pengobatan dengan Trilipix®?
Teruskan pengobatan dengan Trilipix® selama dianjurkan oleh dokter Anda. Pengobatan ini merupakan pengobatan jangka panjang.
Dokter Anda mungkin dapat mempertimbangkan untuk menghentikan pengobatan dengan Trilipix® berdasarkan kriteria tertentu.
Jika Anda memiliki pertanyaan terkait berapa lama pengobatan dengan Trilipix®, hubungi dokter atau apoteker Anda.

Apabila Anda mengkonsumsi Trilipix® lebih dari yang seharusnya
Apabila Anda mengkonsumsi Trilipix® lebih dari yang seharusnya, atau ada orang lain yang tidak sengaja meminum obat anda, segera hubungi dokter Anda atau Rumah Sakit terdekat untuk penanganan segera. Tunjukanlah kemasan obat tersebut jika memungkinkan. Penanganan medis mungkin diperlukan.

Apabila Anda lupa mengkonsumsi Trilipix®
Jangan mengkonsumsi dosis ganda untuk menutupi dosis yang telah Anda lewatkan. Minumlah dosis selanjutnya sesuai jadwal pengobatan Anda

Jangan mengubah sendiri dosis yang diresepkan oleh dokter. Bicaralah dengan dokter atau apoteker jika Anda berpikir efektivitas obat Anda terlalu lemah atau, sebaliknya, terlalu kuat.

4. Apa kemungkinan efek sampingnya?

Seperti obat-obatan lainnya, pasien yang diobati dengan Trilipix® mungkin mengalami efek samping, meskipun tidak semua pasien mengalaminya. Apabila Anda mengalami efek samping yang serius, hentkan penggunaan Trilipix® dan hubungi dokter Anda. Anda mungkin memerlukan perawatan yang mendesak. Tidak perlu khawatir dengan kemungkinan efek samping yang tertera di bawah ini. Anda belum tentu akan mengalaminya.

Pengobatan dengan Trilipix® mungkin dapat menyebabkan efek samping berikut:
Gangguan saluran pencernaan: susah buang air besar, diare, dispepsia, mual
Gangguan umum dan kondisi tempat pemberian obat: kelelahan, nyeri
Infeksi dan infestasi (gangguan yang disebabkan oleh parasit): radang saluran pernapasan atas, sinusitis, infeksi saluran pernapasan atas, radang paru-paru, flu, infeksi saluran kemih
Hasil laboratorium: peningkatan enzim ALT, peningkatan enzim AST, peningkatan CPK darah,

peningkatan enzim hati
Gangguan tulang dan sendi: nyeri sendi, nyeri punggung, kejang otot, nyeri otot, nyeri di bagian ekstrimitas, nyeri tulang
Gangguan sistem saraf: pusing, sakit kepala
Gangguan psikis: sulit tidur
Gangguan saluran pernapasan: batuk, *pharyngolaryngeal pain*
Gangguan saluran pembuluh darah: darah tinggi

Berikut efek samping yang telah dilaporkan setelah pemasaran Trilipix® (dengan frekuensi yang tidak diketahui): penyakit kronis pada jaringan paru-paru; rhabdomyolysis (penghancuran serat otot).
Jika Anda mengalami efek samping yang tidak tercantum dalam brosur ini, hubungi dokter atau apoteker Anda.

5. Bagaimana cara menyimpan obat ini?
Jangan gunakan Trilipix® setelah tanggal kadaluarsa (EXP) yang tercantum pada kemasan. Simpan pada suhu di bawah 30°C.
Simpan pada kemasan aslinya untuk melindungi dari kelembaban. Jangan digunakan jika kemasan rusak atau ada tanda-tanda kerusakan. Jauhkan dari jangkauan dan pengli hatan anak-anak.
Untuk informasi lebih lanjut, konsultasikan dengan dokter atau apoteker Anda.

6. Berapa isi kemasan Trilipix® dan apakah informasi lainnya?
Trilipix kapsul salut enterik mengandung bahan aktif choline fenofibrate setara dengan asam fenofibric 45 atau 135 mg dan beberapa bahan tambahan.
Trilipix 135 mg juga mengandung E132 sebagai zat pewarna.
Trilipix 45 mg dan 135 mg tersedia dalam kemasan 3 blister @ 10 kapsul.

HARUS DENGAN RESEP DOKTER
Reg No.:
Trilipix 45 mg : DKI1927000703A1
Trilipix 135 mg : DKI1927000703B1

Diproduksi oleh:
Fournier Laboratories Ireland Limited, Carrigtwohill, Co. Cork, Ireland

Dikemas dan dirilis oleh:
Mylan Laboratories SAS, Chatillon sur Chalaronne, France

Diimpor oleh:
PT Abbott Indonesia
Jl. Raya Jakarta- Bogor Km.
37, Depok, Indonesia

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