TRICOR TABLET 160 mg
Film-coated tablets
Fenofibrate

1. NAME OF THE MEDICINAL PRODUCT
Tricor Tablet 160 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 160.0mg fenofibrate.
Excipients with known effect: each tablet contains:
- 138.4mg of Lactose monohydrate
- 0.56mg of Soybean lecithin

3. PHARMACEUTICAL FORM
Film-coated tablet. White, oblong, film-coated tablets engraved “160” on one side and “Fournier logo” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Hypercholesterolaemia and hypertriglyceridaemia alone or combined (types IIa, IIb, IV dyslipidaemias, as well as types III and V dyslipidaemias) in patients unresponsive to dietary and other non-drug therapeutic measures (e.g. weight reduction or increased physical activity), particularly when there is evidence of associated risk such as hypertension and smoking.

The treatment of secondary hyperlipoproteinaemias is indicated if the hyperlipoproteinaemia persists despite effective treatment of the underlying disease (e.g. dyslipidaemia in diabetes mellitus).

Appropriate dietary measures initiated before therapy should be continued.

4.2 Posology and method of administration
Response to therapy should be monitored by determination of serum lipid values (total cholesterol, LDL-Cholesterol, triglycerides), if an adequate response has not been achieved after several months (e.g. 3 months) complementary or different therapeutic measures should be considered.

Posology:
Adults: The recommended dose of TRICOR TABLET 160 mg tablets is one tablet taken once daily. Patients currently taking one 160mg tablet can be changed to one 145mg fenofibrate tablet without further dose adjustment.

Special populations
Geriatric population:
In elderly patients, without renal impairment, the usual adult dose is recommended in elderly patients.

Renal impairment: Dosage reduction is required in patients with renal impairment.

In moderate chronic kidney disease (creatinine clearance 30 to 59 mL/min), and if a low dose is available, start with one capsule of 100 mg standard or 67 mg micronized once daily.

If no low dose is available, then fenofibrate is not recommended.
In patients with chronic kidney disease (creatinine clearance < 30ml/min), fenofibrate is contraindicated.

Hepatic impairment: TRICOR TABLET 160 is not recommended for use in patients with hepatic impairment due to lack of data.

Paediatric population: The safety and efficacy of fenofibrate in children and adolescents younger than 18 years has not been established. No data are available. Therefore the use of fenofibrate is not recommended in paediatric subjects under 18 years.

Method of administration: Tablets should be swallowed whole during a meal.

4.3 Contraindications

- Hepatic insufficiency (including biliary cirrhosis and unexplained persistent liver function abnormality),
- Known gallbladder disease
- Severe chronic kidney 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(s) or to any of the excipients listed in section 6.1.

TRICOR TABLET 160 mg should not be taken in patients allergic to peanut or arachis oil or soya lecithin or related products due to the risk of hypersensitivity reactions.

4.4 Special warnings and precautions for use

Secondary causes of hyperlipidemia
Secondary cause of hyperlipidemia, such as uncontrolled type 2 diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemia, obstructive liver disease, pharmacological treatment, alcoholism, should be adequately treated before fenofibrate therapy is considered. For hyperlipidaemic patients taking estrogens or contraceptives containing oestrogens it should be ascertained whether the hyperlipidaemia is of primary or secondary nature (possible elevation of lipid values caused by oral oestrogen).

Liver function:
As with other lipid lowering agents, increases have been reported in transaminase levels in some patients. In the majority of cases these elevations were transient, minor and asymptomatic. It is recommended that transaminase levels be monitored 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 ASAT and ALAT 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, fenofibrate therapy should be discontinued.

Pancreas:
Pancreatitis has been reported in patients receiving fenofibrate. This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct effect of the medicinal product, or to a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.

Muscle:
Muscle toxicity, including rare cases of rhabdomyolysis, with or without renal failure, has been reported with administration of fibrates and other lipid-lowering agents. The incidence of this disorder increases in cases of hypoalbuminaemia and previous renal insufficiency. Patients with pre-disposing factors for myopathy and/or rhabdomyolysis, including age above 70 years old, personal or familial history of hereditary muscular disorders, renal impairment, hypothyroidism

and high alcohol intake, may be at an increased risk of developing rhabdomyolysis. For these patients, the putative benefits and risks of fenofibrate therapy should be carefully weighed up.

Muscle toxicity should be suspected in patients presenting diffuse myalgia, myositis, muscular cramps and weakness and/or marked increases in CPK (levels exceeding 5 times the normal range). In such cases treatment with fenofibrate should be stopped.

The risk of muscle toxicity may be increased if the drug is administered with another fibrate or an HMG-CoA reductase inhibitor, especially in cases of pre-existing muscular disease. Consequently, the co-prescription of fenofibrate with an HMG-CoA reductase inhibitor or another fibrate, should be reserved to patients with severe combined dyslipidaemia and high cardiovascular risk without any history of muscular disease and with a close monitoring of potential muscle toxicity

Renal Function:
Treatment should be interrupted in case of an increase in creatinine levels > 50% and ULN (upper limit of normal). It is recommended that creatinine is measured during the first three months after initiation of treatment and thereafter periodically. (for dose recommendations see 4.2 Posology and method of administration).

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 medicine.

4.5 Interactions with other medicinal products and other forms of interaction
Oral anticoagulants:
Fenofibrate enhances oral anticoagulant effect and may increase risk of bleeding. It is recommended that the dose of anticoagulants is reduced by about one third at the start of treatment and then gradually adjusted if necessary according to INR (International Normalised Ratio) monitoring.

Cyclosporin:
Some severe cases of reversible renal function impairment have been reported during concomitant administration of fenofibrate and cyclosporin. The renal function of these patients must therefore be closely monitored and the treatment with fenofibrate stopped in the case of severe alteration of laboratory parameters.

HMG-CoA reductase inhibitors and other fibrates:
The risk of severe muscle toxicity may be increased if the drug is administered in combination with another fibrate or an HMG-CoA reductase inhibitor. This combination therapy should be used with caution and patients should be monitored closely for signs of muscle toxicity (See 4.4 Special warnings and precautions for use)

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.

Cytochrome P450 enzymes:
In vitro studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.

Patients co-administered fenofibrate and CYP2C19, CYP2A6, and especially CYP2C9 metabolised drugs with a narrow therapeutic index should be carefully monitored and, if necessary, dose adjustment of these drugs is recommended.

4.6 Fertility, pregnancy and lactation
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 TRICOR TABLET 160 mg.

Pregnancy: There are no adequate data from the use of fenofibrate in pregnant women. Animal studies have not demonstrated any teratogenic effects. Embryotoxic effects have been shown at doses in the range of maternal toxicity. The potential risk for humans is unknown. Therefore, TRICOR TABLET 160 mg should only be used during pregnancy after a careful benefit/risk assessment.

Lactation: It is unknown whether fenofibrate and/or its metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Therefore, TRICOR TABLET 160 mg should not be used during breast-feeding.

4.7 Effects on the ability to drive and use machines
TRICOR TABLET 160 mg has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable Effects
The most commonly reported ADRs during TRICOR TABLET 160 mg therapy are digestive, gastric or intestinal disorders.

The following undesirable effects have been observed during placebo-controlled clinical trials (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 (including anaphylactic reactions)	
Nervous system disorders			Headache		
Vascular disorders			Thromboembolism (pulmonary embolism, deep vein thrombosis)**		
Gastrointestinal disorders		Gastrointestinal signs and symptoms (abdominal pain, nausea, vomiting, diarrhoea,	Pancreatitis*		

		flatulence)			
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).
** 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 nonsignificant 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 reporting during clinical trials, the following side effects have been reported spontaneously during postmarketing use of TRICOR TABLET 160 mg. 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
Only anecdotal cases of fenofibrate overdosage have been received. In the majority of cases no overdose symptoms were reported.

No specific antidote is known. If an overdose is suspected, treat symptomatically and institute appropriate supportive measures as required. Fenofibrate cannot be eliminated by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Serum Lipid Reducing Agents/Cholesterol and Triglycerides Reducers/Fibrates.
ATC code: C10 AB 05
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 increases the lipolysis and elimination of atherogenic triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein CIII. Activation of PPARα also induces an increase in the synthesis of apoproteins AI and AII.

The above stated effects of fenofibrate on lipoproteins lead to a reduction in very low- and low density fractions (VLDL and LDL) containing apoprotein B and an increase in the high density lipoprotein fraction (HDL) containing apoprotein AI and AII.

In addition, through modulation of the synthesis and the catabolism of VLDL fractions, fenofibrate increases the LDL clearance and reduces small and dense LDL, the levels of which are elevated in the atherogenic lipoprotein phenotype, a common disorder in patients at risk for coronary heart disease.

During clinical trials with fenofibrate, total cholesterol was reduced by 20 to 25%, triglycerides by 40 to 55% and HDL cholesterol was increased by 10 to 30%.

In hypercholesterolaemic patients, where LDL cholesterol levels are reduced by 20 to 35%, the overall effect on cholesterol results in a decrease in the ratios of total cholesterol to HDL cholesterol, LDL cholesterol to HDL cholesterol, or Apo B to Apo AI, or a decrease of the levels of non-HDL cholesterol all of which are markers of atherogenic risk.

Extravascular deposits of cholesterol (tendinous and tuberous xanthoma) may be markedly reduced or even entirely eliminated during fenofibrate therapy.

Patients with raised levels of fibrinogen treated with fenofibrate have shown significant reductions in this parameter, as have those with raised levels of Lp(a). Other inflammatory markers such as C Reactive Protein are reduced with fenofibrate treatment.

The uricosuric effect of fenofibrate leading to reduction in uric acid levels of approximately 25% should be of additional benefit in those dyslipidaemic patients with hyperuricaemia.

Fenofibrate has been shown to possess an anti-aggregatory effect on platelets in animals and in a clinical study, which showed a reduction in platelet aggregation induced by ADP, arachidonic acid and epinephrine.

5.2 Pharmacokinetic properties

TRICOR TABLET 160 mg is a film-coated tablet containing 160 mg of micronised fenofibrate and is suprabioavailable (larger bioavailability) compared to the previous formulations.

Absorption: Maximum plasma concentrations (Cmax) occur within 4 to 5 hours after oral administration. Plasma concentrations are stable during continuous treatment in any given individual. The absorption of fenofibrate is increased when administered with food.

Distribution: Fenofibric acid is strongly bound to plasma albumin (more than 99%).

Metabolism and excretion: After oral administration, fenofibrate is rapidly hydrolised by esterases to the active metabolite fenofibric acid. No unchanged fenofibrate can be detected in the plasma. Fenofibrate is not a substrate for CYP3A4. 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 administration of a single dose and continuous treatment have demonstrated that the drug does not accumulate. Fenofibric acid is not eliminated by haemodialysis.

The plasma elimination half-life of fenofibric acid is approximately 20 hours.

5.3 Preclinical Safety Data
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 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 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
Core: Sodium laurilsulfate, lactose monohydrate, povidone, microcrystalline cellulose, silica colloidal anhydrous, crospovidone, sodium stearyl fumarate.

Coating: polyvinyl alcohol, titanium dioxide (E171), talc, (soybean) lecithin, xanthan gum.

6.2 Incompatibilities
Not applicable.

6.3 Shelf-life
Please refer to the product carton for expiry.

6.4 Special precautions for storage
Store in the original package in order to protect from moisture.
Store at a temperature at or below 30°C.

6.5 Nature and contents of container

Thermoformed blister strips (PVC/PE/PVDC) sealed with aluminum complex. Box of 30 tablets.

6.6 Special precautions for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT OWNER
Abbott Products Operations AG
Hegenheimermattweg 127, 4123 Allschwil, Switzerland

8. DATE OF REVISION
24 April 2023 (SIN-TRICOR-0423/0)