Trolate
Capsule

Compositions:
TROLATE 100 MG
Each capsule contains
Fenofibrate 100 mg

TROLATE 300 MG
Each capsule contains
Fenofibrate 300 mg

List of Excipients:
TROLATE 100 MG
Lactose, sodium starch glycolate, polysorbate 80, ethanol 96%, magnesium stearate, talc, capsule shells (gelatin, titanium dioxide, FD&C red 40, D&C yellow 10).

TROLATE 300 MG
Lactose, sodium starch glycolate, polysorbate 80, ethanol 96%, magnesium stearate, talc, capsule shells (gelatin, titanium dioxide, FD&C red 3, D&C yellow 10, shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, purified water, strong ammonia solution, potassium hydroxide, black iron oxide).

Product Description:
TROLATE 100 MG
Hard gelatin capsule size 3, body and cap ivory opaque (38.740).

TROLATE 300 MG
Hard gelatin capsule size 1, body white opaque (44.700), cap orange opaque (21.796). Body and cap printed DEXA logo in black.

Pharmacodynamics:
ATC code: C10AB05
Fenofibrate is a fibric acid derivative whose lipid modifying effects reported in humans are mediated via activation of peroxisome proliferator activated receptor type alpha (PPAR-α). Through activation of PPAR-α, 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 PPAR-α 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.
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 dyslipidemic patients with hyperuricemia.
Fenofibrate has been shown to possess an antiaggregatory effect on platelets in animals and in a clinical study, which showed a reduction in platelet aggregation induced by ADP, arachidonic acid, and epinephrine.

Pharmacokinetics:
Fenofibrate is a prodrug which immediately after absorption is hydrolyzed by tissue and plasma esterases to its active major metabolite, fenofibric acid. Peak plasma concentrations of around 6 to 9.5 mg/l are attained approximately 4 to 6 hours following a single 300 mg dose in healthy fasting subjects. Steady-state concentrations of approximately 10 mg/l were reached after 120 hours in healthy subjects given 300 mg daily in 2 divided doses (200 mg in the morning and 100 mg in the evening), although much lower steady-state values have also been reported.
Fenofibric acid is more than 99% bound to plasma proteins and the volume of distribution has been reported as 0.89 l/kg in healthy subjects. The drug is eliminated mainly in the urine, in metabolized form, with some in the feces, in varying proportions depending on the extent of absorption. The elimination patterns in animal species differ, a factor that may be important in interpreting toxicological findings. Mean elimination half-life values of 19.6 to 26.6 hours have been reported in healthy subjects.
In patients with mild to severe chronic renal failure (including end-stage renal failure), the plasma half-life of fenofibric acid was considerably prolonged, with no correlation between the elimination half-life and serum creatinine level or creatinine clearance. Fenofibric acid is not removed by hemodialysis. The use of fenofibrate is therefore not recommended in patients with chronic renal failure, since marked accumulation of the drug is likely to occur, even at reduced dosage levels.

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 fibers) 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 gastrointestinal 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 tumors 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 nonclinical 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.

Indications:
TROLATE is indicated to treatment:
- Hypercholesterolemia (type IIa).
- Hypertriglyceridemia (type IV).
- Mix hyperlipidemia (type IIb and III).

Recommended Dosage:
Adults:
Initial dose: 100 mg 3 times a day or 300 mg/day as a single dose, should be given with meals thereby optimizing the absorption of the medication.
If after strict cholesterol diet the concentration of cholesterol stays at >4 g/l, dose can be increased to 100 mg 4 times daily.
Initial dose should be maintained until cholesterol level gets back to normal. If cholesterol level is stabilized, dosage of 100 mg twice daily can be given provided that cholesterol level is checked every 3 months. If there is a new increase in the plasma cholesterol concentration, dose should go back to initial dose of 100 mg 3 times daily.

Children:
Over 10 years: maximum 5 mg/kg daily.

Route of Administration:
Oral. Tablets should be swallowed whole during a meal.

Contraindications:
- Pregnancy and lactation.
- 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 or to any of the excipients listed.

63734-00XX-YY
Last revised: dd/mm/yyyy

Warnings and precautions:

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 hyperlipidemic patients taking estrogens or contraceptives containing estrogens it should be ascertained whether the hyperlipidemia is of primary or secondary nature (possible elevation of lipid values caused by oral estrogen).

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 hypoalbuminemia and previous renal insufficiency. Patients with predisposing 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 preexisting muscular disease. Consequently, the coprescription of fenofibrate with an HMG-CoA reductase inhibitor or another fibrate, should be reserved to patients with severe combined dyslipidemia 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.

Interactions with Other Medicines 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 normalized ratio) monitoring.

Ciclosporin

Some severe cases of reversible renal function impairment have been reported during concomitant administration of fenofibrate and ciclosporin. 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.

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 coadministered fenofibrate and CYP2C19, CYP2A6, and especially CYP2C9 metabolized drugs with a narrow therapeutic index should be carefully monitored and, if necessary, dose adjustment of these drugs is recommended. Combination therapy of hepatotoxic substances like perhexiline maleate or IMAO is not recommended.

Use during Pregnancy and Lactation:

Fertility

Reversible effects on fertility have been observed in animals. There are no clinical data on fertility from the use of TROLATE capsule.

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, TROLATE capsule should not be used during pregnancy.

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, TROLATE capsule should not be used during breastfeeding.

Adverse Effects:

In general, side effects are mild and rarely reported. In prolonged therapy, the following side effects have been reported:

- Gastrointestinal disturbances about 5%.
- Headache about 1%.
- Muscular spasm about 1%.
- Transient elevation of transaminases and creatin phosphokinase.
- Skin allergic reactions.
- Fatigue and vertigo.

Overdose and Treatment:

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 hemodialysis.

Presentations and Registration Numbers:

TROLATE 100 MG: Box, 3 PVC-Alu blisters x 10 capsules; SINXXXXXX
TROLATE 300 MG: Box, 3 PVC-Alu blisters x 10 capsules; SINXXXXXX

ON MEDICAL PRESCRIPTION ONLY.

STORE AT TEMPERATURES BELOW 30ºC, PROTECT FROM LIGHT.

Manufactured by
PT Dexa Medica
Jl. Jend. Bambang Utoyo No. 138
Palembang-Indonesia

Date of review: 25 October 2023