PLEASE READ CAREFULLY

LIPOTHIN 200MG CAPSULE

CONTENT
Each capsule contains 200 mg micronised fenofibrate.

DESCRIPTION
White powder filled in orange-orange capsule no. 1.

INDICATIONS
Lipothin 200 is indicated as an adjunctive therapy to diet for treatment of endogenous hypertriglyceridaemia isolated (type IV), hypercholesterolaemia (type IIa) or combined hypertriglyceridaemia (type IIb and III).

RECOMMENDED DOSAGE
Patients should be placed on an appropriate lipid-lowering diet before receiving **Lipothin 200**, and should continue this diet during treatment. The recommended dosage is one **Lipothin 200** capsule daily with the main meal.

METHOD OF ADMINISTRATION
For oral administration.

The recommended dose is one capsule taken daily during the evening meal. Since it less well absorbed from an empty stomach, **Lipothin 200** should always be taken with food.

CONTRAINDICATIONS
- Hypersensitivity to the active substance or to any of the excipients.
- Hepatic insufficiency (including biliary cirrhosis and unexplained persistent liver function abnormality).
- Known gallbladder disease.
- Severe renal insufficiency (estimated glomerular filtration rate < 30 L/min/1.73 m^2).
- Chronic or acute pancreatitis with the exception of acute pancreatitis due to severe hypertriglyceridaemia.
- Known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen.

PRECAUTIONS / WARNING
- Secondary causes of hyperlipidaemia

  Secondary causes of hyperlipidaemia, such as uncontrolled type 2 diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemia, obstructive liver disease, pharmacological treatment, alcoholism, should be adequately treated before fenofibrate therapy is initiated. Secondary cause of hypercholesterolaemia related to pharmacological treatment can be seen with diuretics.

- Renal impairment

  In renal dysfunction the dose of fenofibrate may need to be reduced, depending on the rate of creatinine clearance.

  Lipothin 200 capsules are contraindicated in severe renal impairment.

  Lipothin 200 capsules should be used with caution in patients with mild to moderate renal insufficiency. Dose should be adjusted in patients whose estimated glomerular filtration rate is 30 to 59 mL/min/1.73 m^2.

  Reversible elevations in serum creatinine have been reported in patients receiving fenofibrate monotherapy or co-administrated with statin. 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.

  Treatment should be interrupted when creatinine level is 50 % above the upper limit of normal. It is recommended that creatinine is measured during the first 3 months after initiation of treatment and periodically thereafter.

- Liver function

  As with other lipid lowering agents, increases have been reported in transaminase levels in some patients. In majority of cases these elevations were transient, minor and asymptomatic. It is recommended that transaminase levels are monitored every 3 months during the first 12 months of treatment and thereafter periodically. Attention should be paid to patients who develop increase transaminase levels and therapy should be discontinued if AST (SGOT) and ALT (GPT) levels increase to more than 3 times the upper limit of the normal range. When symptoms indicative of hepatitis occurs (e.g., jaundice, pruritus), and diagnosis is confirmed by laboratory testing, fenofibrate therapy should be discontinued.

- Pancreas

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

- Muscle

  Muscle toxicity, including very 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, personal or familial history of hereditary muscular disorders, renal impairment, hypothyroidism and high alcohol intake, may also 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 a close monitoring of potential muscle toxicity.

  This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

DRUG INTERACTIONS
- Oral anticoagulant

  Fenofibrate enhances oral anticoagulant effect and may increase risk of bleeding. In patients receiving oral anticoagulant therapy, the dose of anticoagulant should be reduced by about one-third at the commencement of treatment and then gradually adjusted if necessary, according to INR (International Normalised 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 inhibitor or other fibrates

  Concurrent use of fibrates with HMG-CoA reductase inhibitors may cause severe myositis and myoglobinuria. Such combination therapy should be used with caution and patients monitored closely for signs of muscle toxicity. There is currently no evidence to suggest that fenofibrate affects the pharmacokinetics of simvastatin.

- 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

  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.

- Other

  No proven clinical interaction of fenofibrate with other drugs have been reported, although in vitro interaction studies suggest displacement of phenylbutazone from plasma protein binding sites. In common with other fibrates, fenofibrate induces microsomal mixed-function oxidases involved in fatty acid metabolism in rodents and may interact with drugs metabolised by these enzymes.

PREGNANCY AND LACTATION
- Pregnancy

  There are no adequate data from the use of fenofibrate in pregnant women. The potential risk for human is unknown.

- Breastfeeding

  There are no data on the excretion of fenofibrate and/or its metabolites into breast milk.

  It is therefore recommended that **Lipothin 200** should not be administered to women who are pregnant or are breastfeeding.

SIDE EFFECTS / ADVERSE REACTIONS

System organ class	Common	Uncommon	Rare	Very Rare	Unknown
Blood and lymphatic system disorders			Haemoglobin decreased White blood cell count decreased		
Immune system disorders			Hypersensitivity		
Nervous system disorders		Headache			
Vascular disorders		Thromboembolism (pulmonary embolism, deep vein thrombosis)			
Gastrointestinal disorders	Gastrointestinal signs and symptoms (abdominal pain, nausea, vomitting, diarrhoea, flatulence)	Pancreatitis			
Hepatobiliary disorders	Transaminases increased	Cholelithiasis	Hepatitis		Jaundice, complications of cholelithiasis (e.g., cholecystitis, cholangitis, biliary colic)
Skin and subcutaneous tissue disorders		Cutaneous hypersensitivity (e.g., rashes, pruritus, urticaria)	Alopecia Photosensitivity reactions		Severe cutaneous reactions (e.g., erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis)
Musculoskeletal, connective tissue and bone disorders		Muscle disorder (e.g., myalgia, myositis, muscular spasms and weakness)			Rhabdomyolysis
Reproductive system and breast disorders		Sexual dysfunction			
Investigations	Blood homocysteine level increased	Blood creatinine increased	Blood urea increased		
General disorders and administration site conditions					Fatigue
Respiratory, thoracic and mediastinal disorders					Interstitial lung disease

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

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Lipothin 200 has no or negligible influence on the ability to drive and use machines.

PHARMACODYNAMICS
Lipothin 200 is a formulation containing 200 mg of micronised fenofibrate.

Fenofibrate is a fibric acid derivative whose lipid modifying effects reported in humans are mediated via activation of Peroxisome Proliferator Activated Receptor type α (PPARα). Through activation of PPARα, fenofibrate increases lipolysis and elimination of atherogenic triglyceride rich particles from plasma by activating lipoprotein lipase and reducing production of Apoprotein C-III. Activation of PPAR α also induces an increase in the synthesis of Apoproteins A-I and A-II.

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.

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

Plasma uric acid levels are increased in approximately 20 % of hyperlipidaemic patients, particularly in those with type IV disease.

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 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
- Absorption:
  - Maximum plasma concentrations (C_{max}) 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 hydrolysed 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.
  - Fenofibric acid is not eliminated during haemodialysis. The plasma elimination half-life of fenofibric acid is approximately 20 hours.

PACKING/ PACK SIZES
Lipothin 200 capsules are packed in Alu-PVC blister strip, each of 10 capsules, which are supplied in paper box of 3 and 30 blisters.

STORAGE CONDITIONS, USER INSTRUCTIONS AND PHARMACEUTICAL PRECAUTIONS
Do not store above 30°C.
Protect from moisture and light.
Keep out of reach of children.
Jauhi daripada kanak-kanak.

Shelf life: Please refer to the outer box label.
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Manufactured by:
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