

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ANTARA® safely and effectively. See full prescribing information for ANTARA.

ANTARA (fenofibrate) Capsules

Initial U.S. Approval: 1993

INDICATIONS AND USAGE

Antara is a peroxisome proliferator receptor alpha (PPARα) activator indicated as an adjunct to diet:

- to reduce elevated LDL-C, Total-C, triglycerides, and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia when response to diet and non-pharmacological interventions alone has been inadequate. (1.1).
- to reduce triglyceride (TG) levels in patients with severe hypertriglyceridemia (1.2).

Important Limitations of Use: Fenofibrate was not shown to reduce coronary heart disease morbidity and mortality in patients with type 2 diabetes mellitus. (1.3).

DOSAGE AND ADMINISTRATION

- Antara capsules can be taken without regard to meals (2.1).
- Primary hypercholesterolemia and mixed dyslipidemia: 130 mg per day (2.2).
- Hypertriglyceridemia: 43 to 130 mg per day; the dose should be adjusted according to patient response (2.3).
- Renal impairment: Initial dose of 43 mg per day (2.4).
- Geriatric patients: Select dose on the basis of renal function (2.5).

DOSAGE FORMS AND STRENGTHS

- 43 mg capsules, imprinted with “43” and a segmented band, on the light green cap and “ANTARA” with “LUPIN” on the white to off-white body (3).
- 130 mg capsules, imprinted with “130” and a segmented band, on the dark green cap and “ANTARA” and “LUPIN” on the white body (3).

CONTRAINDICATIONS

- Severe renal dysfunction, including patients receiving dialysis (4, 12.3)
- Active liver disease (4, 5.3)
- Gallbladder disease (4, 5.5)
- Nursing mothers (4, 8.3)
- Hypersensitivity to fenofibrate (4, 5.9)

WARNINGS AND PRECAUTIONS

- Myopathy and rhabdomyolysis have been reported in patients taking fenofibrate. The risk for serious muscle toxicity appears to be increased when fenofibrate is co-administered with a statin in elderly patients and in patients with diabetes, renal failure, or hypothyroidism (5.2).
- Fenofibrate can increase serum transaminases. Monitor liver tests, including ALT, periodically during therapy (5.3).
- Fenofibrate can reversibly increase serum creatinine levels. Monitor renal function periodically in patients with renal impairment (5.4).
- Fenofibrate increases cholesterol excretion into the bile, leading to risk of cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. (5.5).
- Exercise caution in concomitant treatment with coumarin anticoagulants. Reduce the dosage of coumarin to maintain the PT/INR at the desired level to prevent bleeding complications (5.6).

ADVERSE REACTIONS

Most common adverse reactions (> 2% and greater than 1% in placebo) are abnormal liver tests, increased AST, increased ALT, increased CPK, and rhinitis (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Lupin Pharma at 1-800-399-2561 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Coumarin Anticoagulants (7.1)
- Immunosuppressants (7.2)
- Bile-Acid Resins (7.3)

USE IN SPECIFIC POPULATIONS

- Geriatric use: Determine dose selection based on renal function (8.5).
- Renal impairment: Avoid in patients with severe renal impairment; dose reduction required in patients with mild to moderate renal impairment (8.6).

See 17 for PATIENT COUNSELING INFORMATION

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FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Primary Hypercholesterolemia and Mixed Dyslipidemia
- 1.2 Hypertriglyceridemia
- 1.3 Important Limitation of Use

2 DOSAGE AND ADMINISTRATION

- 2.1 General Consideration
- 2.2 Hypercholesterolemia and Mixed Dyslipidemia
- 2.3 Severe Hypertriglyceridemia
- 2.4 Impaired Renal Function
- 2.5 Elderly Patients

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Mortality and Coronary Heart Disease Morbidity
- 5.2 Skeletal Muscle
- 5.3 Liver Function
- 5.4 Serum Creatinine
- 5.5 Cholelithiasis
- 5.6 Coumarin Anticoagulants
- 5.7 Pancreatitis
- 5.8 Hematologic Changes
- 5.9 Hypersensitivity Reactions
- 5.10 Venothromboembolic Disease

6 ADVERSE REACTIONS

- 6.1 Clinical Studies Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Coumarin Anticoagulants
- 7.2 Immunosuppressants
- 7.3 Bile-Acid Resins

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia
- 14.2 Severe Hypertriglyceridemia

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Primary Hypercholesterolemia and Mixed Dyslipidemia

Antara is indicated as adjunctive therapy to diet to reduce elevated low-density lipoprotein cholesterol (LDL-C), total cholesterol (Total-C), Triglycerides (TG), and apolipoprotein B (Apo B), and to increase high-density lipoprotein cholesterol (HDL-C) in adult patients with primary hyperlipidemia or mixed dyslipidemia.

1.2 Hypertriglyceridemia

Antara is also indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia. Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually reduce fasting triglycerides and eliminate chylomicronemia thereby obviating the need for pharmacologic intervention.

Markedly elevated levels of serum triglycerides (e.g. > 2,000 mg/dL) may increase the risk of developing pancreatitis. The effect of fenofibrate therapy on reducing this risk has not been adequately studied.

1.3 Important Limitations of Use

Fenofibrate was not shown to reduce coronary heart disease morbidity and mortality in patients with type 2 diabetes mellitus [*see Warnings and Precautions (5.1)*].

After the LDL-C goal has been achieved, if the TG is still > 200 mg/dL, non-HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low density lipoprotein (VLDL). Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV and V hyperlipoproteinemia.

2 DOSAGE AND ADMINISTRATION

2.1 General Considerations

Patients should be placed on an appropriate lipid-lowering diet before receiving Antara, and should continue this diet during treatment with Antara. Antara capsules can be given without regard to meals.

The initial treatment for dyslipidemia is dietary therapy specific for the type of lipoprotein abnormality. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. Estrogen therapy, thiazide diuretics and beta-blockers, are sometimes associated with massive rises in plasma triglycerides, especially in subjects with familial hypertriglyceridemia. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy of hypertriglyceridemia.

Lipid levels should be monitored periodically and consideration should be given to reducing the dosage of Antara if lipid levels fall significantly below the targeted range.

Therapy should be withdrawn in patients who do not have an adequate response after two months of treatment with the maximum recommended dose of 130 mg once daily.

2.2 Hypercholesterolemia and Mixed Dyslipidemia

The initial dose of Antara is 130 mg per day.

2.3 Severe Hypertriglyceridemia

The initial dose is 43 to 130 mg per day. Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at 4 to 8 week intervals. The maximum dose is 130 mg per day.

2.4 Impaired Renal Function

Treatment with Antara should be initiated at a dose of 43 mg per day in patients having mild to moderately impaired renal function, and increased only after evaluation of the effects on renal function and lipid levels at this dose. The use of Antara should be avoided in patients with severe renal impairment [*see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

2.5 Elderly Patients

Dose selection for the elderly should be made on the basis of renal function [*see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

- 43 mg capsules, imprinted with "43" and a segmented band, on the light green cap and "ANTARA" with "LUPIN" on the white to off-white body.
- 130 mg capsules, imprinted with "130" and a segmented band, on the dark green cap and "ANTARA" and "LUPIN" on the white body.

4 CONTRAINDICATIONS

Antara is contraindicated in:

- patients with severe renal impairment, including those receiving dialysis [*see Clinical Pharmacology (12.3)*].
- patients with active liver disease, including those with primary biliary cirrhosis and unexplained persistent liver function abnormalities [*see Warnings and Precautions (5.3)*].
- patients with pre-existing gallbladder disease [*see Warnings and Precautions (5.5)*].
- nursing mothers [*see Use in Specific Populations (8.3)*].
- patients with hypersensitivity to fenofibric acid, choline fenofibrate or fenofibrate [*see Warnings and Precautions (5.9)*].

5 WARNINGS AND PRECAUTIONS

5.1 Mortality and Coronary Heart Disease Morbidity

The effect of Antara on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established.

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.

Because of chemical, pharmacological, and clinical similarities between TRICOR (fenofibrate tablets), clofibrate, and gemfibrozil, the adverse findings in 4 large randomized, placebo-controlled clinical studies with these other fibrate drugs may also apply to Antara.

In the Coronary Drug Project, a large study of post myocardial infarction of 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, post-cholecystectomy 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 the WHO study (RR=1.29).

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). The rate of gallbladder surgery was not statistically significant between study groups, but did trend higher in the gemfibrozil group, (1.9% vs. 0.3%, $p=0.07$).

5.2 Skeletal Muscle

Fibrates increase the risk for myopathy, and have been associated with rhabdomyolysis. 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 creatine phosphokinase (CPK) levels.

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and Antara therapy should be discontinued if markedly elevated CPK levels occur or myopathy/myositis is suspected or diagnosed.

Data from observational studies suggest that the risk for rhabdomyolysis is increased when fibrates, in particularly gemfibrozil, are co-administered with an HMG-CoA reductase inhibitor (statin). The combination should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination [(see *Clinical Pharmacology* (12.3)].

5.3 Liver Function

Fenofibrate at doses equivalent to 87 mg to 130 mg Antara per day has been associated with increases in serum transaminases [AST (SGOT) or ALT (SGPT)].

In a pooled analysis of 10 placebo-controlled trials, increases to >3 times the upper limit of normal occurred in 5.3% of patients taking fenofibrate versus 1.1% of patients treated with placebo. When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. The incidence of increases in transaminases levels related to fenofibrate therapy appears to be dose related.

Hepatocellular, chronic active and cholestatic hepatitis associated 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 periodic monitoring of liver function, including serum ALT (SGPT) should be performed for the duration of therapy with Antara, and therapy discontinued if enzyme levels persist above three times the normal limit.

5.4 Serum Creatinine

Elevations in serum creatinine have been reported in patients on fenofibrate. These elevations tend to return to baseline following discontinuation of fenofibrate. The clinical significance of these observations is unknown. Monitor renal function in patients with renal impairment taking Antara. Renal monitoring should also be considered for patients taking Antara at risk for renal insufficiency such as the elderly and patients with diabetes.

5.5 Cholelithiasis

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

5.6 Coumarin Anticoagulants

Caution should be exercised when anticoagulants are given in conjunction with Antara because of the potentiation of coumarin-type anti-coagulants in prolonging the prothrombin time/International Normalized Ratio (INR/INR). To prevent bleeding complications, frequent monitoring of PT/INR and dose adjustment of the anticoagulant are recommended until PT/INR has stabilized [see *Drug Interactions* (7.1)].

5.7 Pancreatitis

Pancreatitis has been reported in patients taking fenofibrate, gemfibrozil, and clofibrate. 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.

5.8 Hematologic Changes

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

5.9 Hypersensitivity Reactions

Acute hypersensitivity reactions such as Stevens-Johnson syndrome and toxic necrolysis requiring patient hospitalization and treatment with steroids have been reported in individuals treated with fenofibrates. Urticaria was seen in 1.1

vs. 0%, and rash in 1.4 vs. 0.8% of fenofibrate and placebo patients, respectively, in controlled trials.

5.10 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 pulmonary embolism or thrombophlebitis than the placebo group (5.2% vs. 3.3% at five years; p < 0.01).

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect rates observed in clinical practice.

Adverse events reported by 2% or more of patients treated with fenofibrate and greater than placebo during double-blind, placebo-controlled trials, regardless of causality, are listed in Table 1. Adverse reactions led to discontinuation of treatment in 5.0% of patients treated with fenofibrate and in 3.0% treated with placebo. Increases in liver function tests were the most frequent events, causing discontinuation of fenofibrate treatment in 1.6% of patients in double-blind trials.

Table 1 Adverse Reactions Reported by 2% or More of Patients Treated with Fenofibrate and Greater than Placebo During the Double-Blind, Placebo-Controlled Trials

Body System Adverse Reaction	Fenofibrate* (N=439)	Placebo (N=365)
Body As A Whole		
Abdominal Pain	4.6%	4.4%
Back Pain	3.4%	2.5%
Headache	3.2%	2.7%
Digestive		
Abnormal Liver Function Tests	7.5%**	1.4%
Nausea	2.3%	1.9%
Constipation	2.1%	1.4%
Metabolic and Nutritional Disorders		
Increased AST	3.4%**	0.5%
Increased ALT	3.0%	1.6%
Increased Creatine Phosphokinase	3.0%	1.4%
Respiratory		
Respiratory Disorder	6.2%	5.5%
Rhinitis	2.3%	1.1%

* Dosage equivalent to 130 mg fenofibrate
**Significantly different from placebo

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of fenofibrate: myalgia, rhabdomyolysis, increased creatine phosphokinase, pancreatitis, increased alanine aminotransaminase, increased aspartate aminotransaminase, renal failure, muscle spasms, acute renal failure, hepatitis, cirrhosis, nausea, abdominal pain, anemia, headache, arthralgia, and asthenia. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a casual relationship to drug exposure.

7 DRUG INTERACTIONS

7.1 Coumarin Anticoagulants

Potentiation of coumarin-type anticoagulant effects has been observed with prolongation of the PT/INR.

Caution should be exercised when coumarin anticoagulants are given in conjunction with Antara. The dosage of the anticoagulants should be reduced to maintain the PT/INR at the desired level to prevent bleeding complications. Frequent PT/INR determinations are advisable until it has been definitely determined that the PT/INR has stabilized [see *Warnings and Precautions* (5.6)].

7.2 Immunosuppressants

Immunosuppressants such as cyclosporine and tacrolimus can produce nephrotoxicity with decreases in creatinine clearance and because renal excretion is the primary elimination route of fibrate drugs including Antara, there is a risk that an interaction will lead to deterioration. The benefits and risks of using Antara with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed.

7.3 Bile-Acid Resins

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category: C

Safety in pregnant women has not been established. There are no adequate and well controlled studies of fenofibrate in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In female rats given oral dietary doses of 15, 75, and 300 mg/kg/day of fenofibrate from 15 days prior to mating through weaning, maternal toxicity was observed at 0.3 times the maximum recommended human dose (MRHD), based on body surface area comparisons; mg/m².

In pregnant rats given oral dietary doses of 14, 127, and 361 mg/kg/day from gestation day 6-15 during the period of organogenesis, adverse developmental findings were not observed at 14 mg/kg/day (less than 1 times the MRHD, based on body surface area comparisons; mg/m²). At higher multiples of human doses, evidence of maternal toxicity was observed.

In pregnant rabbits given oral gavage doses of 15, 150, and 300 mg/kg/day from gestation day 6 to 18 during the period of organogenesis and allowed to deliver, aborted litters were observed at 150 mg/kg/day (10 times the MRHD, based on body surface area comparisons; mg/m²). No developmental findings were observed at 15 mg/kg/day (at less than 1 times the MRHD, based on body surface area comparisons; mg/m²).

In pregnant rats given oral dietary doses of 15, 75, and 300 mg/kg/day from gestation day 15 through lactation day 21 (weaning), maternal toxicity was observed at less than 1 times the MRHD, based on body surface area comparisons; mg/m².

8.3 Nursing Mothers

Fenofibrate should not be used in nursing mothers. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Fenofibric acid is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Since elderly patients have a higher incidence of renal impairment, dose selection for the elderly should be made on the basis of renal function [see *Dosage and Administration* (2.5) and *Clinical Pharmacology* (12.3)]. Elderly patients with normal renal function should require no dose modifications. Consider monitoring renal function in elderly patients taking Antara.

8.6 Renal Impairment

Fenofibrate should be avoided in patients with severe renal impairment [see *Contraindications* (4)]. Dose reduction is required in patients with mild to moderate renal impairment [see *Dosage and Administration* (2.4) and *Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

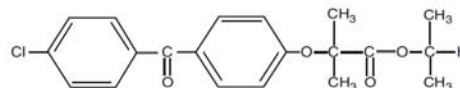
The use of Antara has not been evaluated in subjects with hepatic impairment [see *Contraindications* (4) and *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

There is no specific treatment for overdose with Antara. 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 fenofibrate is highly bound to plasma proteins, hemodialysis should not be considered.

11 DESCRIPTION

Antara (fenofibrate) Capsules, is a lipid regulating agent available as capsules for oral administration. Each capsule contains 43 mg or 130 mg of micronized fenofibrate. The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester with the following structural formula:



The empirical formula is C₂₀H₂₁O₄Cl and the molecular weight is 360.83; fenofibrate is insoluble in water. The melting point is 79°-82°C. Fenofibrate is a white solid which is stable under ordinary conditions.

Inactive Ingredients: Each gelatin capsule contains sugar spheres, hypromellose, sodium lauryl sulfate, dimethicone, simethicone, and talc. The gelatin capsules also contain black iron oxide, D&C Yellow #10, Indigo carmine FD&C Blue #2, shellac, soya lecithin, sulfur dioxide, titanium dioxide and yellow iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

The 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 (PPAR α).

Through this mechanism, fenofibrate increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity). The resulting fall in triglycerides 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 PPAR α also induces an increase in the synthesis of apoproteins A-I, A-II and HDL-cholesterol.

Fenofibrate also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid.

12.2 Pharmacodynamics

A variety of clinical studies have demonstrated that elevated levels of total-C, DL-C, and Apo B, an LDL membrane complex, are associated with human atherosclerosis. Similarly, decreased levels of HDL-C and its transport complex, apolipoprotein A (Apo AI and Apo AII) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C, LDL-C, and triglycerides, and inversely with the level of HDL-C. The independent effect of raising HDL-C or lowering TG on the risk of cardiovascular morbidity and mortality has not been determined.

Fenofibric acid, the active metabolite of fenofibrate, produces reductions in total cholesterol, LDL cholesterol, apolipoprotein B, total triglycerides, and triglyceride-rich lipoprotein (VLDL) in treated patients. In addition, treatment with fenofibrate results in increases in high density lipoprotein (HDL) and apoproteins Apo AI and Apo AII.

12.3 Pharmacokinetics

Fenofibrate is a pro-drug of the active chemical moiety fenofibric acid. Fenofibrate is converted by ester hydrolysis in the body to fenofibric acid which is the active constituent measurable in the circulation.

• **Absorption:** The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radio-labeled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces. Peak plasma levels of fenofibric acid from Antara occur within 4 to 8 hours after administration. There was

less than dose-proportional increase in the systemic exposure of fenofibric acid from 43 mg and 130 mg of Antara under fasting conditions.

Doses of three-capsules of 43 mg Antara given concurrently were dose equivalent to single-capsule doses of 130 mg.

The extent of absorption of fenofibric acid was unaffected when Antara was taken either in fasted state or with a low-fat meal. However, the C_{max} of Antara increased in the presence of a low-fat meal. T_{max} was unaffected in the presence of a low-fat meal. In the presence of a high-fat meal, there was a 26% increase in AUC and 108% increase in C_{max} of fenofibric acid from Antara relative to fasting state.

- Distribution:** In healthy volunteers, steady-state plasma levels of fenofibric acid were shown to be achieved within a week of dosing and did not demonstrate accumulation across time following multiple dose administration. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects.

- Metabolism:** Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; no unchanged fenofibrate is detected in plasma.

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 indicate that neither fenofibrate nor fenofibric acid undergo oxidative metabolism (e.g., cytochrome P450) to a significant extent.

- Excretion:** After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. After administration of radiolabeled fenofibrate, approximately 60% of the dose appeared in the urine and 25% was excreted in the feces.

Fenofibrate acid from Antara is eliminated with a half-life of 23 hours, allowing once daily administration in a clinical setting.

- Geriatrics:** In 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 a similar dosage regimen can be used in the elderly with normal renal function, without increasing accumulation of the drug or metabolites [see *Dosage and Administration* (2.4) and *Use in Special Populations*(8.5)].

- Pediatrics:** The pharmacokinetics of Antara has not been studied in pediatric populations.

- Gender:** No pharmacokinetic difference between males and females has been observed for fenofibrate.

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

- 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 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 (CrCl 50-80 mL/min) to moderate (CrCl 30-50 mL/min) renal impairment 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 Antara should be avoided in patients who have severe renal impairment and dose reduction is required in patients having mild to moderate renal impairment.

- Hepatic Impairment:** No pharmacokinetic studies have been conducted in patients having hepatic insufficiency.

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

Table 2 describes the effects of co-administered drugs on fenofibric acid systemic exposure. Table 3 describes the effects of co-administered fenofibric acid on exposure to other drugs.

Table 2 Effects of Co-Administered Drugs on Fenofibric Acid Systemic Exposure from Antara or Fenofibrate Administration

Co-Administered Drug	Dosage Regimen of Co-Administered Drug	Dosage Regimen of Fenofibrate	Changes in Fenofibric Acid Exposure	
			AUC	Cmax
No dosing adjustments required for Antara with the following co-administered drugs				
Lipid-lowering agents				
Atorvastatin	20 mg once daily for 10 days	Fenofibrate 160 mg ¹ once daily for 10 days	↓2%	↓4%
Pravastatin	40 mg as a single dose	Fenofibrate 3 x 67 mg ² as a single dose	↓1%	↓2%
Fluvastatin	40 mg as a single dose	Fenofibrate 160 mg ¹ as a single dose	↓2%	↓10%
Anti-diabetic agents				
Glimepiride	1 mg once daily as a single dose	Fenofibrate 145 mg ¹ once daily for 10 days	↑1%	↓1%
Metformin	850 mg three times daily for 10 days	Fenofibrate 54 mg ¹ three times daily for 10 days	↓9%	↓6%
Rosiglitazone	8 mg once daily for 5 days	Fenofibrate 145 mg ¹ once daily for 14 days	↑10%	↑3%

¹ TriCor (fenofibrate) oral tablet

² TriCor (fenofibrate) oral micronized capsule

Table 3 Effects of Antara or Fenofibrate Co-Administration on Systemic Exposure of Other Drugs

Dosage Regimen of Fenofibrate	Dosage Regimen of Co-Administered Drug	Changes in Co-Administered Drug Exposure		
		Analyte	AUC	C _{max}
No dosing adjustments required for these co-administered drugs with Antara				
Lipid-lowering agents				
Fenofibrate 160 mg ¹ once daily for 10 days	Atorvastatin, 20 mg once daily for 10 days	Atorvastatin	↓17%	0%
Fenofibrate 3 x 67 mg ² as a single dose	Pravastatin, 40 mg as a single dose	Pravastatin	↑13%	↑13%
		3α-Hydroxyl-iso-pravastatin	↑26%	↑29%
Fenofibrate 160 mg ¹ once daily for 10 days	Pravastatin, 40 mg once daily for 10 days	Pravastatin	↑28%	↑36%
		3α-Hydroxyl-iso-pravastatin	↑39%	↑55%
Fenofibrate 160 mg ¹ as a single dose	Fluvastatin, 40 mg as a single dose	(+)-3R, 5S-Fluvastatin	↑15%	↑16%
Anti-diabetic agents				
Fenofibrate 145 mg ¹ once daily for 10 days	Glimepiride, 1 mg once daily as a single dose	Glimepiride	↑35%	↑18%
Fenofibrate 54 mg ¹ three times daily for 10 days	Metformin, 850 mg three times daily for 10 days	Metformin	↑3%	↑6%
Fenofibrate 145 mg ¹ once daily for 14 days	Rosiglitazone, 8 mg once daily for 5 days	Rosiglitazone	↑6%	↓1%

¹ TriCor (fenofibrate) oral tablet

² TriCor (fenofibrate) oral micronized capsule

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two dietary carcinogenicity studies have been conducted in rats with fenofibrate. In the first 24-month study, Wistar rats were dosed with fenofibrate at 10, 45, and 200 mg/kg/day, approximately 0.3, 1, and 6 times the maximum recommended human dose (MRHD), based on body surface area comparisons (mg/m²). At a dose of 200 mg/kg/day (at 6 times the MRHD), the incidence of liver carcinomas was significantly increased in both sexes. A statistically significant increase in pancreatic carcinomas was observed in males at 1 and 6 times the MRHD; an increase in pancreatic adenomas and benign testicular interstitial cell tumors was observed at 6 times the MRHD in males. In a second 24-month rat carcinogenicity study in a different strain of rats (Sprague-Dawley), doses of 10 and 60 mg/kg/day (0.3 and 2 times the MRHD) produced significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in testicular interstitial cell tumors in males at 2 times the MRHD.

A 117-week carcinogenicity study was conducted in rats comparing three drugs: fenofibrate 10 and 60 mg/kg/day (0.3 and 2 times the MRHD), clofibrate (400 mg/kg/day; 2 times the human dose), and gemfibrozil (250 mg/kg/day; 2 times the

human dose, based on mg/m² surface area). Fenofibrate increased pancreatic acinar adenomas in both sexes. Clofibrate increased hepatocellular carcinoma and pancreatic acinar adenomas in males and hepatic neoplastic nodules in females. Gemfibrozil increased hepatic neoplastic nodules in males and females, while all three drugs increased testicular interstitial cell tumors in males.

In a 21-month study in CF-1 mice, fenofibrate 10, 45, and 200 mg/kg/day (approximately 0.2, 1, and 3 times the MRHD on the basis of mg/m² surface area) significantly increased the liver carcinomas in both sexes at 3 times the MRHD. In a second 18-month study at 10, 60, and 200 mg/kg/day, fenofibrate significantly increased the liver carcinomas in male mice and liver adenomas in female mice at 3 times the MRHD.

Electron microscopy studies have demonstrated peroxisomal proliferation following fenofibrate administration to the rat. An adequate study to test for peroxisome proliferation in humans has not been done, but changes in peroxisome morphology and numbers have been observed in humans after treatment with other members of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Mutagenesis: Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal aberration and unscheduled DNA synthesis in primary rat hepatocytes.

Impairment of Fertility: In fertility studies rats were given oral dietary doses of fenofibrate, males received 61 days prior to mating and females 15 days prior to mating through weaning which resulted in no adverse effect on fertility at doses up to 300 mg/kg/day (~10 times the MRHD, based on mg/m² surface area comparisons).

14 CLINICAL STUDIES

14.1 Hypercholesterolemia (Heterozygous Familial and Non familial) and Mixed Dyslipidemia

The effects of fenofibrate at a dose equivalent to 130 mg Antara per day were assessed from four randomized, placebo-controlled, double-blind, parallel group studies including patients with the following mean baseline lipid values: total-C 306.9 mg/dL; LDL-C 213.8 mg/dL; HDL-C 52.3 mg/dL; and triglycerides 191.0 mg/dL. Fenofibrate therapy lowered LDL-C, Total-C, and the LDL-C/HDL-C ratio. Fenofibrate therapy also lowered triglycerides and raised HDL-C (See Table 4).

Table 4 Mean Percent Change in Lipid Parameters at End of Treatment†

Treatment Group	Total-C	LDL-C	HDL-C	TG
Pooled Cohort				
Mean baseline lipid values (N=646)	306.9 mg/dL	213.8 mg/dL	52.3 mg/dL	191.0 mg/dL
All FEN (n=361)	-18.7% *	-20.6% *	+11.0% *	-28.9% *
Placebo (n=285)	-0.4%	-2.2%	+0.7%	+7.7%
Baseline LDL-C > 160 mg/dL and TG < 150 mg/dL (Type IIa)				
Mean baseline lipid values (N=334)	307.7 mg/dL	227.7 mg/dL	58.1 mg/dL	101.7 mg/dL
All FEN (n=193)	-22.4% *	-31.4% *	+9.8% *	-23.5% *
Placebo (n=141)	+0.2%	-2.2%	+2.6%	+11.7%
Baseline LDL-C > 160 mg/dL and TG ≥ 150 mg/dL (Type IIb)				
Mean baseline lipid values (N=242)	312.8 mg/dL	219.8 mg/dL	46.7 mg/dL	231.9 mg/dL
All FEN (n=126)	-16.8% *	-20.1% *	+14.6% *	-35.9% *
Placebo (n=116)	-3.0%	-6.6%	+2.3%	+0.9%

† Duration of study treatment was 3 to 6 months.

* p<0.05 vs. placebo

In a subset of the subjects, measurements of Apo B were conducted. Fenofibrate treatment significantly reduced Apo B from baseline to endpoint as compared with placebo (-25.1% vs. 2.4%, p<0.0001, n=213 and 143 respectively).

14.2 Severe Hypertriglyceridemia

The effects of fenofibrate on serum triglycerides were studied in two randomized, double-blind, placebo-controlled clinical trials of 147 hypertriglyceridemic patients. Patients were treated for eight weeks under protocols that differed only in that one entered patients with baseline TG levels of 500 to 1500 mg/dL, and the other TG levels of 350 to 499 mg/dL. In patients

with hypertriglyceridemia and normal cholesterolemia with or without hyperchylomicronemia, treatment with fenofibrate at dosages equivalent to 130 mg Antara per day decreased primarily very low density lipoprotein (VLDL) triglycerides and VLDL cholesterol. Treatment of patients with elevated triglycerides often results in an increase of LDL-C (See Table 5).

Table 5 Effects of Fenofibrate in Patients with Hypertriglyceridemia

Study 1		Placebo			Fenofibrate			
Baseline TG levels 350 to 499 mg/dL	N	Baseline (mean)	Endpoint (mean)	% Change (mean)	N	Baseline (mean)	Endpoint (mean)	% Change (mean)
Triglycerides	28	449	450	-0.5	27	432	223	-46.2 *
VLDL Triglycerides	19	367	350	2.7	19	350	178	-44.1 *
Total Cholesterol	28	255	261	2.8	27	252	227	-9.1 *
HDL Cholesterol	28	35	36	4	27	34	40	19.6 *
LDL Cholesterol	28	120	129	1.2	27	128	137	14.5
VLDL Cholesterol	27	99	99	5.8	27	92	46	-44.7 *
Study 2		Placebo			Fenofibrate			
Baseline TG levels 500 to 1500 mg/dL	N	Baseline (mean)	Endpoint (mean)	% Change (mean)	N	Baseline (mean)	Endpoint (mean)	% Change (mean)
Triglycerides	44	710	750	7.2	48	726	308	-54.5 *
VLDL Triglycerides	29	537	571	18.7	33	543	205	-50.6 *
Total Cholesterol	44	272	271	0.4	48	261	223	-13.8 *
HDL Cholesterol	44	27	28	5.0	48	30	36	22.9 *
LDL Cholesterol	42	100	90	-4.2	45	103	131	45.0 *
VLDL Cholesterol	42	137	142	11.0	45	126	54	-49.4 *

* p < 0.05 vs. placebo

The effect of Antara on serum triglycerides was studied in a double-blind, randomized, 3 arm parallel-group trial of 146. The study population was comprised of 61 % male and 39% female patients. Approximately 70% of patients had hypertension and 32% had diabetes. Patients were treated for eight weeks with either Antara 130 mg taken once daily with meals, Antara 130 mg taken once daily between meals, or placebo. Antara 130 mg, whether taken with meals or between meals, had comparable effects on TG and all lipid parameters (See Table 6).

Table 6 Antara Treatment in Patients with Hypertriglyceridemia

	Placebo (n =50)		Antara with meals (n=54)		Antara between meals (n=42)	
	Baseline mg/dL (mean)	% Change at endpoint (mean)	Baseline mg/dL (mean)	% Change at endpoint (mean)	Baseline mg/dL (mean)	% Change at endpoint (mean)
Triglycerides	479	+0.7	475	-36.7 *	487	-36.6 *
Total Cholesterol	237	-0.8	248	-5.1	241	-3.4
HDL Cholesterol	35	+0.8	36	+13.7 *	36	+14.3 *
Non-HDL Cholesterol	202	-1.1	212	-8.2 **	205	-6.6 **
LDL Cholesterol	115	+3.2	120	+15.4 *	122	+14.5
VLDL Cholesterol	87	-1.6	92	-34.4 *	83	-30.4 *

* p ≤0.05 vs placebo

** p ≤0.05 vs placebo (log transformed data)

16 HOW SUPPLIED/STORAGE AND HANDLING

Antara (fenofibrate) Capsules, are available in two strengths:

- 43 mg capsules, imprinted with “43” and a segmented band, on the light green cap and “ANTARA” and “LUPIN” on the white to off-white body, available in bottles of 30 (NDC # 27437-109-06) and 100 (NDC # 27437-109-01).
- 130 mg capsules, imprinted with “130” and a segmented band, on the dark green cap and “ANTARA” and “LUPIN” on the white to off-white body, available in bottles of 30 (NDC # 27437-110-06) and 100 (NDC # 27437-110-01).

Storage Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature] in a tightly closed container.

17 PATIENT COUNSELING INFORMATION

Patients should be advised:

- of the potential benefits and risks of Antara.
- not to use Antara if there is a known hypersensitivity to fenofibrate or fenofibric acid.
- that if they are taking coumarin anticoagulants, Antara may increase their anticoagulant effect, and increased monitoring may be necessary.
- of medications that should not be taken in combination with Antara.
- to continue to follow an appropriate lipid-modifying diet while taking Antara.
- to take Antara once daily, without regard to food, at the prescribed dose.
- to inform their physician of all medications, supplements, and herbal preparations they are taking and any change to their medical condition. Patients should also be advised to inform their physicians prescribing a new medication that they are taking Antara.
- to inform their physician of any muscle pain, tenderness, or weakness; onset of abdominal pain; or any other new symptoms .

Distributed by:

Lupin Pharma

Baltimore, Maryland 21202

United States

Address Medical Inquiries to:

Lupin Pharma Medical Inquiries

111 South Calvert Street, 21st Floor

Baltimore, MD 21202

or Call: 1-800-399-2561