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, for oral use
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 (1.1).
- to reduce triglyceride (TG) levels in adult 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. (5.1).

----------DOSAGE AND ADMINISTRATION----------

- Antara capsules can be taken without regard to meals (2.1).
- Primary hypercholesterolemia and mixed dyslipidemia: 90 mg per day (2.2).
- Severe Hypertriglyceridemia: 30 to 90 mg per day; the dose should be adjusted according to patient response (2.3).
- Renally impaired patients: Initial dose of 30 mg per day (2.4).
- Geriatric patients: Select the dose on the basis of renal function (2.5).

----------DOSAGE FORMS AND STRENGTHS----------

Oral capsules: 30 mg and 90 mg (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)
- Known 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 (with a significantly higher rate observed with gemfibrozil), particularly 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).
- Acute hypersensitivity reactions, including anaphylaxis and angioedema, and delayed hypersensitivity reactions, including severe cutaneous adverse drug reactions have been reported postmarketing. Some cases, were life-threatening and required emergency treatment. Discontinue fenofibrate and treat patients appropriately if reactions occur (5.9).

----------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 Pharmaceuticals, Inc. 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 Binding 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

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 hypercholesterolemia or mixed dyslipidemia.

1.2 Severe Hypertriglyceridemia

Antara is also indicated as adjunctive therapy to diet for treatment of adult patients with severe 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)*].

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.

Patients should be advised to swallow Antara capsules whole. Do not open, crush, dissolve or chew capsules.

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 90 mg once daily.

2.2 Primary Hypercholesterolemia and Mixed Dyslipidemia
The initial dose of Antara is 90 mg per day.

2.3 Severe Hypertriglyceridemia
The initial dose is 30 to 90 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 90 mg per day.

2.4 Impaired Renal Function
Treatment with Antara should be initiated at a dose of 30 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 Geriatric 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
- ANTARA® (fenofibrate) capsules, 30 mg are size '4' capsules with opaque light green cap and opaque light green body, imprinted with LUPIN logo and "ANTARA" in black ink on body, and "30" in black ink on cap, containing white to off-white pellets.
- ANTARA® (fenofibrate) capsules, 90 mg are size '3' capsules with opaque dark green cap and opaque white body, imprinted with LUPIN logo and "ANTARA" in black ink on body, and "90" in black ink on cap, containing white to off-white pellets.

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 known hypersensitivity to fenofibric acid or fenofibrate [see *Warnings and Precautions (5.9)*].

5 WARNINGS AND PRECAUTIONS
5.1 Mortality and Coronary Heart Disease Morbidity
The effects of Antara on coronary heart disease morbidity and mortality and non-cardiovascular mortality have not been established.

The Action to Control Cardiovascular Risk in Diabetes Lipid (ACCORD Lipid) trial was a randomized placebo-controlled study of 5518 patients with type 2 diabetes mellitus on background statin therapy treated with fenofibrate. The mean duration of follow-up was 4.7 years. Fenofibrate plus statin combination therapy showed a nonsignificant 8% relative risk

reduction in the primary outcome of major adverse cardiovascular events (MACE), a composite of non-fatal myocardial infarction, nonfatal stroke, and cardiovascular disease death (hazard ratio [HR] 0.92, 95% CI 0.79- 1.08) (p=0.32) as compared to statin monotherapy. In a gender subgroup analysis, the hazard ratio for MACE in men receiving combination therapy versus statin monotherapy was 0.82 (95% CI 0.69-0.99), and the hazard ratio for MACE in women receiving combination therapy versus statin monotherapy was 1.38 (95% CI 0.98-1.94) (interaction p=0.01). The clinical significance of this subgroup finding is unclear.

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

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%, $p \leq 0.01$). 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).

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.

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)*].

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.

Cases of myopathy, including rhabdomyolysis, have been reported with fenofibrates coadministered with colchicine, and caution should be exercised when prescribing fenofibrate with colchicine [see *Drug Interactions (7.4)*].

5.3 Liver Function

Fenofibrate at doses equivalent to 90 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.

Baseline and 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 (PT/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

Anaphylaxis and angioedema have been reported postmarketing with fenofibrate. In some cases, reactions were life-threatening and required emergency treatment. If a patient develops signs or symptoms of an acute hypersensitivity reaction, advise them to seek immediate medical attention and discontinue fenofibrate.

Delayed Hypersensitivity

Severe cutaneous adverse drug reactions (SCAR), including Stevens-Johnson syndrome, Toxic Epidermal Necrolysis, and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), have been reported postmarketing, occurring days to weeks after initiation of fenofibrate. The cases of DRESS were associated with cutaneous reactions (such as rash or exfoliative dermatitis) and a combination of eosinophilia, fever, systemic organ involvement (renal, hepatic, or respiratory). Discontinue fenofibrate and treat patients appropriately if SCAR is suspected.

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; $p < 0.01$).

5.11 Paradoxical Decreases in HDL Cholesterol Levels

There have been postmarketing and clinical trial reports of severe decreases in HDL cholesterol levels (as low as 2 mg/dL) occurring in diabetic and non-diabetic patients initiated on fibrate therapy. The decrease in HDL-C is mirrored by a decrease in apolipoprotein A1. This decrease has been reported to occur within 2 weeks to years after initiation of fibrate therapy. The HDL-C levels remain depressed until fibrate therapy has been withdrawn; the response to withdrawal of fibrate therapy is rapid and sustained. The clinical significance of this decrease in HDL-C is unknown. It is recommended that HDL-C levels be checked within the first few months after initiation of fibrate therapy. If a severely depressed HDL-C level is detected, fibrate therapy should be withdrawn, and the HDL-C level monitored until it has returned to baseline, and fibrate therapy should not be re-initiated.

6 ADVERSE REACTIONS

6.1 Clinical Trials 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 90 mg fenofibrate
**Significantly different from placebo

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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of fenofibrate. 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 causal relationship to drug exposure: myalgia, rhabdomyolysis, pancreatitis, renal failure, muscle spasms, acute renal failure, hepatitis, cirrhosis, anemia, arthralgia, asthenia, severely depressed HDL-cholesterol levels, and interstitial lung disease. Photosensitivity reactions have occurred days to months after initiation; in some of these cases, patients reported a prior photosensitivity reaction to ketoprofen.

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 decrease 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 of renal function. 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 Binding Resins

Since bile acid binding 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.

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

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/m^2.

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/m^2). 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/m^2). No developmental findings were observed at 15 mg/kg/day (at less than 1 times the MRHD, based on body surface area comparisons; mg/m^2).

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/m^2.

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 have not been established in pediatric patients.

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. Fenofibric acid exposure is not influenced by age. 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)*]. Monitoring renal function in patients with renal impairment is recommended.

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 30 mg or 90 mg of micronized fenofibrate. The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyl) phenoxy] 2-methyl-propanoic acid, l-methylethyl ester with the following structural formula:

The empirical formula is $C_{20}H_{21}O_4Cl$ 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 hypromellose, simethicone emulsion, sodium lauryl sulphate, sugar spheres and talc. The capsule shell contains the following inactive ingredients: black iron oxide, D & C Yellow 10, potassium hydroxide, propylene glycol, gelatin, shellac, sodium lauryl sulphate, titanium dioxide. The 30 mg capsule shell contains following additional inactive ingredients: FD & C Blue 2, yellow iron oxide. The 90 mg capsule shell contains following additional inactive ingredients: FD & C Blue 1, FD & C Yellow 6.

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 lipid-lowering effects of fenofibric acid seen in clinical practice have been explained *in vivo* in transgenic mice and *in vitro* in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor α (PPARα). Through this mechanism, 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 decrease 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 PPARα 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 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 radiolabeled 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 capsules 90 mg occur within 2 to 6 hours after administration.

In the presence of a high-fat meal, there was a 26.7% increase in AUC and 15.35% increase in C_{max} of fenofibric acid from Antara capsule 30mg 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.

Elimination
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 dosing.

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] $\leq$ 30 mL/min or estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73m^2) 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 to moderate (CrCl 30-80

mL/min or eGFR 30-59 mL/min/1.73m^2) 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 [see *Dosage and Administration (2.4)*].

Hepatic Impairment
No pharmacokinetic studies have been conducted in patients having hepatic impairement.

Drug-Drug Interactions
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 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	C_{max}
No dosing adjustments required for Antara with the following co-administered drugs				
Lipid-lowing 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-lowing 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/m^2). 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/m^2 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/m^2 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/m^{2}surface area comparisons).

14 CLINICAL STUDIES

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

The effects of fenofibrate at a dose equivalent to 90 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 90 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 equivalent to 90 mg taken once daily with meals, Antara equivalent to 90 mg taken once daily between meals, or placebo. Antara equivalent to 90 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*

* $p \leq 0.05$ vs placebo
** $p \leq 0.05$ vs placebo (log transformed data)

The effect of ANTARA on cardiovascular morbidity and mortality has not been determined.

16 HOW SUPPLIED/STORAGE AND HANDLING

ANTARA® (fenofibrate) Capsules, 30 mg are size '4' capsules with opaque light green cap and opaque light green body, imprinted with LUPIN logo and "ANTARA" in black ink on body, and "30" in black ink on cap, containing white to off-white pellets.

NDC 27437 - 107 - 06 30's Bottle

ANTARA® (fenofibrate) Capsules, 90 mg are size '3' capsules with opaque dark green cap and opaque white body, imprinted with LUPIN logo and "ANTARA" in black ink on body, and "90" in black ink on cap, containing white to off-white pellets.

NDC 27437 - 108 - 06 30's Bottle
NDC 27437 - 108 - 09 90's Bottle
NDC 27437 - 108 - 01 100's Bottle

Storage
Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 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 swallowing each capsule whole.
- 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 .
- to return to their physician's office for routine monitoring.

Manufactured for:
Lupin Pharmaceuticals, Inc.
Baltimore, Maryland 21202
United States.

MADE IN INDIA

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Revised: April 28, 2019 ID: 257316

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, for oral use

Initial U.S. Approval: 1993

----------RECENT MAJOR CHANGES----------

Warnings and Precautions (5.9) 11/2018

----------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 (1.1).
- to reduce triglyceride (TG) levels in adult 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 (5.1).

----------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).
- Severe Hypertriglyceridemia: 43 to 130 mg per day; the dose should be adjusted according to patient response (2.3).
- Renally impaired patients: Initial dose of 43 mg per day (2.4).
- Geriatric patients: Select the dose on the basis of renal function (2.5).

----------DOSAGE FORMS AND STRENGTHS----------

- Oral capsules: 43 mg and 130 mg (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)
- Known 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 (with a significantly higher rate observed with gemfibrozil), particularly 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).
- Acute hypersensitivity reactions, including anaphylaxis and angioedema, and delayed hypersensitivity reactions, including severe cutaneous adverse drug reactions have been reported postmarketing. Some cases were life-threatening and required emergency treatment. Discontinue fibrate and treat patients appropriately if reactions occur (5.9).

----------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 Pharmaceuticals, Inc. 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 Binding 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

Revised: 04/2019

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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 hypercholesterolemia or mixed dyslipidemia.

1.2 Severe Hypertriglyceridemia

Antara is also indicated as adjunctive therapy to diet for treatment of adult patients with severe 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)*].

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.

Patients should be advised to swallow Antara capsules whole. Do not open, crush, dissolve or chew capsules.

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 Primary 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 Geriatric 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” and “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 known hypersensitivity to fenofibric acid or fenofibrate *[see Warnings and Precautions (5.9)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Mortality and Coronary Heart Disease Morbidity

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

The Action to Control Cardiovascular Risk in Diabetes Lipid (ACCORD Lipid) trial was a randomized placebo-controlled study of 5518 patients with type 2 diabetes mellitus on background statin therapy treated with fenofibrate. The mean duration of follow-up was 4.7 years. Fenofibrate plus statin combination therapy showed a non-significant 8% relative risk reduction in the primary outcome of major adverse cardiovascular events (MACE), a composite of non-fatal myocardial infarction, nonfatal stroke, and cardiovascular disease death (hazard ratio [HR] 0.92, 95% CI 0.79-1.08) (p=0.32) as compared to statin monotherapy. In a gender subgroup analysis, the hazard ratio for MACE in men receiving combination therapy versus statin

monotherapy was 0.82 (95% CI 0.69-0.99), and the hazard ratio for MACE in women receiving combination therapy versus statin monotherapy was 1.38 (95% CI 0.98-1.94) (interaction p=0.01). The clinical significance of this subgroup finding is unclear.

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

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%, $p \leq 0.01$). 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).

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.

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)*].

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.

Cases of myopathy, including rhabdomyolysis, have been reported with fenofibrates co-administered with colchicine, and caution should be exercised when prescribing fenofibrate with colchicine [*see Drug Interactions (7.4)*].

5.3 Liver Function

Fenofibrate at doses equivalent 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.

Baseline and 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 3 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 (PT/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
Anaphylaxis and angioedema have been reported postmarketing with fenofibrate. In some cases, reactions were life-threatening and required emergency treatment. If a patient develops signs or symptoms of an acute hypersensitivity reaction, advise them to seek immediate medical attention and discontinue fenofibrate.

Delayed Hypersensitivity
Severe cutaneous adverse drug reactions (SCAR), including Stevens-Johnson syndrome, Toxic Epidermal Necrolysis, and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), have been reported postmarketing, occurring days to weeks after initiation of fenofibrate. The cases of DRESS were associated with cutaneous reactions (such as rash or exfoliative dermatitis)

and a combination of eosinophilia, fever, systemic organ involvement (renal, hepatic, or respiratory). Discontinue fenofibrate and treat patients appropriately if SCAR is suspected.

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; $p < 0.01$).

5.11 Paradoxical Decreases in HDL Cholesterol Levels

There have been postmarketing and clinical trial reports of severe decreases in HDL cholesterol levels (as low as 2 mg/dL) occurring in diabetic and non-diabetic patients initiated on fibrate therapy. The decrease in HDL-C is mirrored by a decrease in apolipoprotein A1. This decrease has been reported to occur within 2 weeks to years after initiation of fibrate therapy. The HDL-C levels remain depressed until fibrate therapy has been withdrawn; the response to withdrawal of fibrate therapy is rapid and sustained. The clinical significance of this decrease in HDL-C is unknown. It is recommended that HDL-C levels be checked within the first few months after initiation of fibrate therapy. If a severely depressed HDL-C level is detected, fibrate therapy should be withdrawn, and the HDL-C level monitored until it has returned to baseline, and fibrate therapy should not be re-initiated.

6 ADVERSE REACTIONS

6.1 Clinical Trials 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

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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of fenofibrate. 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 causal relationship to drug exposure: myalgia, rhabdomyolysis, pancreatitis, renal failure, muscle spasms, acute renal failure, hepatitis, cirrhosis, anemia, arthralgia, asthenia, severely depressed HDL-cholesterol levels, and interstitial lung disease. Photosensitivity reactions have occurred days to months after initiation; in some of these cases, patients reported a prior photosensitivity reaction to ketoprofen.

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 decrease 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 of renal function. 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 Binding Resins

Since bile acid binding 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.

7.4 Colchicine

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

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/m^2.

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/m^2). 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/m^2). No developmental findings were observed at 15 mg/kg/day (at less than 1 times the MRHD, based on body surface area comparisons; mg/m^2).

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/m^2.

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 have not been established in pediatric patients.

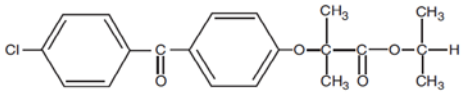
8.5 Geriatric Use
Fenofibric acid is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Fenofibric acid exposure is not influenced by age. Since elderly patients have a higher incidence of renal impairment, 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)*]. Monitoring renal function in patients with renal impairment is recommended.

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, l-methylethyl ester with the following structural formula:



The empirical formula is $C_{20}H_{21}O_4Cl$ 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 lipid-lowering 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 decrease 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 PPARα 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 All) 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 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 fenofibrate 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.
- ***Elimination:*** 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 dosing.
- ***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 or estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73m^2) 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 to moderate (CrCl 30-80 mL/min or eGFR 30-59 mL/min/1.73m^2) 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 *[see Dosage and Administration (2.4)]*.
- ***Hepatic Impairment:*** No pharmacokinetic studies have been conducted in patients having hepatic impairment.
- ***Drug-Drug Interactions:*** *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 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	C_{max}
No dosing adjustments required for Antara with the following co-administered drugs				
Lipid-lowing 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%
Rosiglitaz	8 mg once daily for	Fenofibrate 145 mg[1] once	↑10%	↑3%

Co-Administered Drug	Dosage Regimen of Co-Administered Drug	Dosage Regimen of Fenofibrate	Changes in Fenofibric Acid Exposure	
			AUC	C_{max}
No dosing adjustments required for Antara with the following co-administered drugs				
one	5 days	daily for 14 days		

[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-lowing 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/m^2). 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/m^2 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/m^2 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/m^2 surface area comparisons).

14 CLINICAL STUDIES

14.1 Primary 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 *

* $p \leq 0.05$ vs placebo

** $p \leq 0.05$ vs placebo (log transformed data)

The effect of ANTARA on cardiovascular morbidity and mortality has not been determined.

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).
- 130 mg capsules, imprinted with “130” and a segmented band, on the dark green cap and “ANTARA” and “LUPIN” on the 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 to 30°C (59 to 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 capsules 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, swallowing each capsule whole.

- 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.
- to return to their physician's office for routine monitoring.

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