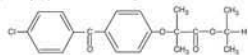


Antara® (fenofibrate) Capsules

DESCRIPTION

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



The empirical formula is C₁₇H₁₅O₄Cl and the molecular weight is 300.83. 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 sulfur dioxide, titanium dioxide, yellow iron oxide, Indigo carmine FD&C Blue #2, D&C Yellow #10 and black ink.

CLINICAL PHARMACOLOGY

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

Fenofibrate, the active metabolite of fenofibrate, produces reductions in total cholesterol, LDL cholesterol, apolipoprotein B, total triglycerides, and triglyceride rich lipoprotein (LDL) in treated patients. In addition, treatment with fenofibrate results in increases in high density lipoprotein (HDL) and apolipoprotein A (apo A) and apo AI.

The effects of fenofibrate acid seen in clinical practice have been explained in *viscité* 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 apolipoprotein C-III (an inhibitor of lipoprotein lipase activity). The resulting fall in triglycerides produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for serum receptors and are catabolized rapidly. Activation of PPAR α also induces an increase in the synthesis of apolipoproteins 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.

Pharmacokinetics/Metabolism:

Plasma concentrations of fenofibrate acid after multiple dose administration of Antara 130 mg capsules are equivalent under low-fat fed conditions, to 200 mg fenofibrate capsules.

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 fenofibrate acid and its glucuronate conjugates, and 25% was excreted in the feces. Peak plasma levels of fenofibrate acid from Antara occur within 4 to 8 hours after administration.

There was less than dose-proportional increase in the systemic exposure of fenofibrate acid from three strengths (43 mg, 87 mg, and 130 mg) of Antara under fasting conditions.

Doses of two- or three-capsules of 43 mg Antara given concurrently were dose-equivalent to single-capsule doses of 87 mg and 130 mg, respectively.

The extent of absorption of fenofibrate 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 20% increase in AUC and 100% increase in C_{max} of fenofibrate acid from Antara relative to fasting state.

Distribution: In healthy volunteers, steady-state plasma levels of fenofibrate 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, fenofibrate acid; no unchanged fenofibrate is detected in plasma.

Fenofibrate acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibrate acid is reduced at the carboxyl moiety to a benzhydryl metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine.

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

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

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

Special Populations:

Geriatrics: In elderly volunteers 71–87 years of age, the oral clearance of fenofibrate 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, without increasing accumulation of the drug or its metabolites.

Pediatrics: Antara has not been investigated in adequate and well-controlled trials in pediatric patients.

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. Therefore, inter-ethnic pharmacokinetic differences are very unlikely.

Renal insufficiency: In a study in patients with severe renal impairment (creatinine clearance <50 mL/min), the rate of clearance of fenofibrate acid was greatly reduced, and the compound accumulated during chronic dosing. However, in patients having moderate renal impairment (creatinine clearance of 30 to 90 mL/min), the oral clearance and the oral volume of distribution of fenofibrate acid are increased compared to healthy adults (2.1 L/h and 95 L versus 1.1 L/h and 30 L, respectively). Therefore, the dosage of Antara should be minimized in patients who have severe renal impairment, while no modification of dosage is required in patients having moderate renal impairment.

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

Drug-drug interactions: In *in vitro* studies using human liver microsomes indicate that fenofibrate and fenofibrate acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C8 at therapeutic concentrations.

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Potential of coarctant-type anticoagulants has been observed with prolongation of the prothrombin time/INR.

While acid sequestrants have been shown to bind other drugs given concurrently, Fenofibrate should be taken at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption (see WARNINGS and PRECAUTIONS).

Clinical Trials

Hypercholesterolemia (Bicrucanone Familial and Nontamulian) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb): 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 209.9 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 1).

Treatment Group	Total-C	LDL-C	HDL-C	TG
Posed Cohort				
Mean baseline lipid values (n=646)				
AI FEN (n=361)	306.9 mg/dL	213.8 mg/dL	52.3 mg/dL	191.0 mg/dL
AI FEN (n=285)	-18.7%*	-20.6%*	+11.6%*	-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 IIIa)				
Mean baseline lipid values (n=334)				
AI FEN (n=193)	307.7 mg/dL	227.7 mg/dL	58.1 mg/dL	101.7 mg/dL
AI FEN (n=141)	-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 IIIb)				
Mean baseline lipid values (n=242)				
AI FEN (n=126)	312.8 mg/dL	219.8 mg/dL	46.7 mg/dL	231.9 mg/dL
AI FEN (n=116)	-16.2%*	-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<0.001, n=213 and 143 respectively).

Hypertriglyceridemia (Fredrickson Type I and IV): The effects of fenofibrate on serum triglycerides were studied in two randomized, double-blind, placebo-controlled clinical trials of 147 hypertriglyceridemic patients (Fredrickson Types IV and V). Patients were treated for eight weeks under protocols that differed only in that one entered patients with baseline triglyceride (TG) levels of 500 to 1500 mg/dL, and the other TG levels of 850 to 1500 mg/dL. In patients with hypertriglyceridemia and normal cholesterolemia with or without hypercholesterolemia (Type IV/V hyperlipidemia), 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 Type IV hyperlipoproteinemia and elevated triglycerides often results in an increase of low density lipoprotein (LDL) cholesterol (see Table 2).

Study 1	Placebo			Fenofibrate				
	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)
Baseline TG levels 350 to 499 mg/dL								
Triglycerides	28	440	450	-0.5	27	432	223	-48.2*
VLDL Triglycerides	19	367	450	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	12	27	128	137	14.5
VLDL Cholesterol	27	99	99	5.8	27	92	48	-44.7*
Study 2								
Baseline TG levels 500 to 1500 mg/dL								
Triglycerides	44	710	750	7.2	48	726	308	-54.5*
VLDL Triglycerides	29	537	571	16.7	33	543	205	-50.6*
Total Cholesterol	44	272	271	0.4	48	261	223	-13.9*
HDL Cholesterol	44	27	28	5.0	48	30	36	22.9*
HDL Cholesterol	42	100	90	-4.7	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 patients with Fredrickson Types IV and V dyslipidemia. 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 3).

Placebo (n=50)	Antara with meals (n=54)		Antara between meals (n=42)			
	Baseline (mean mg/dL)	Mean % change at endpoint	Baseline (mean mg/dL)	Mean % change at endpoint		
Triglycerides	479	+0.7	475	-36.7*	487	-36.9*
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	-8.6
LDL Cholesterol	115	+3.2	120	+15.4*	122	+14.5
VLDL Cholesterol	87	-1.6	92	-34.4*	83	-30.4*

* p < 0.05 vs placebo. The effect of fenofibrate on cardiovascular morbidity and mortality has not been determined.

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INDICATIONS AND USAGE

Treatment of Hypercholesterolemia: Antara is indicated as adjunctive therapy 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 (Fredrickson Types IIa and IIb). Lipid-lowering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and non-pharmacological interventions alone has been inadequate (see National Cholesterol Education Program [NCEP] Treatment Guidelines, below).

Treatment of Hypertriglyceridemia: Antara is also indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia). Improving glycemic control in diabetic patients showing fasting hypertriglyceridemia will usually reduce fasting triglycerides and eliminate chylomicrons 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 Antara therapy on reducing this risk has not been adequately studied.

Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low density lipoprotein (VLDL). Induction of plasma retinoliferation for 14 hours is helpful in distinguishing Types I, IV and V hyperlipoproteinemias.¹

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, like thiazide diuretics and beta-blockers, is sometimes associated with marked 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.

The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet (see WARNINGS and PRECAUTIONS).

Type	Lipoprotein Elevated	Major Lipid Elevation	Minor
I (rare)	Chylomicrons	TG	T ++
IIa	LDL	C	-
IIb	LDL, VLDL	C, TG	TG
III (rare)	LDL	C, TG	TG
IV	VLDL	TG	T ++
V (rare)	Chylomicrons, VLDL	TG	T ++

C=cholesterol; LDL=low density lipoprotein; VLDL=very low density lipoprotein; TG=triglycerides; LDL=intermediate density lipoprotein

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)	
		LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD ¹ or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129, drug optional) ²
≥ 2 Risk Factors (10-year risk <20%)	<130	≥130	≥160 (100-159, drug optional) ²
0-1 Risk Factor ³	<160	≥160	≥190 (160-189, LDL-lowering drug optional)

¹ CHD=coronary heart disease. ² Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrates. Clinical judgment also may call for deferring drug therapy in this subcategory. ³ Almost all people with 0-1 risk factor have 10-year risk <10%, thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

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

CONTRAINDICATIONS

Antara is contraindicated in patients who exhibit hypersensitivity to fenofibrate. Fenofibrate is contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, and patients with unexplained persistent liver function abnormality. Fenofibrate is contraindicated in patients with preexisting gallbladder disease (see WARNINGS).

WARNINGS

Liver Function: Fenofibrate at doses equivalent to 87 mg to 130 mg Antara per day has been associated with increases in serum transaminases (AST [SGOT] or ALT [SGPT]). In a pooled analysis of 10 placebo-controlled trials, increases to >3 times the upper limit of normal occurred in 5.3% of patients taking fenofibrate versus 1.1% of patients treated with placebo. When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. The incidence of increases in transaminases related to fenofibrate therapy appear to be dose related. In an 8-week dose-ranging study, the incidence of ALT or AST elevations to at least three times the upper limit of normal was 13% in patients receiving dosages equivalent to 87 mg to 130 mg Antara per day and was 0% in those receiving dosages equivalent to 43 mg or less Antara per day, or placebo. Hepatocellular chronic active and cholestatic hepatitis associated with fenofibrate therapy have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic active hepatitis.

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

Cholelithiasis:

Fenofibrate, like cholestyramine 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.

Concomitant Oral Anticoagulants:

Caution should be exercised when anticoagulants are given in conjunction with Antara because of the potentiation of coumarin-type anticoagulants in prolonging the prothrombin time/INR. The dosage of the anticoagulant should be reduced to maintain the prothrombin time/INR at the desired level to prevent bleeding complications. Frequent prothrombin time/INR determinations are advisable until it has been definitely determined that the prothrombin time/INR has stabilized.

