

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-695

APPROVED LABELING

1 **Antara™**
2 (fenofibrate) Capsules

3
4 R_x Only

5
6 **DESCRIPTION**

7 Antara (fenofibrate) Capsules, is a lipid regulating agent available as capsules for oral administration. Each
8 capsule contains 43 mg, 87 mg, or 130 mg of micronized fenofibrate. The chemical name for fenofibrate is
9 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester with the following
10 structural formula:
11



12
13 The empirical formula is C₂₀H₂₁O₄Cl and the molecular weight is 360.83; fenofibrate is insoluble in water.
14 The melting point is 79-82°C. Fenofibrate is a white solid which is stable under ordinary conditions.

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

18
19 **CLINICAL PHARMACOLOGY**

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

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

32 The effects of fenofibric acid seen in clinical practice have been explained *in vivo* in transgenic mice
33 and *in vitro* in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor α
34 (PPAR α).

35 Through this mechanism, fenofibrate increases lipolysis and elimination of triglyceride-rich particles
36 from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of
37 lipoprotein lipase activity). The resulting fall in triglycerides produces an alteration in the size and
38 composition of LDL from small, dense particles (which are thought to be atherogenic due to their
39 susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for
40 cholesterol receptors and are catabolized rapidly. Activation of PPAR α also induces an increase in the
41 synthesis of apoproteins A-I, A-II and HDL-cholesterol.

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

44 **Pharmacokinetics/Metabolism**

45 Plasma concentrations of fenofibric acid after multiple dose administration of Antara 130 mg capsules are
46 equivalent, under low-fat fed conditions, to 200 mg Fenofibrate capsules.
47

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48 **Absorption**

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

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

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

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

63 **Distribution**

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

67 **Metabolism**

68 Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite,
69 fenofibric acid; no unchanged fenofibrate is detected in plasma.

70 Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount
71 of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated
72 with glucuronic acid and excreted in urine.

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

75 **Excretion**

76 After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibric
77 acid and fenofibric acid glucuronide. After administration of radiolabelled fenofibrate, approximately 60%
78 of the dose appeared in the urine and 25% was excreted in the feces.

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

81 **Special Populations**

82 **Geriatrics**

83 In elderly volunteers 77 – 87 years of age, the oral clearance of fenofibric acid following a single oral dose
84 of fenofibrate was 1.2 L/h, which compares to 1.1 L/h in young adults. This indicates that a similar dosage
85 regimen can be used in the elderly, without increasing accumulation of the drug or metabolites.

86 **Pediatrics**

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

88 **Gender**

89 No pharmacokinetic difference between males and females has been observed for fenofibrate.

90 **Race**

91 The influence of race on the pharmacokinetics of fenofibrate has not been studied, however fenofibrate is
92 not metabolized by enzymes known for exhibiting inter-ethnic variability. Therefore, inter-ethnic
93 pharmacokinetic differences are very unlikely.

94 **Renal insufficiency**

95 In a study in patients with severe renal impairment (creatinine clearance < 50 mL/min), the rate of
96 clearance of fenofibric acid was greatly reduced, and the compound accumulated during chronic dosage.
97 However, in patients having moderate renal impairment (creatinine clearance of 50 to 90 mL/min), the oral
98 clearance and the oral volume of distribution of fenofibric acid are increased compared to healthy adults
99 (2.1 L/h and 95 L versus 1.1 L/h and 30 L, respectively). Therefore, the dosage of Antara should be

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100 minimized in patients who have severe renal impairment, while no modification of dosage is required in
101 patients having moderate renal impairment.

Hepatic insufficiency

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

Drug-drug interactions

105 *In vitro* studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not
106 inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak
107 inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic
108 concentrations.

109 Potentiation of coumarin-type anticoagulants has been observed with prolongation of the prothrombin
110 time/INR.

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

Clinical Trials

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb)

117 The effects of fenofibrate at a dose equivalent to 130 mg Antara per day were assessed from four
118 randomized, placebo-controlled, double-blind, parallel-group studies including patients with the following
119 mean baseline lipid values: total-C 306.9 mg/dL; LDL-C 213.8 mg/dL; HDL-C 52.3 mg/dL; and
120 triglycerides 191.0 mg/dL. Fenofibrate therapy lowered LDL-C, Total-C, and the LDL-C/HDL-C ratio.
121 Fenofibrate therapy also lowered triglycerides and raised HDL-C (see Table 1).
122

Table 1
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.

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

Hypertriglyceridemia (Fredrickson Type IV and V)

128 The effects of fenofibrate on serum triglycerides were studied in two randomized, double-blind, placebo-
129 controlled clinical trials¹ of 147 hypertriglyceridemic patients (Fredrickson Types IV and V). Patients were
130 treated for eight weeks under protocols that differed only in that one entered patients with baseline

The Antara label has been changed to read:

NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

| Risk Category | LDL Goal (mg/dL) | LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL) | LDL Level at Which to Consider Drug Therapy (mg/dL) |
|--|-------------------------|---|--|
| CHD [†] or CHD risk equivalents (10-year risk >20%) | <100 | ≥100 | ≥30 (100-129: drug optional) ^{††} |
| 2+ Risk Factors (10-year risk ≥20%) | <130 | ≥130 | 10-year risk 10-20%: ≥30 10-year risk <10%: ≥60 |
| 0-1 Risk Factor ^{†††} | <160 | ≥160 | ≥90 (160-189: LDL-lowering drug optional) |

[†] CHD=Coronary heart disease

^{††} 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 fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.

^{†††} 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.

Comment: These changes reflect updated NCEP treatment guidelines and were approved by the medical officer.

The **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, OVERDOSAGE, DOSAGE AND ADMINISTRATION** sections are all unchanged except for the following revisions:

- replacing “Tricor” with “Antara” or “fenofibrate”.
- replacing “Tricor (fenofibrate capsules) micronized” with “Antara”
- replacing “67 mg” with “43 mg”, “134 mg” with “87” mg”, and “200 mg” with “130 mg”.

Comment: These are acceptable changes reflecting the different trade name and different dosage strengths.

The **HOW SUPPLIED** section has been changed to reflect the different strengths, colors, and manufacturer.

The Tricor label states:

“TRICOR® (fenofibrate capsules), micronized, is available as hard gelatin capsules in three strengths:

67 mg yellow capsules, imprinted with ☐ on cap and Abbo-Code identification letters FR on body, available in bottles of 90 (NDC 0074-4342-90).

134 mg white capsules, imprinted with  on cap and Abbo-Code identification letters AR on body, available in bottles of 90 (NDC 0074-6447-90).

200 mg orange capsules, imprinted with  on cap and Abbo-Code identification letters SR on body, available in bottles of 90 (NDC 0074-6415-90).

Storage

Store at controlled room temperature, 15-30°C (59-86°F). Keep out of the reach of children. Protect from moisture.

Manufactured for Abbott Laboratories, North Chicago, IL 60064, U.S.A. by Laboratoires Fournier, S.A., 21300 Chenôve, France

Made in France”

The Antara label reads:

Antara (fenofibrate) Capsules, micronized, is available in three strengths:

43 mg capsules, imprinted with “43” and a segmented band, on the light green cap and “RH405” with the Reliant logo on the white to off-white body, available in bottles of 30 (NDC # 65726-401-10) and 100 (NDC # 65726-401-25).

87 mg capsules, imprinted with “87” and a segmented band, on the dark green cap and “RH405” with the Reliant logo on the light green body, available in bottles of 30 (NDC # 65726-402-10) and 100 (NDC # 65726-402-25).

130 mg capsules, imprinted with “130” and a segmented band, on the dark green cap and “RH405” with the Reliant logo on the white body, available in bottles of 30 (NDC # 65726-403-10) and 100 (NDC # 65726-403-25).

Storage

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

Comment: These changes have been approved by the chemists.

The **REFERENCES** section is unchanged.

The company logo and identifying information at the end of the package insert have been changed to reflect the new sponsor, sponsor address, date of manufacture and package insert identifier.

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131 triglyceride (TG) levels of 500 to 1500 mg/dL, and the other TG levels of 350 to 500 mg/dL. In patients
 132 with hypertriglyceridemia and normal cholesterolemia with or without hyperchylomicronemia (Type IV/V
 133 hyperlipidemia), treatment with fenofibrate at dosages equivalent to 130 mg Antara per day decreased
 134 primarily very low density lipoprotein (VLDL) triglycerides and VLDL cholesterol. Treatment of patients
 135 with Type IV hyperlipoproteinemia and elevated triglycerides often results in an increase of low density
 136 lipoprotein (LDL) cholesterol (see Table 2).
 137

Table 2
Effects of Fenofibrate in Patients With Fredrickson
Type IV/V Hyperlipidemia

| 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 | 12 | 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

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

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INDICATIONS AND USAGE

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Treatment of Hypercholesterolemia

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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-altering 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).

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Treatment of Hypertriglyceridemia

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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 chylomicronemia will usually reduce fasting triglycerides and eliminate chylomicronemia thereby obviating the need for pharmacologic intervention.

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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.

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Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low density lipoprotein (VLDL). Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV and V hyperlipoproteinemia².

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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 massive rises in plasma triglycerides, especially in subjects with

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165 familial hypertriglyceridemia. In such cases, discontinuation of the specific etiologic agent may obviate the
166 need for specific drug therapy of hypertriglyceridemia.

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

171

Fredrickson Classification of Hyperlipoproteinemias

| Type | Lipoprotein Elevated | Lipid Elevation | |
|------------|----------------------|-----------------|-------|
| | | Major | Minor |
| I (rare) | Chylomicrons | TG | ↑↔C |
| IIa | LDL | C | - |
| IIb | LDL, VLDL | C | TG |
| III (rare) | IDL | C, TG | - |
| IV | VLDL | TG | ↑↔C |
| V (rare) | Chylomicrons, VLDL | TG | ↑↔ |

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

172

NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

| Risk Category | LDL Goal (mg/dL) | LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL) | LDL Level at Which to Consider Drug Therapy (mg/dL) |
|--|------------------|--|--|
| CHD [†] or CHD risk equivalents (10-year risk >20%) | <100 | ≥100 | ≥130 (100-129:drug optional) ^{††} |
| 2+ Risk Factors (10-year risk ≤20%) | <130 | ≥130 | 10-year risk 10-20%:≥130 10-year risk <10%:≥160 |
| 0-1 Risk Factor ^{†††} | <160 | ≥160 | ≥190 (160-189: LDL-lowering drug optional) |

[†] CHD=Coronary heart disease

^{††} 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 fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.

^{†††} 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.

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

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CONTRAINDICATIONS

180 Antara is contraindicated in patients who exhibit hypersensitivity to fenofibrate.

181 Fenofibrate is contraindicated in patients with hepatic or severe renal dysfunction, including primary
182 biliary cirrhosis, and patients with unexplained persistent liver function abnormality.

183 Fenofibrate is contraindicated in patients with preexisting gallbladder disease (see WARNINGS).

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WARNINGS

186 **Liver Function:** Fenofibrate at doses equivalent to 87 mg to 130 mg Antara per day has been associated
187 with increases in serum transaminases [AST (SGOT) or ALT (SGPT)]. In a pooled analysis of 10 placebo-

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188 controlled trials, increases to > 3 times the upper limit of normal occurred in 5.3% of patients taking
189 fenofibrate versus 1.1% of patients treated with placebo.

190 When transaminase determinations were followed either after discontinuation of treatment or during
191 continued treatment, a return to normal limits was usually observed. The incidence of increases in
192 transaminases related to fenofibrate therapy appear to be dose related. In an 8-week dose-ranging study,
193 the incidence of ALT or AST elevations to at least three times the upper limit of normal was 13% in
194 patients receiving dosages equivalent to 87 mg to 130 mg Antara per day and was 0% in those receiving
195 dosages equivalent to 43 mg or less Antara per day, or placebo. Hepatocellular, chronic active and
196 cholestatic hepatitis associated with fenofibrate therapy have been reported after exposures of weeks to
197 several years. In extremely rare cases, cirrhosis has been reported in association with chronic active
198 hepatitis.

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

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

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

211 **Concomitant HMG-CoA Reductase Inhibitors:** The combined use of Antara and HMG-CoA reductase
212 inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the
213 increased risk of this drug combination.

214 In a single-dose drug interaction study in 23 healthy adults the concomitant administration of fenofibrate
215 and pravastatin resulted in no clinically important difference in the pharmacokinetics of fenofibric acid,
216 pravastatin or its active metabolite 3 α -hydroxy iso-pravastatin when compared to either drug given alone.

217 The combined use of fibric acid derivatives and HMG-CoA reductase inhibitors has been associated, in
218 the absence of a marked pharmacokinetic interaction, in numerous case reports, with rhabdomyolysis,
219 markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to
220 acute renal failure.

221 The use of fibrates alone, including Antara may occasionally be associated with myositis, myopathy, or
222 rhabdomyolysis. Patients receiving Antara and complaining of muscle pain, tenderness, or weakness
223 should have prompt medical evaluation for myopathy, including serum creatine kinase level determination.
224 If myopathy/myositis is suspected or diagnosed, Antara therapy should be stopped.

225 **Mortality:** The effect of Antara on coronary heart disease morbidity and mortality and non-cardiovascular
226 mortality has not been established.

227 **Other Considerations:** In the Coronary Drug Project, a large study of post myocardial infarction of
228 patients treated for 5 years with clofibrate, there was no difference in mortality seen between the clofibrate
229 group and the placebo group. There was however, a difference in the rate of cholelithiasis and cholecystitis
230 requiring surgery between the two groups (3.0% vs. 1.8%).

231 Because of chemical, pharmacological, and clinical similarities between Atromid-S (clofibrate), and
232 Lopid (gemfibrozil), the adverse findings in 4 large randomized, placebo-controlled clinical studies with
233 these other fibrate drugs may also apply to Antara.

234 In a study conducted by the World Health Organization (WHO), 5000 subjects without known coronary
235 artery disease were treated with placebo or clofibrate for 5 years and followed for an additional one year.
236 There was a statistically significant, higher age-adjusted all-cause mortality in the clofibrate group
237 compared with the placebo group (5.70% vs. 3.96%, $p < 0.01$). Excess mortality was due to a 33%
238 increase in non-cardiovascular causes, including malignancy, post-cholecystectomy complications, and
239 pancreatitis. This appeared to confirm the higher risk of gallbladder disease seen in clofibrate-treated
240 patients studied in the Coronary Drug Project.

241 The Helsinki Heart Study was a large (n=4081) study of middle-aged men without a history of coronary
242 artery disease. Subjects received either placebo or gemfibrozil for 5 years, with a 3.5 year open extension
243 afterward. Total mortality was numerically higher in the gemfibrozil randomization group but did not
244 achieve statistical significance (p=0.19, 95% confidence interval for relative risk G:P=.91-1.64). Although
245 cancer deaths trended higher in the gemfibrozil group (p=0.11), cancers (excluding basal cell carcinoma)
246 were diagnosed with equal frequency in both study groups. Due to the limited size of the study, the relative
247 risk of death from any cause was not shown to be different than that seen in the 9 year follow-up data from
248 World Health Organization study (RR=1.29). Similarly, the numerical excess of gallbladder surgeries in
249 the gemfibrozil group did not differ statistically from that observed in the WHO study.

250 A secondary prevention component of the Helsinki Heart Study enrolled middle-aged men excluded
251 from the primary prevention study because of known or suspected coronary heart disease. Subjects
252 received gemfibrozil or placebo for 5 years. Although cardiac deaths trended higher in the gemfibrozil
253 group, this was not statistically significant (hazard ratio 2.2, 95% confidence interval: 0.94-5.05). The rate
254 of gallbladder surgery was not statistically significant between study groups, but did trend higher in the
255 gemfibrozil group, (1.9% vs. 0.3%, p=0.07). There was a statistically significant difference in the number
256 of appendectomies in the gemfibrozil group (6/311 vs. 0/317, p=0.029).

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258 **PRECAUTIONS**

259 **Initial therapy:** Laboratory studies should be done to ascertain that the lipid levels are consistently
260 abnormal before instituting Antara therapy. Every attempt should be made to control serum lipids with
261 appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as
262 diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known
263 to exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed
264 if possible prior to consideration of triglyceride-lowering drug therapy.

265 **Continued therapy:** Periodic determination of serum lipids should be obtained during initial therapy in
266 order to establish the lowest effective dose of Antara. Therapy should be withdrawn in patients who do not
267 have an adequate response after two months of treatment with the maximum recommended dose of 130 mg
268 per day.

269 **Pancreatitis:** Pancreatitis has been reported in patients taking fenofibrate, gemfibrozil, and clofibrate.
270 This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct
271 drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with
272 obstruction of the common bile duct.

273 **Hypersensitivity Reactions:** Acute hypersensitivity reactions including severe skin rashes requiring
274 patient hospitalization and treatment with steroids have occurred very rarely during treatment with
275 fenofibrate, including rare spontaneous reports of Stevens-Johnson syndrome, and toxic epidermal
276 necrolysis. Urticaria was seen in 1.1 vs 0%, and rash in 1.4 vs 0.8% of fenofibrate and placebo patients
277 respectively in controlled trials.

278 **Hematologic Changes:** Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have
279 been observed in patients following initiation of fenofibrate therapy. However, these levels stabilize during
280 long-term administration. Extremely rare spontaneous reports of thrombocytopenia and agranulocytosis
281 have been received during post-marketing surveillance outside of the U.S. Periodic blood counts are
282 recommended during the first 12 months of Antara administration.

283 **Skeletal muscle:** The use of fibrates alone, including Antara, may occasionally be associated with
284 myopathy. Treatment with drugs of the fibrate class has been associated on rare occasions with
285 rhabdomyolysis, usually in patients with impaired renal function. Myopathy should be considered in any
286 patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of creatine
287 phosphokinase levels.

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

292

293 **Drug Interactions:**

294 **Oral Anticoagulants: CAUTION SHOULD BE EXERCISED WHEN COUMARIN**
295 **ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ANTARA. THE DOSAGE OF**
296 **THE ANTICOAGULANTS SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN**
297 **TIME/INR AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS.**
298 **FREQUENT PROTHROMBIN TIME/INR DETERMINATIONS ARE ADVISABLE UNTIL IT**
299 **HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN TIME/INR HAS**
300 **STABILIZED.**

301 **HMG-CoA reductase inhibitors:** The combined use of Antara and HMG-CoA reductase inhibitors
302 should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased
303 risk of this drug combination (see WARNINGS).

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

306 **Cyclosporine:** Because cyclosporine can produce nephrotoxicity with decreases in creatinine clearance and
307 rises in serum creatinine, and because renal excretion is the primary elimination route of fibrate drugs
308 including Antara, there is a risk that an interaction will lead to deterioration. The benefits and risks of
309 using Antara with immunosuppressants and other potentially nephrotoxic agents should be carefully
310 considered, and the lowest effective dose employed.

311 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** In a 24-month study in rats (10, 45, and
312 200 mg/kg; 0.3, 1, and 6 times the maximum recommended human dose on the basis of mg/meter² of
313 surface area), the incidence of liver carcinoma was significantly increased at 6 times the maximum
314 recommended human dose in males and females. A statistically significant increase in pancreatic
315 carcinomas occurred in males at 1 and 6 times the maximum recommended human dose; there were also
316 increases in pancreatic adenomas and benign testicular interstitial cell tumors at 6 times the maximum
317 recommended human dose in males. In a second 24-month study in a different strain of rats (doses of 10
318 and 60 mg/kg; 0.3 and 2 times the maximum recommended human dose based on mg/meter² surface area),
319 there were significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases
320 in interstitial cell tumors of the testes at 2 times the maximum recommended human dose.

321 A comparative carcinogenicity study was done in rats comparing three drugs: fenofibrate (10 and
322 70 mg/kg; 0.3 and 1.6 times the maximum recommended human dose), clofibrate (400 mg/kg; 1.6 times the
323 human dose), and gemfibrozil (250 mg/kg; 1.7 times the human dose) (multiples based on mg/meter²
324 surface area). Pancreatic acinar adenomas were increased in males and females on fenofibrate;
325 hepatocellular carcinoma and pancreatic acinar adenomas were increased in males and hepatic neoplastic
326 nodules in females treated with clofibrate; hepatic neoplastic nodules were increased in males and females
327 treated with gemfibrozil while testicular interstitial cell tumors were increased in males on all three drugs.

328 In a 21-month study in mice at doses of 10, 45, and 200 mg/kg (approximately 0.2, 0.7 and 3 times the
329 maximum recommended human dose on the basis of mg/meter² surface area), there were statistically
330 significant increases in liver carcinoma at 3 times the maximum recommended human dose in both males
331 and females. In a second 18-month study at the same doses, there was a significant increase in liver
332 carcinoma in male mice and liver adenoma in female mice at 3 times the maximum recommended human
333 dose.

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

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

341 **Pregnancy Category C:** Fenofibrate has been shown to be embryocidal and teratogenic in rats when given
342 in doses 7 to 10 times the maximum recommended human dose and embryocidal in rabbits when given at 9
343 times the maximum recommended human dose (on the basis of mg/meter² surface area). There are no
344 adequate and well-controlled studies in pregnant women. Fenofibrate should be used during pregnancy
345 only if the potential benefit justifies the potential risk to the fetus.

346 Administration of 9 times the maximum recommended human dose of fenofibrate to female rats before
347 and throughout gestation caused 100% of dams to delay delivery and resulted in a 60% increase in post-

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348 implantation loss, a decrease in litter size, a decrease in birth weight, a 40% survival of pups at birth, a 4%
349 survival of pups as neonates, and a 0% survival of pups to weaning, and an increase in spina bifida.

350 Administration of 10 times the maximum recommended human dose to female rats on days 6-15 of
351 gestation caused an increase in gross, visceral and skeletal findings in fetuses (domed head/hunched
352 shoulders/rounded body/abnormal chest, kyphosis, stunted fetuses, elongated sternal ribs, malformed
353 sternbrae, extra foramen in palatine, misshapen vertebrae, supernumerary ribs).

354 Administration of 7 times the maximum recommended human dose to female rats from day 15 of
355 gestation through weaning caused a delay in delivery, a 40% decrease in live births, a 75% decrease in
356 neonatal survival, and decreases in pup weight, at birth as well as on days 4 and 21 post-partum.

357 Administration of 9 and 18 times the maximum recommended human dose to female rabbits caused
358 abortions in 10% of dams at 9 times and 25% of dams at 18 times the maximum recommended human dose
359 and death of 7% of fetuses at 18 times the maximum recommended human dose.

360 **Nursing mothers:** Fenofibrate should not be used in nursing mothers. Because of the potential for
361 tumorigenicity seen in animal studies, a decision should be made whether to discontinue nursing or to
362 discontinue the drug.

363 **Pediatric Use:** Safety and efficacy in pediatric patients have not been established.

364 **Geriatric Use:** Fenofibric acid is known to be substantially excreted by the kidney, and the risk of adverse
365 reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are
366 more likely to have decreased renal function, care should be taken in dose selection.

367

368 **ADVERSE REACTIONS**

369 **CLINICAL:** Adverse events reported by 2% or more of patients treated with fenofibrate during the
370 double-blind, placebo-controlled trials, regardless of causality, are listed in the table below. Adverse
371 events led to discontinuation of treatment in 5.0% of patients treated with fenofibrate and in 3.0% treated
372 with placebo. Increases in liver function tests were the most frequent events, causing discontinuation of
373 fenofibrate treatment in 1.6% of patients in double-blind trials.

374

| BODY SYSTEM | Fenofibrate* | Placebo |
|-------------------------------|---------------------|----------------|
| Adverse Event | (N=439) | (N=365) |
| BODY AS A WHOLE | | |
| Abdominal Pain | 4.6% | 4.4% |
| Back Pain | 3.4% | 2.5% |
| Headache | 3.2% | 2.7% |
| Asthenia | 2.1% | 3.0% |
| Flu Syndrome | 2.1% | 2.7% |
| DIGESTIVE | | |
| Liver Function Tests Abnormal | 7.5%** | 1.4% |
| Diarrhea | 2.3% | 4.1% |
| Nausea | 2.3% | 1.9% |
| Constipation | 2.1% | 1.4% |
| METABOLIC AND | | |
| NUTRITIONAL DISORDERS | | |
| SGPT Increased | 3.0% | 1.6% |
| Creatine Phosphokinase | 3.0% | 1.4% |
| Increased | | |
| SGOT Increased | 3.4%** | 0.5% |
| RESPIRATORY | | |
| Respiratory Disorder | 6.2% | 5.5% |
| Rhinitis | 2.3% | 1.1% |

* Dosage equivalent to 130 mg Antara

** Significantly different from Placebo

375

376 Additional adverse events reported by three or more patients in placebo-controlled trials or reported in
377 other controlled or open trials, regardless of causality are listed below.

378 **BODY AS A WHOLE:** Chest pain, pain (unspecified), infection, malaise, allergic reaction, cyst, hernia,
379 fever, photosensitivity reaction, and accidental injury.

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380 *CARDIOVASCULAR SYSTEM:* Angina pectoris, hypertension, vasodilatation, coronary artery disorder,
381 electrocardiogram abnormal, ventricular extrasystoles, myocardial infarct, peripheral vascular disorder,
382 migraine, varicose vein, cardiovascular disorder, hypotension, palpitation, vascular disorder, arrhythmia,
383 phlebitis, tachycardia, extrasystoles, and atrial fibrillation.
384 *DIGESTIVE SYSTEM:* Dyspepsia, flatulence, nausea, increased appetite, gastroenteritis, cholelithiasis,
385 rectal disorder, esophagitis, gastritis, colitis, tooth disorder, vomiting, anorexia, gastrointestinal disorder,
386 duodenal ulcer, nausea and vomiting, peptic ulcer, rectal hemorrhage, liver fatty deposit, cholecystitis,
387 eructation, gamma glutamyl transpeptidase, and diarrhea.
388 *ENDOCRINE SYSTEM:* diabetes mellitus
389 *HEMIC AND LYMPHATIC SYSTEM:* Anemia, leukopenia, ecchymosis, eosinophilia, lymphadenopathy,
390 and thrombocytopenia.
391 *METABOLIC AND NUTRITIONAL DISORDERS:* Creatinine increased, weight gain, hypoglycemia, gout,
392 weight loss, edema, hyperuricemia, and peripheral edema.
393 *MUSCULOSKELETAL SYSTEM:* Myositis, myalgia, arthralgia, arthritis, tenosynovitis, joint disorder,
394 arthrosis, leg cramps, bursitis, and myasthenia.
395 *NERVOUS SYSTEM:* Dizziness, insomnia, depression, vertigo, libido decreased, anxiety, paresthesia, dry
396 mouth, hypertonia, nervousness, neuralgia, and somnolence.
397 *RESPIRATORY SYSTEM:* Pharyngitis, bronchitis, cough increased, dyspnea, asthma, pneumonia,
398 laryngitis, and sinusitis.
399 *SKIN AND APPENDAGES:* Rash, pruritus, eczema, herpes zoster, urticaria, acne, sweating, fungal
400 dermatitis, skin disorder, alopecia, contact dermatitis, herpes simplex, maculopapular rash, nail disorder,
401 and skin ulcer.
402 *SPECIAL SENSES:* conjunctivitis, eye disorder, amblyopia, ear pain, otitis media, abnormal vision,
403 cataract specified, and refraction disorder.
404 *UROGENITAL SYSTEM:* Urinary frequency, prostatic disorder, dysuria, kidney function abnormal,
405 urolithiasis, gynecomastia, unintended pregnancy, vaginal moniliasis, and cystitis.

406
407 **OVERDOSAGE**

408 There is no specific treatment for overdose with Antara. General supportive care of the patient is indicated,
409 including monitoring of vital signs and observation of clinical status, should an overdose occur. If
410 indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual
411 precautions should be observed to maintain the airway. Because fenofibrate is highly bound to plasma
412 proteins, hemodialysis should not be considered.

413
414 **DOSAGE AND ADMINISTRATION**

415 Patients should be placed on an appropriate lipid-lowering diet before receiving Antara, and should
416 continue this diet during treatment with Antara. Antara capsules should be taken with meals, thereby
417 optimizing the bioavailability of the medication.

418 For the treatment of adult patients with primary hypercholesterolemia or mixed hyperlipidemia, the
419 initial dose of Antara is 130 mg per day.

420 For adult patients with hypertriglyceridemia, the initial dose is 43 to 130 mg per day. Dosage should
421 be individualized according to patient response, and should be adjusted if necessary following repeat lipid
422 determinations at 4 to 8 week intervals. The maximum dose is 130 mg per day.

423 Treatment with Antara should be initiated at a dose of 43 mg/day in patients having impaired renal
424 function, and increased only after evaluation of the effects on renal function and lipid levels at this dose. In
425 the elderly, the initial dose should likewise be limited to 43 mg/day.

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

428
429 **HOW SUPPLIED**

430 Antara (fenofibrate) Capsules, micronized, is available in three strengths:
431

Antara™
(fenofibrate) Capsules

432 43 mg capsules, imprinted with "43" and a segmented band, on the light green cap and "RH405" with the
433 Reliant logo on the white to off-white body, available in bottles of 30 (NDC # 65726-401-10) and 100
434 (NDC # 65726-401-25).

435
436 87 mg capsules, imprinted with "87" and a segmented band, on the dark green cap and "RH405" with the
437 Reliant logo on the light green body, available in bottles of 30 (NDC # 65726-402-10) and 100 (NDC #
438 65726-402-25).

439
440 130 mg capsules, imprinted with "130" and a segmented band, on the dark green cap and "RH405" with the
441 Reliant logo on the white body, available in bottles of 30 (NDC # 65726-403-10) and 100 (NDC # 65726-
442 403-25).

443
444 **Storage**

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

447
448

449 **REFERENCES**

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456 Patients with Type IIA or IIB Hyperlipidemia. *Arteriosclerosis*. 6, pp. 670-678, 1986.

457
458 **Rx only**

459
460 October 2004

461
462



463
464

465 Manufactured for:
466 Reliant Pharmaceuticals, Inc.
467 Liberty Corner, NJ 07938, USA
468 By:

469 Ethypharm Industries
470 Le Grand Quevilly, France

471
472

473 **Address Medical Inquiries to:**
474 Reliant Pharmaceuticals, Inc.

475 **Medical Affairs**
476 110 Allen Road
477 Liberty Corner, NJ 07938, USA

478
479

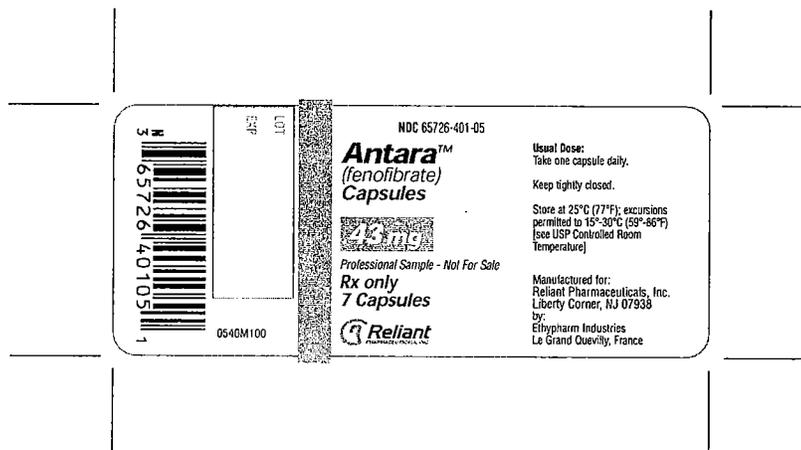
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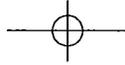
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- PMS 1245
- Non-varnish area inside

Label Size: 1 3/8" x 3 1/4"





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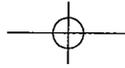
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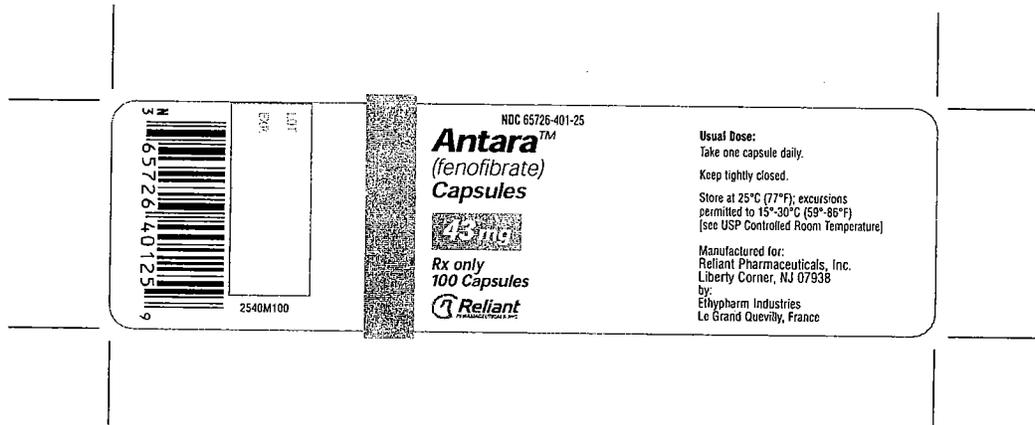
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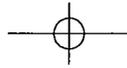
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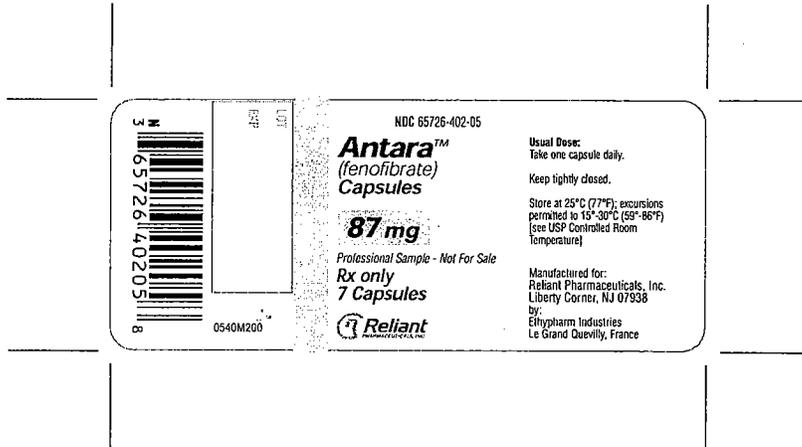
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▒ PMS 115

▒ PMS 1245

□ Non-varnish area inside

Label Size: 1 3/8" x 3 1/4"



■ Black

▒ PMS 115

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□ Non-varnish area inside

Label Size: 1 3/8" x 3 1/4"

NDC 65726-402-10

AntaraTM
(fenofibrate)
Capsules

87 mg

Rx only
30 Capsules

Reliant
PHARMACEUTICALS, INC.

Usual Dose:
Take one capsule daily.
Keep tightly closed.

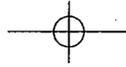
Store at 25°C (77°F); excursions
permitted to 15°-30°C (59°-86°F)
[see USP Controlled Room
Temperature]

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by:
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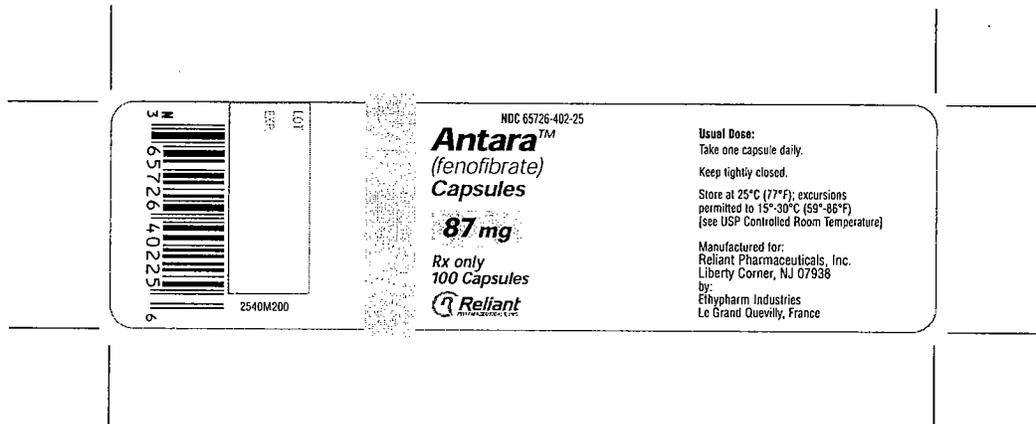
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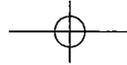
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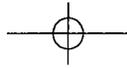
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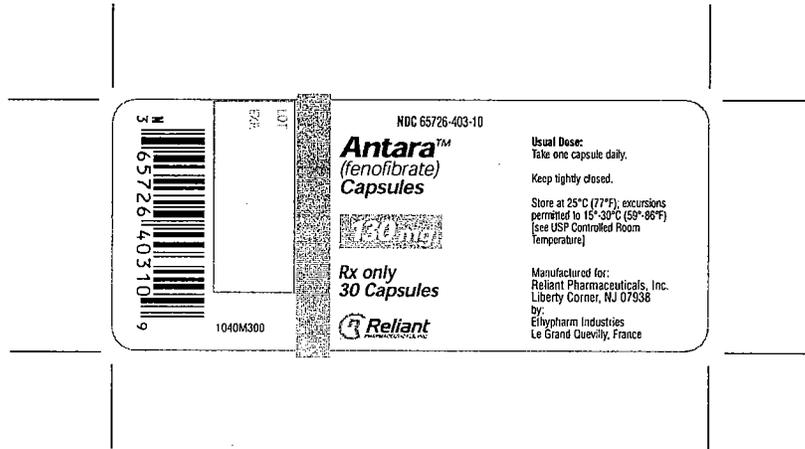
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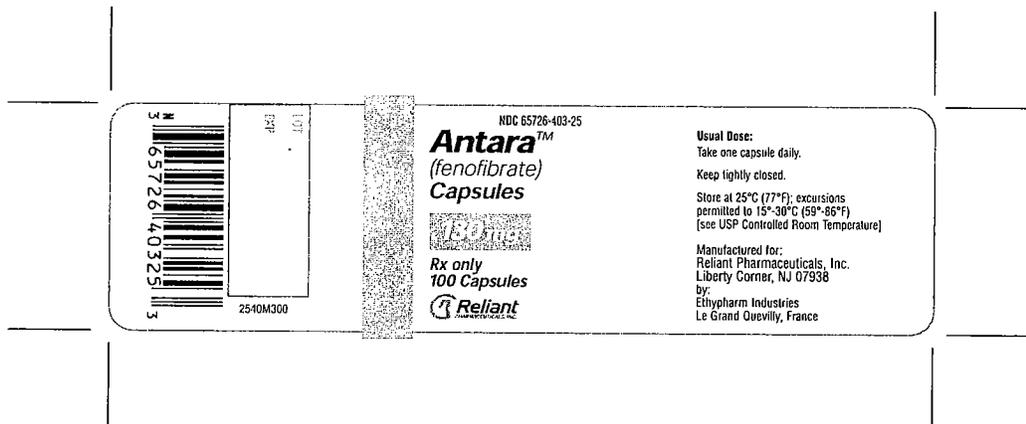
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- PMS 3255
- PMS 1245
- Non-varnish area inside

Label Size: 1 3/8" x 3 1/4"





- Black
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 - Non-varnish area inside
- Label Size: 1 1/4" x 4 1/2"



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