CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75034

APPROVAL LETTER

ANDA 75-034

JUL 20 1998

Apotex Corp.
Attention: Marcy Macdonald
U.S. Agent for TorPharm
50 Lakeview Parkway, Suite 127
Vernon Hills, IL 60061

Dear Madam:

This is in reference to your abbreviated new drug application dated December 20, 1996 submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Gemfibrozil Tablets USP, 600 mg.

Reference is also made to your amendments dated November 17, 1997 and May 19, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Gemfibrozil Tablets USP, 600 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Lopid® Tablets, 600 mg, of Parke Davis, Division of Warner-Lambert Co.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

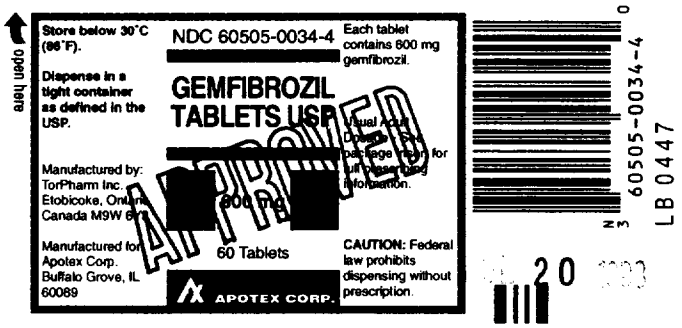
7-20-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75034

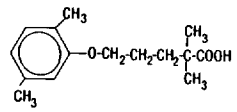
DRAFT FINAL PRINTED LABELING


open here
Store below 30°C (86°F).
Dispense in a tight container as defined in the USP.
Manufactured by:
TorPharm Inc.
Etobicoke, Ontario
Canada M9W 6R1
Manufactured for
Apotex Corp.
Buffalo Grove, IL
60089
NDC 60505-0034-4
GEMFIBROZIL TABLETS USP
600 mg
60 Tablets
APOTEX CORP.
Each tablet contains 600 mg gemfibrozil.
Usual Adult Dosage: See package insert for full prescribing information.
CAUTION: Federal law prohibits dispensing without prescription.
APPROVED
3 60505-0034-4 0
LB 0447
20

GEMFIBROZIL TABLETS USP 600 mg

DESCRIPTION

Gemfibrozil is a lipid regulating agent. Gemfibrozil tablets USP, for oral administration, contain 600 mg gemfibrozil. Each tablet also contains the following inactive ingredients: Colloidal Silicon Dioxide NF, Croscarmellose Sodium NF, Hydroxypropyl Cellulose NF, Hydroxypropyl Methylcellulose 2910 USP, Magnesium Stearate NF, Methylcellulose USP, Polyethylene Glycol NF, Purified Water USP and Titanium Dioxide USP. The chemical name is Pentanoic Acid, 5-(2,5-dimethylphenoxy)-2,2-dimethyl-2,2-Dimethyl-5-(2,5-xylyloxy)valeric acid, with the following structural formula:



The molecular formula is $C_{15}H_{22}O_3$ and the molecular weight is 250.34; the solubility in water and acid is 0.0019% and in dilute base it is greater than 1%. The melting point is 58°- 61°C. Gemfibrozil is a white solid which is stable under ordinary conditions.

CLINICAL PHARMACOLOGY

Gemfibrozil is a lipid regulating agent which decreases serum triglycerides and very low density lipoprotein (VLDL) cholesterol, and increases high density lipoprotein (HDL) cholesterol. While modest decreases in total and low density lipoprotein (LDL) cholesterol may be observed with gemfibrozil therapy, treatment of patients with elevated triglycerides due to Type IV hyperlipoproteinemia often results in a rise in LDL-cholesterol. LDL-cholesterol levels in Type IIb patients with elevations of both serum LDL-cholesterol and triglycerides are, in general, minimally affected by gemfibrozil treatment; however, gemfibrozil usually raises HDL-cholesterol significantly in this group. Gemfibrozil increases levels of high density lipoprotein (HDL) subfractions HDL_2 and HDL_3, as well as apolipoproteins AI and AII. Epidemiological studies have shown that both low HDL-cholesterol and high LDL-cholesterol are independent risk factors for coronary heart disease.

In the primary prevention component of the Helsinki Heart Study (refs 1,2), in which 4081 male patients between the ages of 40 and 55 were studied in a randomized, double-blind, placebo-controlled fashion, gemfibrozil therapy was associated with significant reductions in total plasma triglycerides and a significant increase in high density lipoprotein cholesterol. Moderate reductions in total plasma cholesterol and low density lipoprotein cholesterol were observed for the gemfibrozil treatment group as a whole, but the lipid response was heterogeneous, especially among different Fredrickson types. The study involved subjects with serum non-HDL-cholesterol of over 200 mg/dL and no previous history of coronary heart disease. Over the 5-year study period, the gemfibrozil group experienced a 1.4% absolute (34% relative) reduction in the rate of serious coronary events (sudden cardiac deaths plus fatal and nonfatal myocardial infarctions) compared to placebo, $p = 0.04$ (see Table I). There was a 37% relative reduction in the rate of nonfatal myocardial infarction compared to placebo, equivalent to a treatment-related difference of 13.1 events per thousand persons. Deaths from any cause during the double-blind portion of the study totaled 44 (2.2%) in the gemfibrozil randomization group and 43 (2.1%) in the placebo group.

Table I
Reduction in CHD Rates (events per 1000 patients) by Baseline Lipids[1] in the Helsinki Heart Study, Years 0 - 5[2]

	All Patients			LDL-C > 175; HDL-C > 46.4			LDL-C > 175; TG > 177			LDL-C > 175; TG > 200; HDL-C < 35		
	P[3]	G[3]	Dif[4]	P	G	Dif	P	G	Dif	P	G	Dif
Incidence of Events[5]	41	27	14	32	29	3	71	44	27	149	64	85

[1]lipid values in mg/dL at baseline
[2]P=placebo group; G=Gemfibrozil group
[3]difference in rates between placebo and gemfibrozil groups
[4]fatal and nonfatal myocardial infarctions plus sudden cardiac deaths (events per 1000 patients over 5 years)

Among Fredrickson types, during the 5-year double-blind portion of the primary prevention component of the Helsinki Heart Study, the greatest reduction in the incidence of serious coronary events occurred in Type IIb patients who had elevations of both LDL-cholesterol and total plasma triglycerides. This subgroup of Type IIb gemfibrozil group patients had a lower mean HDL-cholesterol level at baseline than the Type IIa subgroup that had elevations of LDL-cholesterol and normal plasma triglycerides. The mean increase in HDL-cholesterol among the Type IIb patients in this study was 12.6% compared to placebo. The mean change in LDL-cholesterol among Type IIb patients was -4.1% with gemfibrozil compared to a rise of 3.9% in the placebo subgroup. The Type IIb subjects in the Helsinki Heart Study had 26 fewer coronary events per thousand persons over 5 years in the gemfibrozil group compared to placebo. The difference in coronary events was substantially greater between gemfibrozil and placebo for that subgroup of patients with the triad of LDL-cholesterol >175 mg/dL (>4.5 mmol), triglycerides > 200 mg/dL (>2.2 mmol), and HDL-cholesterol <35 mg/dL (<0.90 mmol) (see Table I).

Further information is available from a 3.5 year (8.5 year cumulative) follow-up of all subjects who had participated in the Helsinki Heart Study. At the completion of the Helsinki Heart Study, subjects could choose to start, stop, or continue to receive gemfibrozil, without knowledge of their own lipid values or double-blind treatment. 60% of patients originally randomized to placebo began therapy with gemfibrozil and 80% of patients originally randomized to gemfibrozil continued medication. After approximately 6.5 years following randomization, all patients were informed of their original treatment group and lipid values during the 5 years of the double-blind treatment. After further elective changes in gemfibrozil treatment status, 61% of patients in the group originally randomized to gemfibrozil were taking drug; in the group originally randomized to placebo, 65% were taking gemfibrozil. The event rate per 1000 occurring during the open-label follow-up period is detailed in Table II.

Table II

Cardiac Events and All-Cause Mortality
(events per 1000 patients) Occurring during the 3.5 Year Open-Label Follow-up to the Helsinki Heart Study[1]

Group:	PDrop N=215	PN N=494	PG N=1283	GDrop N=221	GN N=574	GG N=1207
Cardiac Events	38.8	22.9	22.5	37.2	28.3	25.4
All-Cause Mortality	41.9	22.3	15.6	72.3	19.2	24.9

[1]The six open-label groups are designated first by the original randomization (P=placebo, G= Gemfibrozil) and then by the drug taken in the follow-up period (N = Attend clinic but took no drug, G = Gemfibrozil, Drop = No attendance at clinic during open-label).

Cumulative mortality through 8.5 years showed a 20% relative excess of deaths in the group originally randomized to gemfibrozil versus the originally randomized placebo group and a 20% relative decrease in cardiac events in the group originally randomized to gemfibrozil versus the originally randomized placebo group (see Table III). This analysis of the originally randomized "intent-to-treat" population neglects the possible complicating effects of treatment switching during the open-label phase. Adjustment of hazard ratios taking into account open-label treatment status from years 6.5 to 8.5 could change the reported hazard ratios for mortality toward unity.

Table III

Cardiac Events, Cardiac Deaths, Non-Cardiac Deaths and All-Cause Mortality in the Helsinki Heart Study, Years 0 - 8.5[1]

Event	Gemfibrozil at Study Start	Placebo at Study Start	Gemfibrozil: Placebo Hazard Ratio[2]	CI Hazard Ratio[3]
Cardiac Events[4]	110	131	0.80	0.62 - 1.03
Cardiac Deaths	36	38	0.96	0.63 - 1.54
Non-Cardiac Deaths	65	45	1.40	0.95 - 2.05
All-Cause Mortality	101	83	1.20	0.90 - 1.61

[1]Intention-to-Treat Analysis of originally randomized patients neglecting the open-label treatment switches and exposure to study conditions.
[2]Hazard ratio for risk of event in the group originally randomized to gemfibrozil compared to the group originally randomized to placebo neglecting open-label treatment switch and exposure to study condition.
[3]95% confidence intervals of gemfibrozil:placebo group hazard ratio.
[4]Fatal and non-fatal myocardial infarctions plus sudden cardiac deaths over the 8.5 year period.

It is not clear to what extent the findings of the primary prevention component of the Helsinki Heart Study can be extrapolated to other segments of the dyslipidemic population not studied (such as women, younger or older males, or those with lipid abnormalities limited solely to HDL-cholesterol) or to other lipid-altering drugs.

The secondary prevention component of the Helsinki Heart Study was conducted over 5 years in parallel and at the same centers in Finland in 628 middle-aged males excluded from the primary prevention component of the Helsinki Heart Study because of a history of angina, myocardial infarction or unexplained ECG changes (ref. 3). The primary efficacy endpoint of the study was cardiac events (the sum of fatal and non-fatal myocardial infarctions and sudden cardiac deaths). The hazard ratio (gemfibrozil:placebo) for cardiac events was 1.47 (95% confidence limits 0.88 - 2.48, $p = 0.14$). Of the 35 patients in the gemfibrozil group who experienced cardiac events, 12 patients suffered events after discontinuation from the study. Of the 24 patients in the placebo group with cardiac events, 4 patients suffered events after discontinuation from the study. There were 17 cardiac deaths in the gemfibrozil group and 8 in the placebo group (hazard ratio 2.18; 95% confidence limits 0.94 - 5.05, $p = 0.06$). Ten of these deaths in the gemfibrozil group and 3 in the placebo group occurred after discontinuation from therapy. In this study of patients with known or suspected coronary heart disease, no benefit from gemfibrozil treatment was observed in reducing cardiac events or cardiac deaths. Thus, gemfibrozil has shown benefit only in selected dyslipidemic patients without suspected or established coronary heart disease. Even in patients with coronary heart disease and the triad of elevated LDL-cholesterol, elevated triglycerides, plus low HDL-cholesterol, the possible effect of

Further information is available from a 3.5 year (8.5 year cumulative) follow-up of all subjects who had participated in the Helsinki Heart Study. At the completion of the Helsinki Heart Study, subjects could choose to start, stop, or continue to receive gemfibrozil, without knowledge of their own lipid values or double-blind treatment. 60% of patients originally randomized to placebo began therapy with gemfibrozil and 60% of patients originally randomized to gemfibrozil continued medication. After approximately 6.5 years following randomization, all patients were informed of their original treatment group and lipid values during the 5 years of the double-blind treatment. After further elective changes in gemfibrozil treatment status, 61% of patients in the group originally randomized to gemfibrozil were taking drug; in the group originally randomized to placebo, 65% were taking gemfibrozil. The event rate per 1000 occurring during the open-label follow-up period is detailed in Table II.

Table II
Cardiac Events and All-Cause Mortality
(events per 1000 patients) Occurring during the 3.5 Year Open-Label Follow-up to the Helsinki Heart Study*

Group:	PDrop N=215	PN N=494	PG N=1283	GDrop N=221	GN N=574	GG N=1207
Cardiac Events	38.8	22.9	22.5	37.2	26.3	25.4
All-Cause Mortality	41.9	22.3	15.6	72.3	19.2	24.9

*The six open-label groups are designated first by the original randomization (P =placebo, G= Gemfibrozil) and then by the drug taken in the follow-up period (N = Attend clinic but took no drug, G = Gemfibrozil, Drop = No attendance at clinic during open-label).

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Table III
Cardiac Events, Cardiac Deaths, Non-Cardiac Deaths and All-Cause Mortality in the Helsinki Heart Study, Years 0 - 8.5*

Event	Gemfibrozil at Study Start	Placebo at Study Start	Gemfibrozil: Placebo Hazard Ratio†	CI Hazard Ratio‡
Cardiac Events§	110	131	0.80	0.62 - 1.03
Cardiac Deaths	36	38	0.98	0.63 - 1.54
Non-Cardiac Deaths	65	45	1.40	0.95 - 2.05
All-Cause Mortality	101	83	1.20	0.90 - 1.61

*Intention-to-Treat Analysis of originally randomized patients neglecting the open-label treatment switches and exposure to study conditions.
†Hazard ratio for risk of event in the group originally randomized to gemfibrozil compared to the group originally randomized to placebo neglecting open-label treatment switch and exposure to study condition.
‡95% confidence intervals of gemfibrozil:placebo group hazard ratio.
§Fatal and non-fatal myocardial infarctions plus sudden cardiac deaths over the 8.5 year period.

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The secondary prevention component of the Helsinki Heart Study was conducted over 5 years in parallel and at the same centers in Finland in 628 middle-aged males excluded from the primary prevention component of the Helsinki Heart Study because of a history of angina, myocardial infarction or unexplained ECG changes (ref. 3). The primary efficacy endpoint of the study was cardiac events (the sum of fatal and non-fatal myocardial infarctions and sudden cardiac deaths). The hazard ratio (gemfibrozil:placebo) for cardiac events was 1.47 (95% confidence limits 0.88 - 2.48, $p = 0.14$). Of the 35 patients in the gemfibrozil group who experienced cardiac events, 12 patients suffered events after discontinuation from the study. Of the 24 patients in the placebo group with cardiac events, 4 patients suffered events after discontinuation from the study. There were 17 cardiac deaths in the gemfibrozil group and 8 in the placebo group (hazard ratio 2.18, 95% confidence limits 0.94 - 5.05, $p = 0.06$). Ten of these deaths in the gemfibrozil group and 3 in the placebo group occurred after discontinuation from therapy. In this study of patients with known or suspected coronary heart disease, no benefit from gemfibrozil treatment was observed in reducing cardiac events or cardiac deaths. Thus, gemfibrozil has shown benefit only in selected dyslipidemic patients without suspected or established coronary heart disease. Even in patients with coronary heart disease and the triad of elevated LDL-cholesterol, elevated triglycerides, plus low HDL-cholesterol, the possible effect of gemfibrozil on coronary events has not been adequately studied.

No efficacy in the patients with established coronary heart disease was observed during the Coronary Drug Project with the chemically and pharmacologically related drug, clofibrate. The Coronary Drug Project was a 6-year randomized, double-blind study involving 1000 clofibrate, 1000 nicotinic acid, and 3000 placebo patients with known coronary heart disease. A clinically and statistically significant reduction in myocardial infarctions was seen in the concurrent nicotinic acid group compared to placebo; no reduction was seen with clofibrate.

The mechanism of action of gemfibrozil has not been definitely established. In man, gemfibrozil has been shown to inhibit peripheral lipolysis and to decrease the hepatic extraction of free fatty acids, thus reducing hepatic triglyceride production. Gemfibrozil inhibits synthesis and increases clearance of VLDL carrier apolipoprotein B, leading to a decrease in VLDL production.

Animal studies suggest that gemfibrozil may, in addition to elevating HDL-cholesterol, reduce incorporation of long-chain fatty acids into newly formed triglycerides, accelerate turnover and removal of cholesterol from the liver, and increase excretion of cholesterol in the feces. Gemfibrozil is well absorbed from the gastrointestinal tract after oral administration. Peak plasma levels occur in 1 to 2 hours with a plasma half-life of 1.5 hours. Plasma levels appear proportional to dose and do not demonstrate accumulation across time following multiple doses.

Gemfibrozil mainly undergoes oxidation of a ring methyl group to successively form a hydroxymethyl and a carboxyl metabolite. Approximately seventy percent of the administered human dose is excreted in the urine, mostly as the glucuronide conjugate, with less than 2% excreted as unchanged gemfibrozil. Six percent of the dose is accounted for in the feces.

INDICATIONS AND USAGE

Gemfibrozil tablets are indicated as adjunctive therapy to diet for:

1. Treatment of adult patients with very high elevations of serum triglyceride levels (Types IV and V hyperlipidemia) who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them. Patients who present such risk typically have serum triglycerides over 2000 mg/dl, and have elevations of VLDL-cholesterol as well as fasting chylomicrons (Type V hyperlipidemia). Subjects who consistently have total serum or plasma triglycerides below 1000 mg/dl are unlikely to present a risk of pancreatitis. Gemfibrozil therapy may be considered for those subjects with triglyceride elevations between 1000 and 2000 mg/dl, who have a history of pancreatitis or of recurrent abdominal pain typical of pancreatitis. It is recognized that some Type IV patients with triglycerides under 1000 mg/dl, may, through dietary or alcoholic indiscretion, convert to a Type V pattern with massive triglyceride elevations accompanying fasting chylomicronemia, but the influence of gemfibrozil therapy on the risk of pancreatitis in such situations 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). Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV and V hyperlipoproteinemia (ref. 4).

2. Reducing the risk of developing coronary heart disease only in Type IIb patients without history of or symptoms of existing coronary heart disease who have had an inadequate response to weight loss, dietary therapy, exercise, and other pharmacologic agents (such as bile acid sequestrants and nicotinic acid, known to reduce LDL- and raise HDL-cholesterol) and who have the following triad of lipid abnormalities: low HDL-cholesterol levels in addition to elevated LDL-cholesterol and elevated triglycerides (see WARNINGS, PRECAUTIONS, and CLINICAL PHARMACOLOGY). The National Cholesterol Education Program has defined a serum HDL-cholesterol value that is consistently below 35 mg/dl, as constituting an independent risk factor for coronary heart disease (ref. 5). Patients with significantly elevated triglycerides should be closely observed when treated with gemfibrozil. In some patients with high triglyceride levels, treatment with gemfibrozil is associated with a significant increase in LDL-cholesterol. BECAUSE OF POTENTIAL TOXICITY SUCH AS MALIGNANCY, GALLBLADDER DISEASE, ABDOMINAL PAIN LEADING TO APPENDECTOMY AND OTHER ABDOMINAL SURGERIES, AN INCREASED INCIDENCE IN NONCORONARY MORTALITY, AND THE 44% RELATIVE INCREASE DURING THE TRIAL PERIOD IN AGE-ADJUSTED ALL-CAUSE MORTALITY SEEN WITH THE CHEMICALLY AND PHARMACOLOGICALLY RELATED DRUG, CLOFIBRATE, THE POTENTIAL BENEFIT OF GEMFIBROZIL IN TREATING TYPE IIA PATIENTS WITH ELEVATIONS OF LDL-CHOLESTEROL ONLY IS NOT LIKELY TO OUTWEIGH THE RISKS. GEMFIBROZIL IS ALSO NOT INDICATED FOR THE TREATMENT OF PATIENTS WITH LOW HDL-CHOLESTEROL AS THEIR ONLY LIPID ABNORMALITY.

In a subgroup analysis of patients in the Helsinki Heart Study with above-median HDL-cholesterol values at baseline (greater than 46.4 mg/dL), the incidence of serious coronary events was similar for gemfibrozil and placebo subgroups (see Table I).

The initial treatment for dyslipidemia is dietary therapy specific for the type of lipoprotein abnormality. Excess body weight and excess alcohol intake may be important factors in hypertriglyceridemia and should be managed prior to any drug therapy. Physical exercise can be an important ancillary measure, and has been associated with rises in HDL-cholesterol. Diseases contributory to hyperlipidemia such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. Estrogen therapy is sometimes associated with massive rises in plasma triglycerides, especially in subjects with familial hypertriglyceridemia. In such cases, discontinuation of estrogen therapy 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 nondrug 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.

CONTRAINDICATIONS

1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.
2. Preexisting gallbladder disease (see WARNINGS).
3. Hypersensitivity to gemfibrozil.

WARNINGS

1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for 5 years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for 5 years and followed one year beyond. There was a statistically significant, 44%, higher age-adjusted total mortality in the clofibrate-treated than in a comparable placebo-treated control group during the trial period. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

Because of the more limited size of the Helsinki Heart Study, the observed difference in mortality from any cause between the gemfibrozil and placebo group is not statistically significantly different from the 29% excess mortality reported in the clofibrate group in the separate WHO study at the 9 year follow-up (see CLINICAL PHARMACOLOGY). Noncoronary heart disease related mortality showed an excess in the group originally randomized to gemfibrozil primarily due to cancer deaths observed during the open-label extension.

During the 5 year primary prevention component of the Helsinki Heart Study mortality from any cause was 44 (2.2%) in the gemfibrozil group and 43 (2.1%) in the placebo group; including the 3.5 year follow-up period since the trial was completed, cumulative mortality from any cause was 101 (4.9%) in the gemfibrozil group and 83 (4.1%) in the group originally randomized to placebo (hazard ratio 1.20 in favor of placebo). Because of the more limited size of the Helsinki Heart Study, the observed difference in mortality from any cause between the gemfibrozil and placebo groups at year 5 or at year 8.5 is not statistically significantly different from the 29% excess mortality reported in the clofibrate group in the separate WHO study at the 9 year follow-up. Noncoronary heart disease related mortality showed an excess in the group originally randomized to gemfibrozil at the 8.5 year follow-up (65 gemfibrozil versus 45 placebo noncoronary deaths).

The incidence of cancer (excluding basal cell carcinoma) discovered during the trial and in the 3.5 years after the trial was completed was 51 (2.5%) in both originally randomized groups. In addition, there were 16 basal cell carcinomas in the group originally randomized to gemfibrozil and 9 in the group randomized to placebo ($p = 0.22$). There were 30 (1.5%) deaths attributed to cancer in the group originally randomized to gemfibrozil and 18 (0.9%) in the group originally randomized to placebo ($p = 0.11$). Adverse outcomes, including coronary events, were higher in gemfibrozil patients in a corresponding study in men with a history of known or suspected coronary heart disease in the secondary prevention component of the Helsinki Heart Study. (See CLINICAL PHARMACOLOGY.)

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the gemfibrozil treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the gemfibrozil group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Gemfibrozil therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary heart disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, gemfibrozil should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, gemfibrozil should be discontinued.

4. Concomitant Anticoagulants - Caution should be exercised when anticoagulants are given in conjunction with gemfibrozil. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with gemfibrozil and lovastatin has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. IN VIRTUALLY ALL PATIENTS WHO HAVE HAD AN UNSATISFACTORY LIPID RESPONSE TO EITHER DRUG ALONE, ANY POTENTIAL LIPID BENEFIT OF COMBINED THERAPY WITH LOVASTATIN AND GEMFIBROZIL DOES NOT OUTWEIGH THE RISKS OF SEVERE MYOPATHY, RHABDOMYOLYSIS, AND ACUTE RENAL FAILURE (see Drug Interactions). The use of fibrates alone, including gemfibrozil, may occasionally be associated with myositis. Patients receiving gemfibrozil and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, gemfibrozil therapy should be withdrawn.

6. Cataracts - Subcapsular bilateral cataracts occurred in 10% and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS

1. **Initial Therapy** - Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting gemfibrozil therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy** - Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions** - (A) **HMG-CoA reductase inhibitors:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin (or other HMG-CoA reductase inhibitors) and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH GEMFIBROZIL. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility** - Long-term studies have been conducted in rats at 0.2 and 2 times the human dose (based on surface area, mg/meter^2). Based on two-week toxicokinetic studies, exposure (AUC) of the dose groups was estimated to be 0.2 and 1.3 times the human exposure. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant ($p = 0.1$). Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors. The higher dose female rats had a significant increase in the combined incidence of benign and malignant liver neoplasms.

Long-term studies have been conducted in mice at 0.1 and 1 times the human dose (based on surface area). Based on two-week toxicokinetic studies, exposure (AUC) of the two dose groups was estimated to be 0.1 and 0.7 times the human exposure. There were no statistically significant differences from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Electron microscopy studies have demonstrated a dose-related hepatic peroxisome proliferation following gemfibrozil administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately 0.6 and 2 times the human dose (based on surface area) to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category C** - Gemfibrozil has been shown to produce adverse effects in rats and rabbits at doses between 0.5 and 3 times the human dose (based on surface area) but no developmental toxicity or teratogenicity among offspring of either species. There are no adequate and well-controlled studies in pregnant women. Gemfibrozil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of gemfibrozil to female rats at 0.6 and 2 times the human dose (based on surface area) before and throughout gestation caused a dose-related decrease in conception rate and, at the high dose, an increase in stillborns and a slight reduction in pup weight during lactation. There were also dose-related increased skeletal variations. Anophthalmia occurred, but rarely.

Administration of 0.6 and 2 times the human dose (based on surface area) of gemfibrozil to female rats from gestation day 15 through weaning caused dose-related decreases in birth weight and suppressions of pup growth during lactation.

Administration of 1 and 3 times the human dose (based on surface area) of gemfibrozil to female rabbits during organogenesis caused a dose-related decrease in litter size and, at the high dose, an increased incidence of parietal bone variations.

6. **Nursing Mothers** - It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for gemfibrozil in animal studies, 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.

7. **Hematologic Changes** - Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of gemfibrozil therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of gemfibrozil administration.

8. **Liver Function** - Abnormal liver function tests have been observed occasionally during gemfibrozil administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when gemfibrozil is discontinued. Therefore periodic liver function studies are recommended and gemfibrozil therapy should be terminated if abnormalities persist.

9. **Kidney Function** - There have been reports of worsening renal insufficiency upon the addition of gemfibrozil therapy in individuals with baseline plasma creatinine >2.0 mg/dl. In such patients, the use of alternative therapy should be considered against the risks and benefits of a lower dose of gemfibrozil.

10. **Use in Children** - Safety and efficacy in children and adolescents have not been established.

ADVERSE REACTIONS

In the double-blind controlled phase of the primary prevention component of the Helsinki Heart Study, 2046 patients received gemfibrozil for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the gemfibrozil group:

	GEMFIBROZIL (N=2046)	PLACEBO (N=2035)
	Frequency in percent of subjects	
Gastrointestinal reactions	34.2	23.8
Dyspepsia	19.6	11.9
Abdominal pain	9.8	5.6
Acute appendicitis (histologically confirmed in most cases where data were available)	1.2	0.8
Atrial fibrillation	0.7	0.1
Adverse events reported by more than 1% of subjects, but without a significant difference between groups:		
Diarrhea	7.2	6.5
Fatigue	3.8	3.5
Nausea/Vomiting	2.5	2.1
Eczema	1.9	1.2
Rash	1.7	1.3
Vertigo	1.5	1.3
Constipation	1.4	1.3
Headache	1.2	1.1

Gallbladder surgery was performed in 0.9% of gemfibrozil and 0.5% of placebo subjects in the primary prevention component, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study. Gallbladder surgery was also performed more frequently in the gemfibrozil group compared to placebo (1.9% vs 0.3%, $p = 0.07$) in the secondary prevention component. A statistically significant increase in appendectomy in the gemfibrozil group was seen also in the secondary prevention component (6 on gemfibrozil vs 0 on placebo, $p = 0.014$).

Nervous system and special senses adverse reactions were more common in the gemfibrozil group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among gemfibrozil treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that gemfibrozil is causally related to the occurrence of MUSCULOSKELETAL SYMPTOMS (see WARNINGS), and to ABNORMAL LIVER FUNCTION TESTS and HEMATOLOGIC CHANGES (see PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil treated patients in other controlled clinical trials of 805 patients. Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with gemfibrozil is probable or not established.

	CAUSAL RELATIONSHIP PROBABLE	CAUSAL RELATIONSHIP NOT ESTABLISHED
General:		weight loss
Cardiac:		extrasystoles
Gastrointestinal:	cholestatic jaundice	pancreatitis hepatoma colitis
Central Nervous System:	dizziness somnolence paresthesia peripheral neuritis decreased libido depression headache	confusion convulsions syncope
Eye:	blurred vision	retinal edema
Genitourinary:	impotence	decreased male fertility renal dysfunction
Musculoskeletal:	myopathy myasthenia myalgia painful extremities arthralgia synovitis rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS)	
Clinical Laboratory:	increased creatine phosphokinase increased bilirubin increased liver transaminases (AST [SGOT], ALT [SGPT]) increased alkaline phosphatase	positive antinuclear antibody
Hematopoietic:	anemia leukopenia bone marrow hypoplasia eosinophilia	thrombocytopenia
Immunologic:	angioedema laryngeal edema urticaria	anaphylaxis Lupus-like syndrome vasculitis
Integumentary:	exfoliative dermatitis rash dermatitis pruritus	alopecia

DOSAGE AND ADMINISTRATION

The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

OVERDOSAGE

There have been reported cases of overdosage with gemfibrozil. In one case a 7 year old child recovered after ingesting up to 9 grams of gemfibrozil. Symptomatic supportive measures should be taken should an overdose occur.

HOW SUPPLIED

Gemfibrozil Tablets USP, white to off-white, film-coated, modified oval, biconvex tablets coded "APO bisect 034" on one side and "600" on the other side, each containing 600 mg gemfibrozil, are available as follows:
N 60505-0034-4: Bottles of 60
N 60505-0034-8: Bottles of 500

Storage: Store below 30°C (86°F).

REFERENCES

1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middleaged men with dyslipidemia. *N Engl J Med* 1987; 317:1237-1245.
2. Manninen V, Elo O, Frick MH, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260:641-651.
3. Frick MH, Heinonen OP, et al: Efficacy of gemfibrozil in dyslipidemic subjects with suspected heart disease: An ancillary study in the Helsinki Heart Study frame population. *Annals of Medicine* 1993;25:41-45.
4. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury JB et al. (eds.): *The Metabolic Basis of Inherited Disease*, 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622-642.
5. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol. *Arch Int Med* 1988; 148:36-69.

Caution - Federal law prohibits dispensing without prescription.

Manufactured by
TorPharm Inc.
50 Steinway Blvd.
Etobicoke, Ontario
M9W 6Y3
Canada

Manufactured for:
Apotex Corp.
Buffalo Grove, Illinois
60089

Revised: September 1997

L88447

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75034

CHEMISTRY REVIEW(S)

ANDA NUMBER 75-034

FIRM: TorPharm Inc.

DOSAGE FORM: Tablet

STRENGTH: 600 mg

DRUG: Gemfibrozil

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable on June 10, 1998 per J. D Ambrogio (HFD-324).

BIO STUDY: *In vivo* study is acceptable.

The *in vitro* dissolution testing is acceptable.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

The drug product is compendial.

Analysis was performed on the subject drug product using the USP methods. No problems were encountered, and the methods are suitable for regulatory analysis.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION? Yes

60s: 120 cc round, white HDPE bottle; Resin:

cap: 38-400 polypropylene manufactured by resin - polypropylene. white manufactured by Liner backing - foamseal closure liner manufactured by Liner facing - manufactured by

cap: 38-400 polypropylene screw cap manufactured by resin - polypropylene (white) colorant manufactured by Liner backing - foamseal closure liner manufactured by Liner facing - manufactured by

500s: 750 cc HDPE round, white HDPE bottle; resin:

cap: 45-400 polypropylene screw cap manufactured by resin - polypropylene (white) colorant manufactured by . Liner backing - foamseal closure liner manufactured by Liner facing - manufactured by

Studies: 3 months accelerated and 3 months room temperature data are submitted for each container/closure system for test batch #60059. Storage conditions are:

(1) 40°C ± 2°C/75% RH ± 5% RH

(2) 25°C ± 2°C/60% RH ± 5% RH

Data are satisfactory to support a tentative 24 month expiry date.

LABELING:

Satisfactory per the December 1, 1997 review.

STERILIZATION VALIDATION (IF APPLICABLE):

N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):

Exhibit lot #60059 - theoretical yield tablets (% of the proposed production batch size).

Active ingredient by DMF is acceptable.

SIZE OF STABILITY BATCH - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA SAME PROCESS):

Same batch.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY? Yes

Proposed production batch size - tablets.

Review Chemist: Shirley S. Brown /S/ 6/29/98
Supervisor: Michael Smela /S/ 6/29/98
Date: June 29, 1998

Chemistry Closed

1. **CHEMISTRY REVIEW NO.** 3

2. **ANDA #** 75-034

3. **NAME AND ADDRESS OF APPLICANT**

Apotex USA Inc.
US Agent for TorPharm, a Division of Apotex Inc.
1641 Barclay Blvd.
Buffalo Grove, IL 60089-4544

4. **LEGAL BASIS FOR SUBMISSION**

Accepted by OGD.

5. **SUPPLEMENT(s)**

N/A

6. **PROPRIETARY NAME**

N/A

7. **NONPROPRIETARY NAME**

Gemfibrozil

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**

N/A

9. **AMENDMENTS AND OTHER DATES:**

December 20, 1996	Original Submission
April 10, 1997	New Correspondence (general inquiry to request approval of an alternate stability protocol. This request is also for ANDA's 74-680, 74-737, 74-890, 74-943 and 74-948.
November 17, 1997	Amendment responding to FDA's September 5, 1997 Chemistry Comments to the applicant
December 5, 1997	New Correspondence: TorPharm Inc. was a subsidiary of Apotex Inc. and now has become an operating division of Apotex Inc. TorPharm, Inc.'s name has been changed to TorPharm, a Division of Apotex Inc.
*May 19, 1998	Amendment responding to FDA's May 14, 1998 Chemistry Comments to the applicant

10. **PHARMACOLOGICAL CATEGORY** 11. **Rx or OTC**

Lipid regulating agent Rx

12. **RELATED IND/NDA/DMF(s)**

NDA N18422 - Lopid by Parke-Davis
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

DMF

13. **DOSAGE FORM** 14. **POTENCY**

Tablet 600 mg

15. **CHEMICAL NAME AND STRUCTURE**

See USP XXIII, page 701.

16. **RECORDS AND REPORTS**

N/A

17. **COMMENTS**

The applicant noted and acknowledged the following comments in their response:

1. A satisfactory compliance evaluation of the firms listed in the ANDA is necessary for approval.

   The applicant stated that a pre-approval inspection was conducted by the FDA on May 5 - May 13, 1998 and the results are pending.

2. The information purporting to demonstrate safety of Methylcellulose at the level present in your product will be reviewed by the appropriate medical division in the Office of Review Management.

Chemistry issues per HFD-625 are closed.

18. **CONCLUSIONS AND RECOMMENDATIONS**

The application is not approvable.

A. COMPONENTS AND COMPOSITION

The report on the information forwarded to the Medical Division for consultation regarding safety of the level of Methylcellulose contained in the formulation is pending.

B. ESTABLISHMENT INSPECTION - Pending. See item 33 of this review.

19. **REVIEWER:** /S/
Shirley S. Brown

DATE COMPLETED: 5/29/98
May 29, 1998

CONSULTIVE CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

Division of Metabolism and Endocrine Drug Products (HFD-510)

ANDA 75-034
Gemfibrozil Tablets, USP, 600 mg
Torpharm Inc.

Consult request:

OGD requests an evaluation by DMEDP (HFD-510) of the Applicant's response to their ANDA 75-034 file concerning a certain deficiency in a deficiency letter previously communicated to the Applicant. DMEDP has review responsibility for the innovator's product, Lopid (gemfibrozil tablets, USP), 600 mg tablets. The deficiency is stated as follows: "The level of Methycellulose USP at 183.6 mg/tablet appears to be greater than the maximum concentration for the same route of administration in a currently marketed drug product. Please provide a justification for the excessive amount of Methylcellulose in the drug product."

Remarks:

The Applicant explains that Methycellulose is utilized as a dry binder to impart compressibility to the granulation. The Applicant points out that Microcrystalline Cellulose is present in Lopid 600 mg tablets and that Methylcellulose and Microcrystalline Cellulose are very similar in functionality as a dry binder. The Applicant further indicates that Citrucel Orange and Citrucel Sugar Free are two currently marketed products which contain levels of Methycellulose exceeding that of the proposed formulation. These products contain 2 grams of Methycellulose per adult dose. Furthermore, the Applicant indicates that Methylcellulose is classified as GRAS in the CFR.

This reviewer finds the following:

1. Methycellulose, USP is an official compendial item.

2. Citrucel Orange and Citrucel Sugar Free are products currently marketed OTC by Smith-Kline Beecham for use as a laxative. These products indeed contain 2 grams of Methycellulose per adult dose.

3. Methylcellulose is classified as a Multiple Purpose GRAS Food Substance in 21 CFR 182.

4. The innovator, Parke Davis, currently markets Lopid (gemfibrozil tablets, USP), 600 mg oral tablets, under approved NDA 18-422 for use as a lipid-regulating agent. However, the formulation information provided in this NDA shows that the tablets contain Microcrystalline Cellulose, NF and Hydroxypropylcellulose, NF, but not Methylcellulose.

Conclusion:

NDA 18-422 for the innovator's product, Lopid (gemfibrozil tablets, USP), 600 mg oral tablets, provides no information on Methylcellulose, therefore, no evaluation from a chemistry point of view of the ANDA Applicant's response can be made which is based on the innovator's NDA . The ANDA Applicant's response is recommended to be consulted to Pharmacology for an evaluation of the safety regarding the use of Methylcellulose at the proposed level.

/S/ 6/4/98

Stephen K. Moore, Ph.D.
Chemistry Team Leader I
ONDC/DNDCII
DMEDP (HFD-510)/CDER/FDA

cc: ANDA 75-034 file
HFD-510/Consult file
HFD-510/S.Moore/R.Steigerwalt/E.Galliers
HFD-102/L. Ripper LRipper 6/18/98
HFD-625/S.Brown/M.Smela/S.O'Keefe

file: A75034o.gem

1. **ADDENDUM TO CHEMISTRY REVIEW NO.** 3

2. **ANDA #** 75-034

3. **Amended Items**

18. **CONCLUSION AND RECOMMENDATION**

The application is approvable.

20. **COMPONENTS AND COMPOSITION**

The safety of Methylcellulose at the proposed level in the drug product was reviewed by Pharmacology, and it was determined that the use of the proposed level of Methylcellulose represents a safe level of exposure of Methylcellulose. (Review completed 6/5/98)

Satisfactory

33. **ESTABLISHMENT INSPECTION**

The EER is acceptable on June 10, 1998 per J.D Ambrogio (HFD-324).

Satisfactory

cc: ANDA 75-034
ANDA DUP
DIV FILE
Field Copy
Reading File (for facsimiles only)

Endorsements:

/S/ 6/29/98
HFD-625/SBrown

/S/ 6/29/98
HFD-625/MSmela

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FT by:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75034

PHARMACOLOGY REVIEW

ANDA 75-034 **Review Completed: June 5, 1998**

Sponsor: Torpharm, Inc.

Date Consult Received by Reviewer: June 5, 1998

PHARMACOLOGY COMMENTS ON CONSULT REQUEST

DRUG: Gemfibrozil Tablets. USP, 600 mg

CONSULT REQUEST: OGD requested an evaluation by DMEDP (HFD-510) of the Applicant's response to their ANDA 75-034 concerning a deficiency letter communicated to the Applicant. The deficiency is stated as follows: "The level of methylcellulose USP at mg/tablet appears to be greater than the maximum concentration for the same route of administration in a currently marketed drug product. Please provide a justification for the excessive amount of methylcellulose in the drug product."

APPLICANT RESPONSE: The Applicant provided information regarding the use of methylcellulose in several marketed products. In particular, the Applicant cites the use in Citrucel Orange and Citrucel Sugar Free which contain methylcellulose at levels of grams of methylcellulose per adult dose. Methylcellulose is classified as GRAS in the CFR.

PHARMACOLOGY COMMENTS

1. Methyl cellulose is classified as a Multiple Purpose GRAS Food Substance in 21 CFR 182.

2. MA Eastwood, WG Brydon, DM Anderson indicate in their manuscript, "The effects of dietary methylcellulose in man", Food Addit. Contam; Vol 7, ISS1, 1990, pp9-19 that the Acceptable Daily Intake (ADI) for methylcellulose established by the EEC and the joint FAO/WHO Expert Committee on Food Additives (JECFA) is 25 mg/kg body weight. In this citation, 5 male volunteers were administered 10 times this recommended amount (i.e., 250 mg/kg body weight) for 23 consecutive days without any significant adverse effects.

3. The safe chronic use of products such as Citrucel Orange at an adult daily dose of 2 g/day indicate safety in humans at doses considerably greater than those that would be administered in the Applicant's preparation of Gemfibrozil

4. The recommended daily dose of 1200 mg gemfibrozil would contain approximately 367.2 mg methylcellulose/day (~6 mg/kg/day based on a 60 kg human).

5. The daily exposure to methylcellulose in this formulation would fall under the established ADI of 25 mg/kg/day.

CONCLUSION: Based upon the above information, the use of the proposed level of methylcellulose under ANDA 75-034 represents a safe level of exposure to methylcellulose.

/S/ 6/5/98

Ronald W. Steigerwalt, Ph.D.
Pharmacology Team Leader

cc: ANDA 75-034 file
HFD510/Consult file
HFD510/Steigerwalt/S.Moore/E.Galliers
HFD-102/L. Ripper LRipper 6/18/98

6/8/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75034

BIOEQUIVALENCY REVIEW(S)

JUL 25 1997

Gemfibrozil
600 mg Tablets
ANDA #75-034
Reviewer: Moheb H. Makary
WP # 75034SD.D96

TorPharm Inc.
Ontario, Canada
Submission Date:
December 20, 1996

Review of In-Vivo Bioequivalence Study, and Dissolution Data

I. Objective:

The firm has submitted in vivo bioequivalence study on its Gemfibrozil 600 mg Tablets under fasting conditions and dissolution data to compare the test product with Parke-Davis's Lopid[R] 600 mg Tablets. The formulation for the drug product Gemfibrozil 600 mg tablet was also submitted.

II. Background:

Gemfibrozil is used clinically as a lipid-regulatory agent which lowers the serum triglycerides and produces a variable reduction in total serum cholesterol. The mechanism whereby gemfibrozil lowers plasma triglycerides is not well established.

Following oral administration of gemfibrozil in man, absorption is rapid and complete. Peak plasma concentrations are attained 1 to 2 hours after administration of single doses up to 2000 mg or after repeated doses up to 800 mg twice daily. Plasma drug concentration is directly proportional to dose and tends to rise during repeated administration, although steady state is achieved within 7 to 14 days with twice daily doses. After the administration of gemfibrozil, 600 mg twice daily, mean peak plasma concentrations are about 10 to 15 mg/L.

The recommended dosage of gemfibrozil is 600 mg twice daily given 30 minutes before morning and evening meals. Gemfibrozil is currently marketed as Lopid[R] by Parke-Davis, 300 mg capsules and 600 mg tablets.

III. Study #090-19-11059 For Single Dose Fasting Bioequivalence Of TorPharm's Gemfibrozil 600 mg Tablet

Study site:

Investigators:

Study date: July 12 and 20, 1996

Analytical date: Analysis of study samples took place during the period 8/26/96 to 9/17/96.

Study design: Single-dose, two-way crossover under fasting conditions.

Sponsor: TorPharm Inc.
Ontario, Canada

Subjects: Thirty-eight (38) healthy male subjects enrolled in the study. Thirty-seven (37) subjects completed the study. Subject #27 failed to return to the clinical facility for period II.

Selection criteria: Subjects selected for the study met the following acceptance criteria:

1. Ages 18 - 50 years, who have been on a normal diet.
2. Healthy, as determined by physical examination, medical history and clinical laboratory diagnostic tests (blood chemistry, hematology, urinalysis).
3. No concurrent illness, acute or chronic diseases or history of serious cardiovascular, pulmonary, endocrine, immunologic, dermatologic, renal, G.I., hepatic, gallstones, hematologic, neurologic, or psychiatric disease.
4. No history of alcohol or drug abuse within the past year.
5. No history of hypersensitivity to gemfibrozil or other lipid regulatory agents.

Restrictions:

1. No alcohol consumption beginning 24 hours prior to dosing.
2. No xanthine consumption beginning 12 hours prior to dosing.
3. No Rx or OTC drugs beginning 14 days prior to the study.

Dose and treatment: All subjects completed an overnight fast (at least nine hours) before any of the following drug treatments:

Test Product: a) 1x600 mg Gemfibrozil Tablet (TorPharm Inc.), lot #60054 , batch size

tablets, potency 99.4 %, content uniformity 98.9%

Reference Product: b) 1x600 mg Lopid^{R} Tablet (Parke-Davis), lot #054N5V, Exp. 11/97, potency 100.2%, content uniformity 99.6%.

Washout period: Seven days between doses.

Food and fluid intake: A 600 mg (one tablet) Gemfibrozil of either test or reference products was administered with 240 mL of water following a 10 hour fast. Subjects continued fasting until the standardized meals were served after five hours post-dose. Water was allowed ad lib except within 1 hour of drug administration.

Blood samples: Blood samples were collected in Vacutainers containing EDTA from each subject just before dosing in both study phases and at the following times after dosing: 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 7, 8, 9, 10 and 12 hours after dosing. Samples were cooled in an ice bath and centrifuged under refrigeration. Plasma samples were stored at -20°C pending assay.

Assay Methodology

Statistical Methods

AUC(0-t), AUCinf, Cmax, Tmax, Ke and T1/2 were calculated from the individual concentration versus time data for Gemfibrozil. An analysis of variance (ANOVA) was applied to log-transformed bioequivalence parameters and non-transformed bioequivalence parameters to determine any statistically significant ($p<0.05$) differences between the drug formulations. 90% confidence intervals were calculated for each log transformed and non-transformed bioequivalence parameter.

IV. In Vivo Results:

The study was conducted at
during the period of July 12 and 19, 1996. A total of 38 healthy adult male volunteers enrolled in and 37 healthy adult male volunteers completed the study.

Ten subjects complained of headache, abdominal cramps, increased blood pressure, lightheaded and vomiting. No medication was required for any event.

The plasma concentrations and pharmacokinetic parameters for Gemfibrozil are summarized in Table I.

Table I

Mean Gemfibrozil Plasma Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 600 mg Gemfibrozil Tablet Under Fasting Conditions

(N=37)

Time hr	TorPharm Test Product Lot #60054 ug/mL (CV%)	Parke-Davis Reference Product Lot #054N5V ug/mL (CV%)
0	0	0
0.5	7.39 (54.9)	10.66 (53.2)
1	39.53 (39.8)	18.25 (53.3)
1.33	20.78 (37.8)	20.43 (41.0)
1.67	21.00 (34.7)	21.34 (38.3)
2	20.69 (34.5)	20.98 (38.0)
2.33	20.12 (32.0)	18.91 (38.1)
2.67	18.12 (35.1)	16.85 (35.2)
3	16.20 (37.1)	15.06 (32.0)
3.5	12.57 (34.3)	12.76 (37.7)
4	10.59 (37.2)	10.03 (35.1)
5	6.64 (57.3)	6.08 (41.9)
6	4.31 (52.7)	4.06 (41.2)
7	2.46 (59.2)	2.51 (52.4)
8	1.63 (69.9)	1.59 (59.0)
9	1.11 (56.6)	1.15 (67.7)
10	0.76 (63.0)	0.80 (74.1)
12	0.47 (95.8)	0.45 (93.2)

Pharmacokinetic Parameters

	Test Mean(CV)	Reference Mean(CV)	% Difference	90% CI log-transf
AUC(0-t) (ug.hr/mL)	83.49(23)	82.76(26)	0.88	98.2-105.5
AUCinf (ug.hr/mL)	86.89(23)	85.69(27)	1.40	98.5-106.1
Cmax (ug/mL)	25.46(24)	25.79(29)	-1.28	91.5-110.7
Tmax (hr)	1.92	1.69		
Kel(1/hr)	0.32	0.34		
t1/2 (hr)	2.45	2.38		

1. For TorPharm's test product, the mean AUC(0-t), AUCinf and Cmax values are 0.88%, 1.40% higher and 0.35% lower, respectively, than those for the reference product values. The differences are not statistically significant. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUC(0-t), AUCinf and Cmax. The reviewer's calculations are in agreement with those submitted by the firm.

2. The Gemfibrozil plasma levels reached a peak at 1.67 hours for both the test and reference products following their administration under fasting conditions.

3. The elimination rate constant (KE) could not be estimated for subjects #15, 22, 28, 30 and 38 after the TorPharm, and for subjects #15, 22, 28, 30 and 32 after the reference product. Therefore, half-life and AUCinf could not be estimated for these subjects.

4. Subject #35 experienced a mild episode of vomiting. After excluding this subject from the statistical analysis of the study for the reason mention above, the resulting 90% confidence intervals for Gemfibrozil are as following:

LnAUC(0-t)	98.8-106.1%
LnAUCinf	99.3-106.8%
LnCmax	93.9-112.5%

All confidence intervals remain within the acceptable 80-125% range.

V. In Vitro Dissolution Testing: (USP Method)

Method:	USP 23 apparatus II (paddle) at 50 rpm
Medium:	900 mL of 0.2 M phosphate buffer, pH 7.5
Number of Tablets:	12
Test product:	TorPharm's Gemfibrozil 600 mg tablets, lot #60054.
Reference products:	Parke-Davis's Lopid 600 mg tablet, lot #054N5V.
Specifications:	NLT % in 30 minutes.

Dissolution testing results are shown in Table II.

VI. Formulation:

TorPharm's formulation for its Gemfibrozil 600 mg tablets is shown in Table III.

VII. Comments

1. The firm's in vivo bioequivalence study under fasting conditions is acceptable. The test product is similar in both rate and extent of absorption to the reference product. The 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are within the acceptable range of 80-125% under fasting conditions.

2. The in vitro dissolution testing submitted by the firm on its Gemfibrozil 600 mg tablets is acceptable.

VIII. Recommendations:

1. The bioequivalence study under fasting conditions conducted by TorPharm Inc., on its Gemfibrozil 600 mg Tablet, lot #60054, comparing it to Lopid[R] 600 mg Tablet manufactured by Parke-Davis, has been found acceptable by the Division of Bioequivalence. The study demonstrated that TorPharm's Gemfibrozil 600 mg Tablet is bioequivalent to the reference product Lopid[R] 600 mg Tablet manufactured by Parke-Davis.

2. The dissolution testing conducted by the firm on its 600 mg Tablets, lot #60054 is acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.2 M phosphate buffer, pH 7.5 at 37C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than % of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

3. From the bioequivalence point of view, the firm has met the requirements of the in vivo bioequivalence and the in vitro dissolution testing.

The firm should be informed of the above recommendations.

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHPATR /S/ Date: 5/8/97

Concur: /S/ Date: 7/25/97
for Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

MMakary/5-5-97 wp 75034SD.D96
cc: ANDA #75-034,original, HFD-658 (Makary), Drug File Division File.

Table II. In Vitro Dissolution Testing

Drug (Generic Name): Gemfibrozil
Dose Strength: 600 mg Tablets
ANDA No.: 75-034
Firm: Torpharm Inc.
Submission Date: December 20, 1996
File Name: 75034SD.D96

I. Conditions for Dissolution Testing:

USP 23 Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 900 mL of 0.2 M phosphate buffer, pH 7.5
Specifications: NLT % in 30 minutes
Reference Drug: Lopid (Parke-Davis)
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #60054 Strength(mg) 600			Reference Product Lot #054N5V Strength(mg) 600		
	Mean %	Range	%CV	Mean %	Range	%CV
10	105		5	97		1
20	104		3	99		1
30	104		3	100		3
45	105		3	100		2

Table III

1. **Formulation Data**

The following table summarizes, by strength, the components and composition of Gemfibrozil Tablets USP 600 mg.

AMOUNT PER TABLET (mg)	
Ingredient	Gemfibrozil Tablets USP 600 mg
600 mg Tablet - 72.73% Tablet Granulation	
Gemfibrozil USP	
Methylcellulose USP	
Croscarmellose Sodium NF	
Colloidal Silicon Dioxide NF	
Magnesium Stearate NF	
600 mg Tablet - Coating	
Hydroxypropyl Cellulose NF	
Hydroxypropyl Methylcellulose 2910 USP	
Polyethylene Glycol NF	
Titanium Dioxide USP	
Purified Water USP	
Total	

Note: Coating ingredient quantities shown here do not include dispensing overage. Overage is dispensed to accommodate for coating operation losses (filling lines. allow for adequate mixing etc.).

*Evaporates during the coating process.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75034

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-034 Date of Submission: December 20, 1996

Applicant's Name: TorPharm Inc.

Established Name: Gemfibrozil Tablets USP, 600 mg

Labeling Deficiencies:

1. CONTAINER (60s and 500s)

   Revise the dispensing statement to read as follows:

   Dispense in a tight...

2. INSERT

   a. GENERAL COMMENT

      Delete ' throughout the text of the insert except where noted below.

   b. DESCRIPTION

      i. Revise the first paragraph to read as follows:

         Gemfibrozil is a lipid regulating agent. Gemfibrozil tablets USP, for oral administration, contain 600 mg gemfibrozil. Each tablet also contains the following inactive ingredients: Colloidal Silicon...

      ii. Revise the chemical name to read the same as the name listed in USP 23.

      iii. Replace with "molecular formula".

      iv. To be in accord with USP 23, revise the molecular weight to read "250.34" rather than

c. CLINICAL PHARMACOLOGY

Penultimate paragraph, penultimate sentence - Revise to read:

...of 1.5 hours.

d. INDICATIONS AND USAGE

i. Revise the first sentence to read:

Gemfibrozil tablets are indicated...

ii. Number 1, fifth sentence - ...mg/dL may,... [Note: Relocate the comma.]

e. WARNINGS

Delete the proprietary name, from item 5 - ...with gemfibrozil and lovastatin has been...

f. Delete Gemfibrozil Tablets USP 600 mg" that appears prior to the "manufactured by" statement.

Please revise your container labels and package insert labeling, as instructed above, and submit final printed labels and labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75034

CORRESPONDENCE

ANDA 75-034

JUL 31 1997

Apotex USA Inc.
Attention: Marcy Macdonald
U.S. Agent for: TorPharm Inc.
1641 Barclay Blvd
Buffalo Grove, IL 60089-4544

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Gemfibrozil Tablets USP, 600 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL (847) 573 9999 • FAX (847) 573-1001

November 17, 1997

Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA # 75-034
Gemfibrozil Tablets USP, 600 mg
Response to Communication of September 5, 1997

Dear Mr. Sporn:

Apotex Corp. as the U.S. agent for TorPharm Inc. of Ontario, Canada is hereby submitting an amendment to the above referenced ANDA.

Please feel free to contact me if you have any further questions.

Effective November 24, 1997, Apotex Corp. will be moving to a new location.

50 Lakeview Parkway, Suite 127, Vernon Hills, IL 60061
Phone: (847) 573-9999 FAX: (847) 573-1001

Sincerely,

Helen Keys
Regulatory Affairs Assistant for

Marcy Macdonald
Associate Director, Regulatory Affairs

Tor Pharm

COVER LETTER

MAJOR AMENDMENT

TorPharm Inc., 50 Steinway Boulevard, Etobicoke, Ontario, Canada, M9W 6Y3, is hereby amending ANDA number 75-034 for Gemfibrozil Tablets USP 600 mg. The amendment is being submitted in response to the FDA Deficiency Letter dated September 5, 1997.

David Coffin-Beach

13Nov97

David Coffin-Beach, B.S.Pharm, Ph.D.
President, TorPharm Inc.
50 Steinway Blvd.
Etobicoke, Ontario
M9W 6Y3

Date

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-0338 Fax: (416) 675-0340

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL (847) 573-9999 • FAX (847) 573-1001

December 5, 1997

NEW CORRESP

Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation & Research
Food & Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #74-680 - Ranitidine Tablets USP 150 mg & 300 mg
ANDA #74-737 - Captopril Tablets USP 12.5 mg, 25 mg, 50 mg & 100 mg
ANDA #74-948 - Cimetidine Tablets USP 100 mg
ANDA #74-890 - Cimetidine Tablets UPS 200 mg, 300 mg, 400 mg & 800 mg
ANDA #74-943 - Diltiazem HCl Extended-Release Capsules USP (Once-a-day dosage) 240 mg

ANDA #75-178 - Enalapril Maleate Tablets USP 2.5 mg, 5 mg, 10 mg & 20 mg
ANDA #75-034 - Gemfibrozil Tablets USP 600 mg
ANDA #75-191 - Pentoxifylline Extended-Release Tablets 400 mg
ANDA #75-167 - Ranitidine Tablets USP 75 mg
ANDA #75-089 - Ticlopidine HCl Tablets 250 mg

Dear Mr. Sporn:

Apotex Corp. as the U.S. agent for TorPharm a Division of Apotex Inc. of Ontario, Canada is hereby submitting information concerning a change in corporate status for TorPharm. Please refer to the attached communication.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director, Regulatory Affairs

RECEIVED
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GENERIC DRUGS

Tor Pharm

24 November 1997

Mr. Douglas Sporn
Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation & Research
Food and Drug Administration
7500 Standish Place
Rockville, Maryland 20855

Re: ANDA #74-680 - Ranitidine Tablets USP 150 mg and 300 mg
ANDA #74-737 - Captopril Tablets USP 12.5 mg, 25 mg, 50 mg and 100 mg
ANDA #74-948 - Cimetidine Tablets USP 100 mg
ANDA #74-890 - Cimetidine Tablets USP 200 mg, 300 mg, 400 mg and 800 mg
ANDA #74-943 - Diltiazem HCl Extended-Release Capsules USP (Once-a-day dosage) 240 mg

ANDA #75-178 - Enalapril Maleate Tablets USP 2.5 mg, 5 mg, 10 mg and 20 mg
ANDA #75-034 - Gemfibrozil Tablets USP 600 mg
ANDA #75-191 - Pentoxifylline Extended-Release Tablets 400 mg
ANDA #75-167 - Ranitidine Tablets USP 75 mg
ANDA #75-089 - Ticlopidine HCl Tablets 250 mg

Dear Mr. Sporn:

TorPharm Inc. has been the sponsor of the referenced applications. At the time of submission of these applications and until recently TorPharm Inc. was a subsidiary of Apotex Inc., also a Canadian corporation. For business reasons unrelated to our obligations in respect to these applications, TorPharm Inc. recently changed its status from a corporate subsidiary of Apotex Inc. to an operating division of Apotex Inc. Consistent with this change in status vis à vis Apotex Inc., the name TorPharm Inc. has been changed to TorPharm, a Division of Apotex Inc.

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-0338 Fax: (416) 675-0340

Separate copies of this letter are enclosed for each of the referenced applications. In addition, by copy of this letter we are notifying the Division of Data Management and Services of this name change, which we understand will be incorporated in the "Orange Book."

Very truly yours,

David Coffin-Beach 24 Nov 97

David Coffin-Beach, B.S. Pharm, Ph.D.
President, TorPharm, a Division of Apotex Inc.

cc: George Scott (HFD-90)

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-0338 Fax: (416) 675-0340

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL (847) 573-9999 • FAX (847) 573-1001

May 19, 1998

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/FA

FACSIMILE AMENDMENT

Re: ANDA 75-034
Gemfibrozil Tablets, USP
600 mg

To Whom It May Concern:

Apotex Corp., as the U.S. agent for TorPharm, a Division of Apotex, Inc., is submitting this amendment in response to FDA deficiency letter dated May 14, 1998.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs

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APOTEX CORP.

1641 BARCLAY BOULEVARD • BUFFALO GROVE • ILLINOIS 60089 • Tel: (847) 541-1141 • Fax: (847) 541-1143
28101 BALLARD ROAD • LAKE FOREST • ILLINOIS 60045 • Tel: (847) 816-9350 • Fax: (847) 816-9356

April 10, 1997

Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

15034

RE: General Inquiry
Request for Alternate Stability Protocol

Dear Mr. Sporn:

As the U.S. agent for TorPharm Inc. of Ontario, Canada, Apotex Corp. is submitting a general inquiry to request approval of an alternate stability protocol.

We appreciate an expeditious review of this information.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Manager, Regulatory Affairs

APOTEX USA INC.

1641 BARCLAY BOULEVARD • BUFFALO GROVE • ILLINOIS 60089 • Tel: (847) 541-1141 • Fax: (847) 541-1143

December 20, 1996

Douglas Sporn, Director
Office of Generic Drugs
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Original ANDA Submission
Gemfibrozil Tablets USP, 600 mg

Dear Mr. Sporn:

Pursuant to Section 505(j) of the Federal, Food, Drug and Cosmetic Act as amended September 24, 1984, Apotex USA, Inc. as US agent for TorPharm Inc. of Ontario, Canada, hereby submits an original abbreviated new drug application for Gemfibrozil Tablets USP, 600 mg.

We are submitting an archival copy under a blue cover (5 volumes), a chemistry review copy plus an additional copy of the analytical methods section under a red cover and the bioavailability/bioequivalence review section under an orange cover.

Apotex, USA hereby certifies that in accordance with 21 CFR 314.94 (d)(5) a true field copy of the technical sections of this submission under a burgundy cover is also included as this ANDA is being submitted by a foreign applicant.

We appreciate an expeditious review of this application. Please direct any inquiries regarding this application to me at the address listed above.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Manager, Regulatory Affairs

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GENERIC DRUGS