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APPLICATION NUMBER:

22-224

SUMMARY REVIEW

12/15/08

Summary Review for Regulatory Action

Date	December 12, 2008
From	Eric Colman, MD
Subject	Deputy Division Director Summary Review
NDA#	22-224
Applicant Name	Abbott Pharmaceuticals
Date of Submission	December 7, 2007
PDUFA Goal Date	October 7, 2008
Proprietary/Established Name	Trilipix/choline fenofibrate/fenofibric acid
Dosage Forms / Strength	Delayed-release capsules/135 mg and 45 mg
Proposed Indication(s)	<ol style="list-style-type: none"> 1. mixed dyslipidemia in combination with a statin 2. severe hypertriglyceridemia as monotherapy 3. primary hypercholesterolemia and mixed dyslipidemia as monotherapy
Recommended Regulatory Action	<i>Approval</i>

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Julie Golden, MD
Statistical Review	Japo Chowdhury, PhD and Todd Sahlroot, PhD
Pharmacology Toxicology Review	Indra Antonipillai, PhD and Karen David Bruno, PhD
CMC Review	Yvonne Yang, PhD
ONDQA Biopharmaceutics Review	Arzu Selen, PhD
Microbiology Review	NA
Clinical Pharmacology Review	Manoj Khurana, PhD and Sally Choe, PhD
DSI	Susan Leibenhaut, MD
OSE/DMETS	Richard Abate, RPh and Kellie Taylor, PharmD
OSE/DRISK	Nancy Carothers, RN
REMS Evaluation	Amy Egan, MD, MPH

OND=Office of New Drugs
 OSE= Office of Surveillance and Epidemiology
 DMETS=Division of Medication Errors and Technical Support
 DSI=Division of Scientific Investigations
 DRISK= Division of Risk Management
 CDTL=Cross-Discipline Team Leader
 REMS=Risk Evaluation and Mitigation Strategy
 ONDQA=Office of New Drug Quality Assurance

1. Introduction

This memorandum documents the conclusions and recommendations made by the various review disciplines and provides a final regulatory recommendation for the Trilipix NDA. Particular attention is given to the applicant's request for a biowaiver for the 45 mg dose of Trilipix, as there was some disagreement between the clinical pharmacology and ONDQA reviewers regarding the granting of this request. Focus is also given to the clinical data on Trilipix's effects on skeletal muscle, the liver, and the kidney. Finally, this memorandum provides the rationale for the language describing the indication for coadministration of Trilipix with a statin.

2. Background

Fenofibrate (Tricor) was first approved by the Agency in the early 1990s. A number of fenofibrate products have subsequently been approved, most as 505b2 applications relying on data demonstrating bioequivalence with Tricor. All fenofibrate products are approved for the treatment of primary hypercholesterolemia, mixed dyslipidemia, and hypertriglyceridemia. In addition to the indications for the treatment of primary hypercholesterolemia, mixed dyslipidemia, and hypertriglyceridemia, Abbott is requesting approval of Trilipix for coadministration with a statin.

Trilipix is the proposed tradename for fenofibric acid, the free acid of choline fenofibrate and the active ingredient of fenofibrate. The Trilipix NDA is a 505b2 application by virtue of Abbott's reference to a drug-drug interaction study between fenofibrate and simvastatin. The company did conduct preclinical, clinical pharmacology, and clinical studies of fenofibric acid in support of approval.

In a September 13, 2005 Special Protocol Assessment, the Division agreed in general with Abbott's plan to study the efficacy and safety of Trilipix in combination with a statin in an effort to gain a co-administration indication. The current labeling for fenofibrate recommends against co-administration with statins because of concern for an increase in risk for rhabdomyolysis above that observed with fenofibrate and statin monotherapy. However, due to unique pharmacokinetic factors, much of this concern is specific to the co-administration of statins with gemfibrozil, rather than fenofibrate.

It should be stressed that fenofibric acid is the active metabolite of fenofibrate. As such, there is no reason to expect that comparable doses of fenofibric acid (Trilipix) and fenofibrate (Tricor) would differ in terms of efficacy or safety.

3. CMC

Dr. Yang states that there are no outstanding issues and recommends that the NDA be approved. Manufacturing site inspections were found to be acceptable. I concur with Dr. Yang's assessment of the CMC data. Based on the identical composition of the beads used for the 45 mg and 135 mg capsules, superimposable dissolution profiles, and adequate in vitro and in vivo characterization of the 135 mg capsule, Dr. Arzu Selen, the ONDQA Biopharmaceutics

reviewer, recommended that a biowaiver be granted for the 45 mg dose of Trilipix. The Clinical Pharmacology reviewers concluded that the company provided evidence of dose-proportionality of Trilipix from 50 to 100 mg. A 45 mg strength was not included in the assessment. Given some concerns regarding the data on dose-linearity, the Clinical Pharmacology reviewers considered the submitted data insufficient to comment on the dose proportionality/linearity over the proposed 45 mg and 135 mg Trilipix strengths. Dr. Selen did not believe that demonstrating dose proportionality/linearity for the 45 mg strength of Trilipix was critical to determining the appropriateness of granting a biowaiver for the lower strength. According to her, "linearity in pharmacokinetics becomes a consideration when the proposed dose is higher than the highest strength. In this case, this should not have been a concern for supporting the low dose capsule."

Although I do not believe that the disagreement between the Clinical Pharmacology reviewers and Dr. Selen about dose proportionality between 45 mg and 135 mg precludes granting the biowaiver and approving the 45 mg dose of Trilipix, I do believe it would be prudent for the company to conduct a post-approval study to compare the pharmacokinetics of 3 x 45 mg Trilipix capsules vs. 1 x 135 mg Trilipix capsule.

4. Nonclinical Pharmacology/Toxicology

Drs. Antonipillai and Davis-Bruno conclude that there are no outstanding issues and recommend that the NDA be approved. I agree with their assessment.

5. Clinical Pharmacology/Biopharmaceutics

Drs. Khurana and Choe conclude that the 135 mg dose of Trilipix is bioequivalent to the 200 mg dose of approved fenofibrate (Tricor) and that the to-be-marketed formulation of Trilipix is bioequivalent to the formulation used in the phase 3 clinical trials. The Clinical Pharmacology reviewers recommend approval of the NDA. I agree with their assessment. There are no outstanding clinical pharmacology issues that prevent approval of Trilipix.

6. Clinical Microbiology

Trilipix is an orally administered drug. Consequently, a microbiology review was not necessary.

7. Clinical/Statistical-Efficacy

The assessments of the clinical efficacy and safety of Trilipix were based in large part on data from 3 randomized, double-blind, active-controlled trials of 12-weeks duration. Approximately 2700 patients with mixed dyslipidemia were enrolled into the 3 studies combined. Each study included a different statin as an active comparator: rosuvastatin, simvastatin, or atorvastatin. There were statin and Trilipix monotherapy arms as well as Trilipix + statin arms in the 3 studies. Primary efficacy analyses were conducted for HDL-C, TG, and LDL-C. For HDL-C, the principal comparisons were Trilipix in combination with

each dose of statin vs. statin monotherapy at the corresponding dose. For TG, the principal comparisons were Trilipix in combination with each dose of statin vs. statin monotherapy at the corresponding dose. For LDL-C, the principal comparisons were Trilipix in combination with each dose of statin vs. Trilipix monotherapy.

As shown in the table below from Dr. Golden's review, treatment with Trilipix + a statin led to statistically significant improvements in HDL-C and TG levels compared with statin monotherapy. Statistically significant improvements in LDL-C levels were noted for Trilipix + a statin compared with Trilipix monotherapy.

	ABT-335 + Low-dose statin			p-value	ABT-335 + Moderate-dose statin			High-dose statin
	ABT-335 (N=490)	Low-dose statin (N=493)	Low-dose statin (N=490)		Moderate-dose statin (N=491)	Moderate-dose statin (N=489)	p-value	
HDL-C	(N=420)	(N=455)	(N=423)		(N=430)	(N=422)		(N=217)
BL mean	38.4	38.4	38.2		38.4	38.1		38.0
Final mean	44.3	40.7	44.8		41.1	44.3		40.6
Mean % Δ	16.3%	7.4%	18.1%	< 0.001 ^a	8.7%	17.5%	< 0.001 ^a	7.9%
TG	(N=459)	(N=477)	(N=470)		(N=472)	(N=462)		(N=235)
BL mean	280.7	286.1	282.1		287.9	286.1		282.5
Final mean	177.3	217.6	146.7		202.5	147.5		186.1
Mean % Δ	-31.0%	-16.8%	-43.9%	< 0.001 ^a	-23.7%	-42.8%	< 0.001 ^a	-28.1%
LDL-C	(N=427)	(N=463)	(N=436)		(N=438)	(N=434)		(N=226)
BL mean	158.4	153.8	155.7		158.0	156.4		156.1
Final mean	146.1	100.6	101.9		91.6	99.1		81.7
Mean % Δ	-5.1%	-33.9%	-33.1%	< 0.001 ^b	-40.8%	-34.6%	< 0.001 ^b	-47.1%

a. ABT-335 in combination with statin vs. corresponding statin monotherapy

b. ABT-335 in combination with statin vs. ABT-335 monotherapy

As Dr. Golden points out in her review, the LDL-C lowering recorded for Trilipix monotherapy was only about 5%, a value that is smaller than the LDL-C reductions seen with Tricor. Because the active ingredient in Trilipix and Tricor is the same – fenofibric acid – and the two compounds have been shown to be bioequivalent, there is no reason to believe that the differential effects on LDL-C noted between studies of Trilipix and Tricor are drug-related. Rather, the baseline lipid levels of the patient populations in the Trilipix and Tricor studies differed to an extent that likely explains the differential LDL-C responses. Relative to the patients in the Tricor studies, the patients in the Trilipix studies had higher TG levels at baseline. Elevated TG levels (and lower LDL-C levels) can diminish the LDL-C lowering effect of fenofibrate.

Dr. Golden recommends that Trilipix be approved as monotherapy for primary and mixed dyslipidemia only in patients who are intolerant of statin therapy. Her recommendation is not specific to Trilipix, but includes all marketed fenofibrate products. There is no question in my mind that statins should be first-line therapy for patients who require pharmacologic treatment for primary hypercholesterolemia or mixed dyslipidemia. Clinical trial data provide convincing evidence of the superior benefit-to-risk profile of statins vs. fenofibrate in these patient populations. However, I believe the issue of relegating Trilipix to second-line therapy for primary hypercholesterolemia and mixed dyslipidemia should be considered within the

larger question of whether all non-statin compounds – bile acid resins, niacin, gemfibrozil, fenofibrate, and ezetimibe – should have their indications changed to explicitly state that they are second-line therapy for statin-intolerant patients. The Division plans to address this topic in the near future, perhaps with input from our advisory committee. Until such time, I recommend that Trilipix monotherapy be approved for the treatment of primary hypercholesterolemia and mixed dyslipidemia with indication language identical to that of approved fenofibrate products.

Dr. Golden recommends that Trilipix monotherapy be approved for the treatment of severe hypertriglyceridemia (e.g., TG \geq 500 mg/dl). I agree with her recommendation.

8. Safety

Since fenofibrate has been on the United States market since the early 1990s, there is extensive data regarding the safety of this drug. The major safety concern with fenofibrate is rhabdomyolysis. Events of lesser concern include hepatobiliary adverse reactions and elevations in serum creatinine and BUN.

Based on preliminary observational data, the risk for rhabdomyolysis when fenofibrate is used in combination with a statin is higher than the risk associated with fenofibrate or statin monotherapy. There were no cases of rhabdomyolysis reported in the 3 pivotal Trilipix clinical studies. Given the size of the Trilipix database, one can rule out a large risk for rhabdomyolysis when Trilipix is used in conjunction with a low-to-moderate dose statin. By design, none of the patients were treated with Trilipix in combination with the highest marketed doses of atorvastatin, rosuvastatin, or simvastatin. The Trilipix labeling appropriately recommends against coadministration with high doses of statins.

To gain a better estimate of the risk for rhabdomyolysis, the Division has required that Abbott conduct a post-approval observational study in which the incidence of hospitalized rhabdomyolysis is compared among patients treated with fenofibrate monotherapy, statin monotherapy, and fenofibrate plus statin therapy. Moreover, Trilipix will have a Medication Guide. This risk management tool, which patients will receive each time they receive an initial Trilipix prescription and refill, will describe the early symptoms of rhabdomyolysis and stress the importance of contacting a health care provider in the event that such symptoms develop. The Medication Guide will also indicate that the risk for rhabdomyolysis is increased when Trilipix is used in combination with a statin and warn against the concomitant use of medication that could raise plasma statin concentrations and in turn further increase the risk for severe muscle injury.

Fenofibrate is associated with mild-to-moderate increases in levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). These enzyme elevations presumably reflect alteration within hepatocytes, but do not appear to predict serious liver injury. As Dr. Golden points out in her review, the incidence of transaminitis in subjects treated with Trilipix monotherapy or coadministration with a statin was higher than that observed in subjects receiving statin monotherapy. None of the subjects in the Trilipix NDA satisfied the criteria for Hy's law nor did any subject develop liver failure. Reports of cholelithiasis and

cholecystitis were rare in subjects exposed to Trilipix. The labeling for the approved fenofibrate compounds recommends periodic monitoring of liver tests. The Trilipix labeling will include the same recommendation.

Fenofibrate increases serum creatinine and BUN levels in some patients. To date, these changes appear to be reversible upon drug discontinuation and have not been linked to serious renal dysfunction. Dr. Golden makes note of modest increases in serum creatinine and BUN in some subjects treated with Trilipix, in particular, in the elderly and those with baseline renal impairment or diabetes. There was no evidence that the increases in serum creatinine and BUN in subjects treated with Trilipix alone was exacerbated by coadministration with a statin. The Trilipix labeling recommends that serum creatinine be monitored in elderly subjects and in patients with renal insufficiency or diabetes. A 45 mg dose of Trilipix is available and recommended for subjects with mild-to-moderate renal insufficiency.

9. Advisory Committee Meeting

Given that fenofibrate has been available in the United States for more than 15 years and there are no controversial issues surrounding this compound, an advisory committee meeting was not considered necessary.

10. Pediatrics

Due to the primacy of statins in the treatment of primary hypercholesterolemia and mixed dyslipidemia in pediatric patients and the rarity of severe hypertriglyceridemia in this population, the Division is waiving the pediatric study requirements for the following indications:

- As monotherapy to reduce elevated LDL-C, Total-C, Triglycerides and Apo B, and to increase HDL-C in patients with primary hypercholesterolemia or mixed dyslipidemia.
- As monotherapy to reduce TG in patients with severe hypertriglyceridemia.

For the following indication the Division is waiving the pediatric study requirements for ages 0-11 years and deferring the requirement for ages 12-17 years:

- In combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal.

The Division is waiving the pediatric study requirements for ages 0 to 11 years because the necessary studies are impossible or highly impractical. This is due to the fact that statins are first-line therapy and the incidence of high TG and/or low HDL-C requiring additional pharmacologic therapy in this age group is very rare.

The Division is deferring submission of a pediatric study for the coadministration indication for ages 12 to 17 years because this indication is ready for approval in the adult population.

The PERC agreed with the Division's proposals regarding the study of Trilipix in pediatric populations.

11. Other Relevant Regulatory Issues

The Division of Scientific Investigations (DSI) inspected a number of clinical sites that took part in the phase 3 Trilipix clinical studies as well as the contract laboratory. The DSI also audited the clinical and analytical portions of the pivotal bioequivalency study comparing Trilipix to fenofibrate. The DSI inspectors recommended that the audited data be accepted for review.

There are no unresolved regulatory issues.

12. Labeling

I agree with DMETS that the tradename Trilipix is acceptable from a promotional standpoint and that the potential is low for look-alike or sound-alike confusion with marketed drugs. DMETS recommended some changes to the proposed carton and container labels to reduce the potential for medication errors. These changes have been made by Abbott.

There was considerable discussion between the Division and Abbott regarding the appropriate wording for Trilipix's indication for coadministration with a statin. The company proposed the following language:

Trilipix is indicated, when coadministered with a statin, to reduce elevated levels of TG, non-HDL-C, VLDL, Apo B, and Total-C, and to increase levels of HDL-C in patients with mixed dyslipidemia.

Based on the currently available cardiovascular outcomes data for fenofibrate (and gemfibrozil), the Division believes that Trilipix is a reasonable option for high-risk patients with elevated TG and low HDL-C despite treatment with an optimal dose of a statin. This is in agreement with the National Cholesterol Education Program's (NCEP) recommendation for fenofibrate as add-on therapy to a statin in high-risk patients with mixed dyslipidemia. The Division is approving the following language for the indication of Trilipix-statin coadministration:

Trilipix is indicated in combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal.

The Trilipix labeling will include a disclaimer that the incremental effect of Trilipix on cardiovascular morbidity and mortality when added to statin therapy is unknown. The ACCORD trial is currently measuring the incremental effect of fenofibrate on risk for

cardiovascular events when added to background simvastatin therapy in patients with type 2 diabetes. Results from this trial should be available in 2010.

The Division is requiring that Trilipix have a Medication Guide. The Division believes that patients should be aware of the potential risk for and signs and symptoms of rhabdomyolysis. The Medication Guide should enhance the safe use of Trilipix when combined with statin therapy.

13. Decision/Action/Risk Benefit Assessment

- **Regulatory Action – I recommend approval of the Trilipix 505b2 NDA.**
- **Risk-Benefit Assessment – Abbott has relied on bioequivalency data and the FDA’s previous findings of efficacy and safety of fenofibrate to support approval of Trilipix monotherapy for the treatment of primary hypercholesterolemia, mixed dyslipidemia, and severe hypertriglyceridemia. The company has provided sufficient clinical trial data to support the use of Trilipix in combination with a statin to reduce TG and increase HDL-C in high-risk patients already receiving statin treatment.**
- **Recommendation for Postmarketing Risk Management Activities – Pursuant to section 505(o)(3) of the Food, Drug, and Cosmetic Act, Abbott is required to conduct an observational study to estimate the incidence and risk factors for hospitalized rhabdomyolysis in patients treated with a fibrate in combination with a statin vs. statin or fibrate monotherapy. The final report for this study is due no later than January 31, 2010. Trilipix will have a Medication Guide to enhance the effective and safe use of the drug when administered with a statin.**
- **Recommendation for other Postmarketing Study Commitments – Abbott has agreed to conduct a dose equivalence study to compare the pharmacokinetics of 3 x 45 mg Trilipix capsules vs. 1 x 135 mg Trilipix capsule. This study will provide additional information about dose proportionality of Trilipix between the 45 mg and 135 mg doses.**

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