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APPLICATION NUMBER:

204977Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	April 22, 2014
From	Eric Colman, MD
Subject	Deputy Division Director Summary Review
NDA#	204977
Applicant Name	Trygg Pharma
Date of Submission	January 31, 2013
PDUFA Goal Date	November 30, 2013
Proprietary Name / Established (USAN) Name	Omtryg/omega-3-acid ethyl esters A
Dosage Forms / Strength	1.2 gram capsules
Proposed Indication(s)	Treatment of severe hypertriglyceridemia
Recommended Action for NME:	Approve

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Iffat Chowdhury, MD
Statistical Review	Lee Ping Pian, PhD
Pharmacology/Toxicology Review	Indra Antonipillai, PhD
CMC Review/OBP Review	Martin Haber, PhD, and Houda Mahayni, PhD
Microbiology Review	Bryan Riley, PhD
Clinical Pharmacology Review	Manoj Khurana, PhD
OSI	Cynthia Kleppinger
CDTL Review	See Deputy Division Director Memo
OSE/DMEPA	Reasol Agustin, PharmD

OND=Office of New Drugs
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 OSI=Office of Scientific Investigations
 CDTL=Cross-Discipline Team Leader

1. Introduction

This submission provides efficacy and safety data in support of approval of Trygg's fish oil mixture for the treatment of severe hypertriglyceridemia. There have been no significant disagreements between reviewers or review disciplines with respect to a final regulatory recommendation.

2. Background

Patients with severely elevated triglyceride (TG) levels (e.g., ≥ 500 mg/dl) are at increased risk for acute pancreatitis. In addition to fenofibrate and niacin, omega-3 fatty acids are often used to lower TG levels in patients at risk for pancreatitis. In 2004, the Division approved Lovaza (omega-3-acid ethyl esters), a fish oil mixture manufactured by Glaxo Smith Kline (GSK), as an adjunct to diet, to reduce TG levels in adult patients with severe (≥ 500 mg/dl) hypertriglyceridemia. The recommended dose of Lovaza is 4 capsules per day.

Lovaza is a mixture of omega-3-acid ethyl esters obtained from the body oil of specific species of fish. Each capsule of Lovaza contains 1 gram (g) of fish oil composed of (b) (4) (approximately 465 mg) eicosapentaenoic acid ethyl ester (EPA) and approximately (b) (4) (approximately 375 mg) docosahexaenoic acid ethyl ester (DHA). Other omega-3-acid ethyl esters found in lower amounts in Lovaza include docosapentaenoic acid ethyl ester (DPA) (b) (4)

Each 1 gram capsule of Lovaza contains at least 900 mg of ethyl esters of omega-3 fatty acids or not less than (b) (4)

On 29 June 2010, Trygg Pharma, Inc. submitted an Investigational New Drug Application (IND) for AKR-963 (hereafter "AKR"), a fish oil mixture for which they planned to seek approval for the treatment of severe hypertriglyceridemia by relying on the Agency's previous finding of safety and effectiveness for Lovaza. The submission contained two protocols: A randomized, double-blind, parallel group, bioequivalence trial and a randomized, double-blind, placebo- and active-controlled, parallel-group, phase 3 study to assess the efficacy and safety of AKR-963 in subjects with severe hypertriglyceridemia.

AKR is a mixture of omega-3-acid ethyl esters obtained from the body oil of specific species of fish. Each capsule of AKR contains 1.2 g of fish oil composed of approximately 465 mg EPA and 375 mg DHA. (b) (4)

(b) (4) Each
capsule of AKR contains approximately 20% more fish oil than Lovaza and is (b) (4)

On 31 January 2013, Trygg Pharma submitted a 505b2 New Drug Application (NDA) requesting approval of AKR for the treatment of severe hypertriglyceridemia with reference to the Agency's previous finding of effectiveness and safety of Lovaza.

The core elements of the NDA submission included a randomized, double-blind, placebo- and active (Lovaza)-controlled, one-year clinical study; a bioequivalence study comparing the pharmacokinetics of AKR to Lovaza; and a bridging toxicology study.

3. CMC

Dr. Martin Haber, the primary CMC reviewer, recommends that this application be approved. I agree with this recommendation.

4. Nonclinical Pharmacology/Toxicology

The sponsor conducted a 28-day comparative bridging toxicity study of AKR and Lovaza in rats using doses of 200 and 400 mg/kg/day. As noted by Dr. Antonipillai, the primary pharmacology/toxicology reviewer, in general, similar histopathology findings were noted with both AKR and Lovaza. Target organs of toxicity for both AKR and Lovaza were liver inflammation, renal inflammation, and mild retinal degeneration. Inflammation of the urinary bladder and hypotrichosis were observed with AKR but not Lovaza. Despite some limitations with the bridging study (no placebo control), Dr. Antonipillai points out that the target organ toxicities were similar for AKR and Lovaza and there is a safety margin of approximately 10X relative to the recommended clinical dose of AKR. For these reasons, Dr. Antonipillai concluded that the non-clinical data support approval of this application. I concur with this conclusion.

5. Clinical Pharmacology

Determination of bioequivalence between different fish oils of omega-3 fatty acid ethyl ester mixtures is based on measurement of the principal omega-3 fatty acids, EPA and DHA. Under fasted conditions, the sponsor provided data indicating that AKR was bioequivalent to Lovaza with regards to the AUC₀₋₇₂ and C_{max} of total plasma EPA and total plasma DHA. The submitted clinical pharmacology data also demonstrated that AKR was bioequivalent to Lovaza with regards to the AUC₀₋₇₂ and C_{max} of plasma free EPA and free DHA. Under conditions of a high-fat meal, the sponsor provided data indicating that AKR was bioequivalent to Lovaza with regards to the AUC₀₋₇₂ and C_{max} of total plasma EPA and total plasma DHA; and AKR was bioequivalent to Lovaza with regards to the AUC_{0-t}, AUC_{0-inf}, and C_{max} of plasma EPA-EE and DHA-EE. Because food significantly increases exposure of AKR, the labeling will instruct patients to take the drug with food. Dr. Manoj Khurana, the

primary clinical pharmacology reviewer, recommends that this application be approved. I agree with that recommendation.

6. Clinical Microbiology

Dr. Bryan Riley, the primary microbiology reviewer, recommends that this application be approved. I agree with this recommendation.

7. Clinical/Statistical-Efficacy

The sponsor conducted a randomized, blinded, placebo- and active-controlled study to compare the efficacy and safety of AKR and Lovaza relative to placebo (corn oil) and AKR to Lovaza in patients with severe hypertriglyceridemia. The primary objective was to demonstrate superiority of AKR (and Lovaza) to placebo with respect to the lowering of serum TG levels following 12 weeks of treatment. The secondary objective was to demonstrate non-inferiority of AKR to Lovaza in terms of TG lowering following 12 weeks of treatment. A non-inferiority margin of -15% was agreed upon prior to initiation of the study. This margin retains 50% of the upper bound of the 95% confidence interval of the placebo-subtracted treatment effect of Lovaza in two previous trials of patients with severe hypertriglyceridemia. Following the first 12 weeks of the trial, subjects randomized initially to placebo were crossed-over to treatment with either AKR or Lovaza for up to Week 68.

A total of 43 subjects were randomized to placebo, 105 to 4 capsules (4.0 grams) per day of Lovaza, and 106 to 4 capsules (4.6 grams) per day of AKR. The three groups were well-matched for baseline demographic characteristics. The mean age was 51 years, 72% were male, 92% were Caucasian, and the baseline BMI was 33 kg/m². The baseline median fasting TG level was 759 mg/dl and LDL-C was 87 mg/dl. Approximately 21% of subjects were taking a statin at baseline. Subjects were not provided with instructions regarding whether to take their study medication with a meal.

Approximately 89% of subjects in each group completed with first 12 weeks of the study. The table below provides the results of the primary objectives of the trial.

Median Percent Change in TG from Baseline to Endpoint

Analysis Variable	Placebo	Lovaza	AKR
N	N=43	N=103	N=104
Baseline median	624 mg/dl	655 mg/dl	702 mg/dl
Median % change	-17.4%	-26.8%	-24.7%
Median of diff vs. placebo		-14.0%	-12.2%
p-value		0.02	0.04
Median of diff vs. Lovaza			2.3%
95% confidence interval			(-6.0, 10.5)
p-value			0.58

Both AKR and Lovaza were associated with statistically significant reductions in serum TG levels vs. corn oil placebo. Although the sponsor concluded that AKR was non-inferior to

Lovaza because the upper bound of the 95% confidence interval for the treatment difference between groups was below the non-inferiority margin of -15%, the constancy assumption was not satisfied. The constancy assumption states that “the historical difference between the active control and placebo is assumed to hold in the setting of the new trial if a placebo control had been used.¹ The placebo-subtracted treatment effect of Lovaza in the two historical trials used to define the 15% non-inferiority margin was -52% compared with -14% in the current study. In fact, the estimated treatment effect of Lovaza is smaller than 15%, the selected non-inferiority margin. (b) (4)

However, the observed treatment effects of AKR and Lovaza on serum TG levels can be considered comparable.

The below table from Dr. Chowdhury’s review provides the median percent changes in other lipid and apolipoprotein parameters.

Median Percent Change in Lipid and Apolipoprotein Parameters from Baseline to Endpoint

	AKR-963 N=104	Lovaza N=103	Placebo N=43	Median of Differences AKR-963 -Placebo	P-Value (AKR-963 vs. Placebo)
LDL-C	+20.3%	+12.8%	-5.9%	+24.7	0.0002
Non-HDL-C	-9.2%	-3.6%	-0.8%	-8.5	0.0258
VLDL-C	-21.2%	-18.1%	+5.6%	-28.7	0.0008
ApoB	+3.8%	+5.3%	0%	+3.2	0.2088
HDL-C	0.0%	0%	0.0%	+3.6	0.3502
Total Cholesterol	-8.1%	-1.0%	-0.8%	-6.9	0.0331

The DHA component of omega-3 fatty acid mixtures is known to increase levels of LDL-C. The clinical significance of this increase is unknown. The labeling for Lovaza mentions this effect and recommends that patients have periodic assessment of their LDL-C levels. This will obviously apply to AKR’s labeling as well.

8. Safety

As noted in Dr. Chowdhury’s review, there were no meaningful differences in the safety profiles between AKR and Lovaza and placebo. Furthermore, Dr. Chowdhury did not note any unexpected safety findings from the clinical study.

¹ D’Agostino R, et al. Non-inferiority trials: design concepts and issues – the encounters of academic consultants in statistics. *Statistics in Medicine*. 2003;22:169-186

9. Pediatrics

The sponsor requested a full waiver for pediatric studies because such studies are impossible or highly impracticable. I believe that granting a full waiver is appropriate.

10. Other Relevant Regulatory Issues

Citizen Petition

On 21 February 2014, the Agency responded to a citizen petition filed by Crowell and Moring LLP. The petition requested that the Agency amend its listed strength for Lovaza capsules, including the strength listing in the Orange Book, to 900 mg, so that the strength “appropriately identifies the amount of active ingredient per administration unit without reference to any other capsule properties such as product weight/fill weight, excipients, or other inactive ingredients”; or adopt a strength of 840 mg for Lovaza capsules based upon the fixed amount of major omega-3-acid ethyl esters specified in the Lovaza NDA reviews and labeling. For the reasons briefly summarized below, the petition was denied.

Lovaza contains a naturally derived, partially purified fish oil concentrate mainly consisting of a mixture of fatty acids. The clinical studies that supported the approval of Lovaza tested the fish oil as a whole to establish the safety and effectiveness of the product. At the time of approval, the fish oil mixture in Lovaza had not been fully characterized, and the available data did not adequately demonstrate the activity or inactivity of all components in the mixture. In accordance with the Agency’s practice regarding naturally derived mixtures that are not fully characterized, the Agency identified the entire fish oil mixture as the active ingredient of Lovaza. Because the petitioner provided no new information or data that would cause the Agency to revise that initial determination, the strength listing for Lovaza will remain 1 g capsules contain at least 900 mg of omega-3-acid ethyl esters.

Active Ingredient and Strength

Because the entire mixture of fish oil constitutes the active ingredient, AKR’s strength listing will be 1.2 g capsules contain at least 900 mg of omega-3-acid ethyl esters. Since the Agency determined that AKR has a different active ingredient than Lovaza – because it (b) (4) – it cannot have the same established name as Lovaza’s, which is omega-3-acid ethyl ester. The established name for AKR will be omega-3-acid ethyl esters A. For a detailed discussion of the active ingredient, strength listing, and established name, see my memoranda dated 24 January 2014.

The sponsor has proposed a proprietary name, Omtryg. The DMEPA finds this name acceptable. I agree with this assessment.

505b2 Committee

The 505b2 committee has reviewed and cleared this application for approval.

Inspections

The Office of Compliance has concluded that the manufacturing site inspections are acceptable.

Financial Disclosure

The sponsor certified that they did not enter into any financial arrangements with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study. They also certified that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor did not disclose such interests. The sponsor further certified that no listed investigator was the recipient of significant payments of other sorts.

11. Labeling

Given that AKR's approval is based on the Agency's previous finding of safety and effectiveness for Lovaza, AKR's labeling will conform to that of Lovaza's.



The Limitations of Use statements in Lovaza's labeling currently read:

The effect of LOVAZA on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined.

The effect of LOVAZA on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined.

These will be revised and simplified in Omtryg's labeling to read:

The effect of OMTRYG on the risk for pancreatitis has not been determined.

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

The Division plans to incorporate this language into the labeling of all prescription omega-3 fatty acid products.

12. Decision

This 505b2 application for AKR capsules relies on the Agency's previous finding of safety and effectiveness for Lovaza capsules. Although we have determined that AKR and Lovaza have different active ingredients, the sponsor has provided evidence that the two fish oils are bioequivalent (based on EPA and DHA) and that AKR reduces serum TG levels significantly versus placebo and comparably to Lovaza in patients with severe hypertriglyceridemia. Thus, I recommend that AKR, 4 capsules daily, be approved as an adjunct to diet to reduce TG levels in adult patients with severe hypertriglyceridemia.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIC C COLMAN
04/23/2014