CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205060Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	May 5, 2014
From	Eric Colman, MD
Subject	Deputy Division Director Summary Review
NDA#	205060
Applicant Name	Astra Zeneca Pharmaceuticals
Date of Submission	July 5, 2013
PDUFA Goal Date	May 5, 2014
Proprietary Name / Established (USAN) Name	Epanova/omega-3-carboxylic acids
Dosage Forms / Strength	1 gram capsule
Proposed Indication(s)	Treatment of severe hypertriglyceridemia
Recommended Action:	Approve

Material Reviewed/Consulted OND Action Package, including:	
CDTL Review	James Smith, MD, MS
Medical Officer Review	Iffat Chowdhury, MD/Giovanni Cizza, MD, PhD
Statistical Review	Cynthia Liu, MA
Pharmacology/Toxicology Review	Parvaneh Espandiari, PhD
CMC Review	Xavier Ysern, PhD/Martin Haber, PhD
OBP Review	Houda Mahayni, PhD
Microbiology Review	Bryan Riley, PhD
Clinical Pharmacology Review	Suryanarayana Sista, PhD
OSI	Cynthia Kleppinger, MD
OSE/DMEPA	Michelle Rutledge, PharmD
OPDP	Ankur Kalola, PharmD
DMPP	Robin Duer, MBA, BSN

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OBP=Office of Biopharmaceutics
OSI=Office of Scientific Investigations
OPDP=Office of Prescription Drug Promotion
DMPP=Division of Medical Policy Programs

1. Introduction

This 505(b)(1) New Drug Application (NDA) provides efficacy and safety data for Epanova (omega-3-carboxylic acids) in support of an indication to treat severe hypertriglyceridemia. There have been no significant disagreements between reviewers or review disciplines with respect to the regulatory recommendation for approval. There are no outstanding issues to preclude approval and agreement has been reached with the sponsor on the final approved labeling.

2. Background

Individuals 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 at-risk subjects. Three omega-3-fatty acid mixtures are currently approved for the treatment of severe hypertriglyceridemia: Lovaza (omega-3-acid ethyl esters), Vascepa (icosapent ethyl), and Omtryg (omega-3-acid ethyl esters A).

3. CMC/Biopharmaceutics

Epanova is a mixture of predominately omega-3 fatty acids, in their carboxylic acid (i.e., "free") form, obtained from (b) (4) fish. Each 1 gram capsule of Epanova is composed of approximately 55% eicosapentaenoic acid (EPA), approximately (b) (4)% docosahexaenoic acid (DHA), and approximately (b) (4)% docosapentaenoic acid (DPA). There are (b) (4) additional omega-3 fatty acids and (b) (4) omega-6 fatty acids in each 1 gram capsule. The principal omega-6 fatty acid is (b) (4), present at approximately (b) (4)%. Total omega-3 fatty acids are limited to no more than (b) (4)% and total omega-6 fatty acids are limited to no more than (b) (4)%. To (b) (4), each capsule of Epanova contains alpha-tocopherol as an inactive ingredient.

The fatty acid composition acceptance criteria for the Epanova drug substance is shown in the following table.

Epanova Fatty Acid Composition Acceptance Criteria

Parameter	Ranges
Polyunsaturated free fatty acids	Not less than 850 mg/g
EPA	500 to 600 mg/g
DHA	150 to 250 mg/g
DPA	(b) (4) mg/g
EPA + DHA	(b) (4) mg/g
Total omega-3 fatty acids	(b) (4) mg/g
Total omega-6 fatty acids	Not more than (b) (4) mg/g
Other polyunsaturated fatty acids	Not more than (b) (4) mg/g
Monounsaturated free fatty acids	Not more than (b) (4)%
Saturated free fatty acids	Not more than %

Drs. Xavier Ysern and Martin Haber, the primary CMC reviewers, recommend that this application be approved, as does Dr. Mahayni, the biopharmaceutics reviewer.

4. Nonclinical Pharmacology/Toxicology

Nonclinical toxicology studies of Epanova were conducted in mice, rats, and dogs. The toxicological findings of note included increased liver enzymes, associated in some cases, with increased liver weight and focal necrosis. In the study of dogs, granuloma/macrophage aggregates were observed in the heart and mineralization was observed in the aorta. According to Dr. Espandiari, safety margins to the maximal human recommended dose (MHRD)(4 grams per day) were established for 5-fold in the 4-week mouse study at 4000 mg/kg/day; 2-fold in the 26-week rat study at 600 mg/kg/day; and 3-fold in the 39-week dog study at 300 mg/kg/day.

Epanova was not genotoxic in the Ames assay, the chromosomal aberration study, or the *in-vivo* rat micronucleus study.

There were no drug-related tumors in the 26-week transgenic mouse study at doses up to 5-fold the MHRD. In the 104-week rat carcinogenicity study, benign sex cord stromal tumors of the ovaries were reported in female rats at doses up to 5-fold the MHRD.

Late in the review cycle, the CMC reviewer identified (b) (4) as a drug substance impurity. While (b) (4) is a known rodent carcinogen, as noted above, there were no drug-related malignant tumors in the two rodent carcinogenicity studies in which this compound was present at (b) (4) mg/kg. Moreover, according to the Carcinogenic Potency Database[1], the lower bound of the 95% confidence interval for the TD_{10} (the dose associated with development of malignant tumors in 10% of animals exposed) is (b) (4) mg/kg/day. (b) (4) in the drug product will be controlled by a specification of no more than (b) (4) ppm or (b) (4) mg/kg. At 4 capsules per day, the maximum recommended human dose, a 60 kg person would consume approximately (b) (4) ng/day of (b) (4). As such, the potential risk to humans posed by this amount of (b) (4) in Epanova is negligible.

Dr. Espandiari recommends that this application be approved.

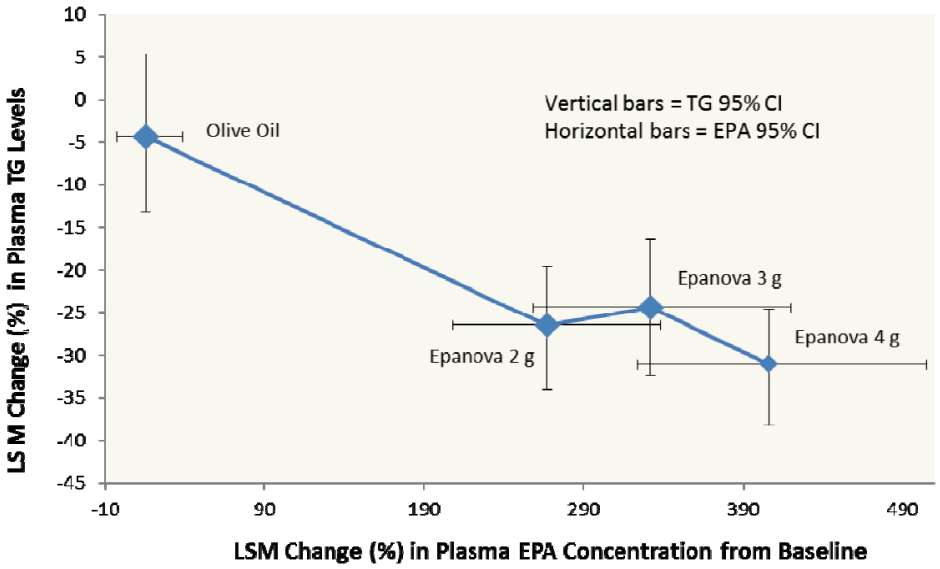
5. Clinical Pharmacology

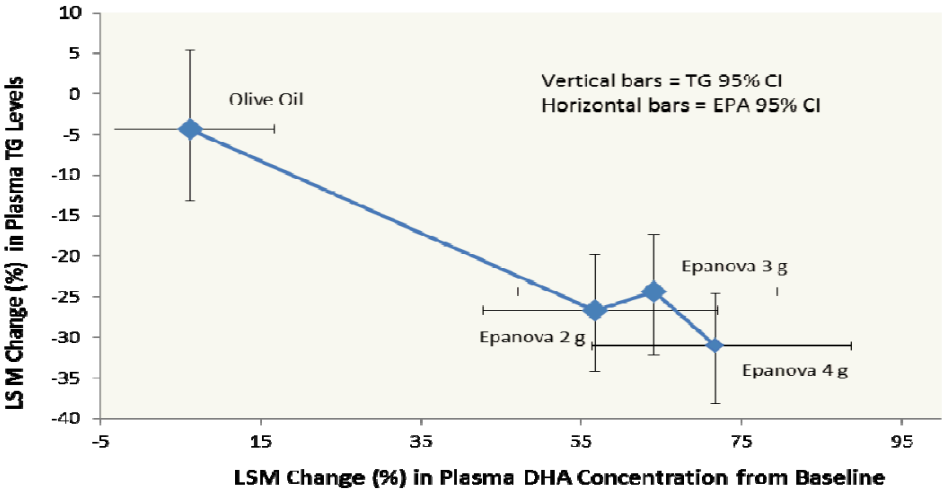
According to Dr. Sista, the primary clinical pharmacology reviewer, Epanova shows linear pharmacokinetics between doses of 2 grams and 8 grams. The median T_{max} of EPA is 4.5 to 5.5 hours; the median T_{max} for DHA is 4.7 to 5.3 hours. The $T_{1/2}$ for EPA is 4.7 to 10.8 hours; the $T_{1/2}$ for DHA is approximately 7 hours. Under fasted conditions, following a single 4 gram

[1] Carcinogenic Potency Database http://toxnet.nlm.nih.gov/cpdb/ltd10chemicalsummary.html. Accessed 5 May 2014.

dose of Epanova, almost all of the EPA and DHA in plasma are incorporated into phospholipids, triglycerides, and cholesterol esters.

As noted in the below figures taken from Dr. Sista's review, in the phase 3 clinical trial conducted to demonstrate the efficacy and safety of Epanova, there was not a clear dose-response relationship between EPA and DHA exposure (and dose of Epanova) and the reduction in serum TG levels.





It is unclear what factor(s) accounts for the "aberrant" values associated with the 3 gram dose of Epanova.

The sponsor evaluated the effects of food on the bioavailability of Epanova (EPA and DHA) in a randomized, open-label, 4-way crossover study.[2] As concluded by Dr. Sista: "There appears to be food-effect with Epanova. Compared to fasting administration, following administration of Epanova with a high-fat meal, there is an increase in relative bioavailability of total and free baseline adjusted EPA by approximately 240% and 180%, respectively. The relative bioavailability of baseline adjusted total DHA was comparable for both administrations, while there was a 140% increase in AUC for baseline adjusted free DHA. Under fed conditions, unadjusted total and free EPA exposures increased by 180% and 150%, respectively, while unadjusted total and free DHA were similar for both fasted and fed conditions."

The Dosing and Administration section of the labeling will reflect the fact that subjects in the phase 3 clinical trial took Epanova without regard to meals.

The following intrinsic factors did not have clinically relevant effects on the pharmacokinetics of EPA and DHA: age, gender, race, and body weight. The effects of hepatic and renal impairment on the pharmacokinetics of EPA and DHA were not studied.

In drug-drug interaction studies, Epanova did not affect the extent or rate of exposure to simvastatin; nor did it alter the anti-platelet effect of low-dose aspirin, as assessed by the VerifyNow aspirin assay. (b) (4), the clinical pharmacology reviewer recommends (b) (4). Epanova did not significantly change the single-dose AUC or C_{max} of R- and S-warfarin or the anti-coagulation pharmacodynamics of 25 mg warfarin.

As has been done with previous omega-3 fatty acid products, a waiver was granted to Epanova for a thorough QT study. In a consult dated 14 December 2013, the QT interdisciplinary review team, based on review of the ECG data from the phase 3 clinical trial, concluded that Epanova did not show proarrhythmic liability.

The clinical pharmacology reviewer recommends approval of the Epanova NDA.

6. Clinical Microbiology

Dr. Bryan Riley, the primary microbiology reviewer, recommends that this application be approved.

7. Clinical/Statistical-Efficacy

The efficacy data for this application were reviewed by Drs. Chowdhury and Smith.

Study Design: The efficacy of Epanova was examined in a randomized, double-blind, placebo-controlled, 12-week clinical trial known as EVOLVE. Male or female subjects age 18 years or older with fasting serum TG levels of $\geq$ 500 mg/dl and $\leq$ 2000 mg/dl were eligible for study participation. Subjects who were taking a statin or ezetimibe, if on a stable dose(s) for 6 weeks

[2] Data for Lovaza (omega-3-acid ethyl esters) not shown.

prior to Week -2, were allowed to enter the study. Individuals with a history of pancreatitis, uncontrolled diabetes (HbA1c $\geq$ 9%), or history of a cardiovascular event within 6 months prior to Visit 1 were among those who were excluded from study participation. Prohibited medications included bile acid sequestrants, fibrates, niacin, omega-3 fatty acid supplementation, and anticoagulants.

Efficacy Endpoints: The primary efficacy endpoint was the percent change in TG levels from baseline (average of Weeks -2, -1, and 0) to the end of treatment (average of Weeks 10 and 12). The secondary efficacy endpoints included the percent change from baseline (average of Weeks -2, -1, and 0) to end of treatment (average of Weeks 10 and 12) in serum non-HDL-C and HDL-C. Other lipid, lipoprotein, and plasma fatty acids variables were tertiary efficacy endpoints.

Methods and Analyses: The primary, secondary, and tertiary continuous efficacy endpoints were analyzed using an ANCOVA model with treatment and use of lipid-altering drugs (yes or no) as factors and baseline as a covariate. Pairwise comparisons of each Epanova group to placebo were performed using the Dunnett's procedure for the primary efficacy endpoint and the Hommel's procedure for the secondary efficacy endpoints to control the type 1 error rate. No multiplicity adjustment was planned for the tertiary endpoints; however, the sponsor used the Dunnett's procedure to adjust p-values for all the tertiary pairwise comparisons. Efficacy analyses were performed on the modified ITT (mITT) population which consisted of all randomized subjects who had received at least one dose of investigational product and had at least one post-randomization efficacy assessment.

Subject Disposition: Following a medication washout and diet lead-in phase, 399 subjects were randomized 1:1:1:1 to one of four treatment groups: placebo (olive oil)(n=99), Epanova 2 grams/day (n=100), Epanova 3 grams/day (n=101), or Epanova 4 grams/day (n=99). Subjects were instructed to follow the National Cholesterol Education Program (NCEP) Therapeutics Lifestyle Changes (TLC) diet and to take 4 capsules of study drug at one time per day without regards to meals.

Baseline Demographics: The baseline demographic characteristics were generally well-matched for the four treatment groups. The mean age was 52 years, the mean BMI was 31 kg/m^2, 77% of the subjects were male, 92% were Caucasian, approximately 35% were taking a statin and/or ezetimibe, and approximately 37% had type 2 diabetes mellitus.

Baseline Lipid Values: The baseline lipid parameters are shown in the below table taken from Dr. Chowdhury's review. There were no statistically significant differences in lipid parameters among the four treatment groups.

Baseline Lipid Parameters

Characteristic	Placebo N=98	Epanova 2 g N=99	Epanova 3 g N=97	Epanova 4 g N=99	Total N=393
TG (mg/dL)					
Mean (SD)	788.5 (305.11)	790.1 (269.01)	820.4 (353.15)	783.6 (335.21)	795.6 (316.18)
Median	682.3	717.0	728.0	655.0	694.3

Characteristic	Placebo N=98	Epanova 2 g N=99	Epanova 3 g N=97	Epanova 4 g N=99	Total N=393
P-Value					0.846
non-HDL-C (mg/dL)					
Mean (SD)	220.2 (54.37)	221.0 (62.30)	228.3 (74.10)	235.3 (72.77)	226.2 (66.39)
Median	214.5	205.3	215.3	225.0	217.0
P-Value					0.416
VLDL-C (mg/dL)					
Mean (SD)	139.0 (51.52)	137.9 (56.45)	143.6 (71.46)	143.9 (66.92)	141.1 (61.89)
Median	124.5	123.3	124.0	126.0	124.0
P-Value					0.864
LDL-C (mg/dL)					
Mean (SD)	81.5 (31.49)	83.0 (32.86)	84.7 (38.74)	90.3 (38.86)	84.9 (35.66)
Median	78.2	77.3	81.0	90.3	81.3
P-Value					0.274
HDL-C (mg/dL)					
Mean (SD)	29.2 (7.93)	28.0 (6.87)	29.0 (7.93)	29.9 (9.22)	29.0 (8.03)
Median	28.7	27.3	28.0	28.7	28.0
P-Value					0.338
Total Cholesterol					
Mean (SD)	249.4 (56.82)	249.0 (62.98)	257.4 (73.80)	265.3 (73.14)	255.3 (67.13)
Median	245.5	240.7	243.7	254.3	245.7
P-Value					0.328

Subject Disposition: The percentage of subjects who completed the 12-week study ranged from 86% in the Epanova 3 gram group to 95% in the placebo group. Seven percent of subjects in the Epanova 3 gram group did not complete the study due to an adverse event compared with none of the subjects in the placebo group. Approximately 5% of subjects in the Epanova 2 gram and 4 gram groups discontinued study drug due to an adverse event.

Primary Efficacy Outcome: Compared with treatment with placebo, treatment with Epanova 2 grams, 3 grams, and 4 grams led to robust, statistically significant reductions in serum TG levels (see below table from Dr. Chowdhury's review).

Baseline and Percent Change from Baseline to Endpoint in TG

	Placebo N=99	Epanova 2 g N=100	Epanova 3 g N=101	Epanova 4 g N=99
Baseline[1] (mg/dL)				
N	98	99	97	99

	Placebo N=99	Epanova 2 g N=100	Epanova 3 g N=101	Epanova 4 g N=99
Mean (SD)	788.5 (305.11)	790.1 (269.01)	820.4 (353.15)	783.6 (335.21)
Median	682.3	717.0	728.0	655.0
Percent Change from Baseline[2]				
N	98	95	94	95
Mean (SD)	9.5 (76.32)	-20.7 (32.37)	-15.5 (65.89)	-25.0 (34.72)
Median	-10.4	-24.5	-23.4	-30.7
LSM[3], (95%CI)	-4.26% (-13.07, 5.44)	-25.94% (-32.84,-18.33)	-25.46% (-32.44, -17.75)	-30.86% (-37.32,-23.74)
LSM, difference from Placebo (95% CI)		-21.68% (-40.70, -2.89)	-21.19% (-40.32, -2.29)	-26.60% (-45.12,-8.38)
P-value[4]		0.005[r]	0.007[r]	<0.001[r]

[1] Baseline = Average of Weeks -2, -1 and 0.
[2] % Change from Baseline to End of Treatment (Average of Weeks 10 and 12).
[3] LSM and LSM differences from the ANCOVA model using natural log transformed data.
[4] P-value from treatment effect in ANCOVA model that included terms for treatment, baseline value as a covariate, and a stratification factor for users and non-users of permitted lipid-altering drugs. P-values are adjusted using Dunnett's procedure for multiple comparisons of each Epanova vs. olive oil.
[r] indicates data were ranked prior to performing ANCOVA.

It is notable that the 2 and 3 gram doses of Epanova were associated with essentially the same magnitude of reduction in serum TG levels.

Secondary Efficacy Outcomes: The changes in the secondary efficacy variables, non-HDL-C and HDL-C, are shown in the following tables excerpted from Ms. Liu's statistical review.

Baseline and Percent Changes from Baseline to Endpoint in Non-HDL-C

Non-HDL Cholesterol	Olive Oil (N=99)	Epanova 2 g (N=100)	Epanova 3 g (N=101)	Epanova 4 g (N=99)
MITT Population				
Baseline (mg/dL) [1]				
N	98	99	97	99
Mean (SD)	220.2 (54.37)	221.0 (62.30)	228.3 (74.10)	235.3 (72.77)
Median	214.5	205.3	215.3	225.0
Min, Max	109.3, 379.7	106.0, 517.0	115.3, 609.3	106.7, 536.0
% Change from Baseline [2]				
N	98	95	94	95
Mean (SD)	7.5 (37.43)	-5.2 (19.62)	-3.9 (28.10)	-7.9 (19.63)
Median	-0.9	-7.7	-3.6	-7.7
Min, Max	-49.3, 201.0	-53.3, 78.6	-70.4, 206.2	-55.4, 55.6
LSM [3]	2.53	-7.61	-6.89	-9.63
95% CI	(-2.31, 7.61)	(-12.02, -2.97)	(-11.35, -2.21)	(-13.95, -5.09)
LSM Difference from Olive Oil		-10.14	-9.42	-12.16
95% CI Bonferroni-corrected		(-21.01, 0.71)	(-20.34, 1.48)	(-22.92, -1.43)
P-value [4]		0.017 [r]	0.019 [r]	0.001 [r]

[1] Baseline = Average of Weeks -2, -1 and 0.
[2] % Change from Baseline to End of Treatment (Average of Weeks 10 and 12).
[3] LSM and LSM differences from the ANCOVA model using natural log transformed data.
[4] P-value from treatment effect in ANCOVA model that included terms for treatment, baseline value as a covariate, and a stratification factor for users and non-users of permitted lipid-altering drugs. P-values are adjusted using Hommel's procedure for multiple comparisons of each Epanova vs. olive oil.
[r] indicates data were ranked prior to performing ANCOVA.

Baseline and Percent Changes from Baseline to Endpoint in HDL-C

HDL Cholesterol	Olive Oil (N=99)	Epanova 2 g (N=100)	Epanova 3 g (N=101)	Epanova 4 g (N=99)
MITT Population				
Baseline (mg/dL) [1]				
N	98	99	97	99
Mean (SD)	29.2 (7.93)	28.0 (6.87)	29.0 (7.93)	29.9 (9.22)
Median	28.7	27.3	28.0	28.7
Min, Max	14.0, 60.0	13.3, 47.3	15.3, 58.7	12.7, 69.3
% Change from Baseline [2]				
N	98	95	94	95
Mean (SD)	5.1 (29.94)	9.8 (22.22)	6.0 (19.69)	7.3 (17.88)
Median	2.2	7.0	6.9	5.0
Min, Max	-48.3, 226.2	-31.8, 102.5	-50.0, 66.7	-36.4, 61.7
LSM [3]	1.92	7.35	3.78	5.77
95% CI	(-1.98, 5.98)	(3.18, 11.68)	(-0.27, 7.99)	(1.65, 10.06)
LSM Difference from Olive Oil		5.42	1.86	3.85
95% CI Bonferroni-corrected		(-4.00, 14.86)	(-7.42, 11.14)	(-5.51, 13.23)
P-value [4]		0.076 [r]	0.091 [r]	0.091 [r]

[1] Baseline = Average of Weeks -2, -1 and 0.
[2] % Change from Baseline to End of Treatment (Average of Weeks 10 and 12).
[3] LSM and LSM differences from the ANCOVA model using natural log transformed data.
[4] P-value from treatment effect in ANCOVA model that included terms for treatment, baseline value as a covariate, and a stratification factor for users and non-users of permitted lipid-altering drugs. P-values are adjusted using Hommel's procedure for multiple comparisons of each Epanova vs. olive oil.
[r] indicates data were ranked prior to performing ANCOVA.

All three doses of Epanova were associated with statistically significant reductions in non-HDL-C versus placebo; however, the magnitudes of the reductions were similar among the Epanova doses. While the three Epanova doses were associated with numerically larger increases in HDL-C versus placebo, the differences were not statistically significant and the increase in the Epanova 3 gram group was the smaller than the increases observed in the Epanova 2 gram and 4 gram groups.

Levels of LDL-C are known to increase in some subjects taking omega-3 fatty acid mixtures that contain DHA. There were modest increases in LDL-C levels in the three Epanova groups

compared with placebo. The clinical significance of Epanova-associated increases in levels of LDL-C, particularly when accompanied by reductions in levels of non-HDL-C, is unknown.

See Dr. Chowdhury's review for the results of the tertiary efficacy endpoints.

8. Safety

The safety data for this application were reviewed by Drs. Cizza and Smith.

Exposure: In addition to the safety data from EVOLVE, the assessment of Epanova's safety is based on data from ESPRIT, a 6-week, placebo-controlled clinical trial of Epanova 2 grams/day and Epanova 4 grams/day in 642 statin-treated subjects with TG levels of 200 mg/dl to 500 mg/dl. Ancillary safety data from two long-term, placebo-controlled clinical trials of Epanova in patients with Crohn's disease were provided by the sponsor and reviewed by Drs. Cizza and Smith. I will focus on the data from EVOLVE and ESPRIT.

In the two trials of subjects with hypertriglyceridemia, a total of 314 were exposed to placebo, 315 to Epanova 2 grams/day, 101 to Epanova 3 grams/day, and 315 to Epanova 4 grams/day.

Deaths: There was one reported death, due to pulmonary embolus, in an Epanova-treated subject from the hypertriglyceridemia pool of subjects.

Serious Adverse Events: The incidence of nonfatal serious adverse events was 1.1% in the Epanova-treated subjects compared with 1.6% in the placebo-treated subjects.

Adverse Events Leading to Discontinuation: The incidence of adverse events leading to discontinuation was 3.7% in the Epanova-treated subjects compared with 0.6% in the placebo-treated subjects. Gastrointestinal events such as abdominal pain, nausea, vomiting and diarrhea accounted for a sizable proportion of the discontinuations in the Epanova-treated subjects.

Common Adverse Events: As shown in the table below taken from Dr. Smith's review, the most commonly-reported adverse events - incidence $\geq$ 3% and numerically greater than placebo - were gastrointestinal-related, with diarrhea reported by 15% of subjects randomized to the Epanova 4 grams/day group.

Commonly-Reported Adverse Events

Adverse Event	Placebo (n=314)	Epanova 2g (n=315)	Epanova 3g (n=101)	Epanova 4g (n=315)
Diarrhea	7 (2%)	23 (7%)	6 (6%)	46 (15%)
Nausea	4 (1%)	12 (4%)	9 (9%)	18 (6%)
Abdominal Pain or Discomfort*	7 (2%)	11 (3%)	2 (2%)	15 (5%)
Eructation	1 (<1%)	9 (3%)	4 (4%)	10 (3%)
Vomiting	1 (<1%)	6 (2%)	4 (4%)	4 (1%)

Adverse Events of Special Interest: In analyses conducted by the sponsor and Dr. Smith, there was no evidence that Epanova significantly increased the risk for bleeding or dysglycemia. As noted with other approved omega-3 fatty acid mixtures, more Epanova-treated subjects versus

placebo-treated subjects had modest increases in ALT and AST. This effect on hepatic transaminase levels does not appear to be associated with an increased risk for clinically-significant liver injury.

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

Advisory Committee Meeting

Because there were no significant issues related to the efficacy or safety of Epanova when used to treat subjects with severe hypertriglyceridemia, the Division did not believe that an advisory committee meeting was necessary.

Proposed Trade Name

The Division of Medication Error Prevention and Analysis (DMEPA) and the Office of Prescription Drug Promotion (OPDP) assessed the proposed trade name, Epanova, and found it acceptable. I agree with this assessment.

Inspections

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

Financial Disclosure

Dr. Chowdhury's review of the financial disclosure information revealed no cause for concern.

11. Labeling

Following several teleconferences, the Division and the sponsor came to agreement on the labeling for Epanova. Notable agreements, as excerpted from Dr. Smith's review, include:

- Limitations of use will not specify the indicated population. They will read, "The effect of EPANOVA on the risk for pancreatitis has not been determined. The effect of EPANOVA on cardiovascular mortality and morbidity has not been determined." This is consistent with the labeling recently approved for Omtryg and reflects the fact that the effect of the drug on these clinical outcomes is unknown for any population.
- 'Dosage and Administration will read, "The dosage of EPANOVA is 2 grams (2 capsules) or 4 grams (4 capsules) once daily. The dosage should be individualized

according to the subject's response and tolerability. In clinical trials, EPANOVA was administered without regard to meals."

- Because the 3-gram dose is not being recommended in Dosage and Administration (no clear incremental benefit with regard to efficacy but not as well tolerated), results from the Epanova 3 g/day dosage group will not be included in Adverse Reactions or the Clinical Studies section. The exclusion of these data do not meaningfully affect the information provided for prescribers in labeling.
- Within-group median % change from baseline for relevant lipid/lipoprotein parameters will be displayed in Section 14 along with the estimated between-group treatment difference to placebo (olive oil) using Hodges-Lehmann estimates. Notation for statistical significance will identify P values generated by the applicant's primary analysis (ANCOVA model using rank-transformed data).

12. Regulatory Recommendation

The sponsor has provided adequate evidence to conclude that Epanova effectively and safely lowers serum TG levels in subjects with severe hypertriglyceridemia. Thus, I agree with the review team that this NDA should be approved. There are no post-marketing requirements or commitments.

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/s/

ERIC C COLMAN
05/05/2014