CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202057Orig1s000

OTHER REVIEW(S)

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 202057 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Vascepa Established/Proper Name: icosapent ethyl Dosage Form: Capsules Strengths: 1 gram		
Applicant: Amarin Pharmaceuticals Ireland Limited Agent for Applicant (if applicable): Amarin Pharma Inc.		
Date of Application: September 25, 2011 Date of Receipt: September 26, 2011 Date clock started after UN:		
PDUFA Goal Date: 7/26/2012	Action Goal Date (if different):	
Filing Date: 11/25/2011	Date of Filing Meeting: 11/9/2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) ***NOT DETERMINED BY AP DATE		
Proposed indication: VASCEPA (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) (b) (4) [redacted] in adult patients with very high (≥ 500 mg/dL) triglycerides.		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) X 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	X Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 102457	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?				

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: Paid ☐ Exempt (orphan, government) X Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: X Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**		X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***		X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:			X	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		X		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 5 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) X All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**X**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**X**	
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	X			

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			**X**	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		Firm has requested a waiver for 0-10 years; a deferral for ages 11-18. They

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

				have not included pediatrics who are 10 years of age
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the DCRMSRMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	X Package Insert (PI) X Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels X Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X			
Is the PI submitted in PLR format?[4]	X			

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

APPEARS THIS WAY ON ORIGINAL

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?		X		Will be consulted once the application is filed.
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)		X		Will be consulted once the application is filed.
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?		X		Will be consulted once the application is filed.
OTC Labeling	**X Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		X		
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		X		There was a PIND meeting held on 7/14/2008 and proposed P3 studies

				were reviewed under SPA.

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 3/16/2011 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** 5/1/2009 ***If yes, distribute letter and/or relevant minutes before filing meeting***	X			

ATTACHMENT

MEMO OF FILING MEETING

DATE: 11/9/2011

BLA/NDA/Supp #: 202057

PROPRIETARY NAME: VASCEPA

ESTABLISHED/PROPER NAME: icosapent ethyl

DOSAGE FORM/STRENGTH: 1 gram Capsules

APPLICANT: Amarin Pharmaceuticals Ireland Limited

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):
VASCEPA (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) (b) (4) levels in adult patients with very high (≥ 500 mg/dL) triglycerides.

(b) (4)

A Pre-IND meeting was held on July 14, 2008. The firm initially proposed (b) (4) as monotherapy for the treatment of adult with severe hypertriglyceridemia, (b) (4)

(b) (4)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kati Johnson	Y
	CPMS/TL:		
Cross-Discipline Team Leader (CDTL)			
Clinical	Reviewer:	Iffat Chowdhury	Y
	TL:	Eric Colman	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		

OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Zhihong Li	Y
	TL:	Jaya Vaidyanathan	Y
Biostatistics	Reviewer:	Japo Choudhury	N
	TL:	Todd Sahlroot	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Stephanie Leuenroth-Quinn	Y
	TL:	Karen Davis Bruno	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Martin Haber	Y
	TL:	Su Tran	Y
Quality Microbiology *(for sterile products)*	Reviewer:	John Metcalfe	Y
	TL:		
CMC Labeling Review	Reviewer:	Martin Haber	Y
	TL:	Su Tran	Y
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		

OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES X NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	X YES ☐ NO
• Electronic Submission comments **List comments**:	X Not Applicable
CLINICAL **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE X Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	X YES ☐ NO
• Advisory Committee Meeting needed?	☐ YES

Comments: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	Date if known: X NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	X Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES X NO
BIOSTATISTICS **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL	☐ Not Applicable

(PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ FILE X REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE X Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable X YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**: Micro was consulted to review the requested microbial limits tests for the drug product.	☐ Not Applicable ☐ YES X NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable X YES ☐ NO X YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	 ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Eric Colman, MD

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments: NME/NCE status has not been resolved as of the APPROVAL date.

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☐	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. X Review issues have been identified for the 74-day letter. List (optional): Review Classification: X Standard Review ☐ Priority Review

ACTIONS ITEMS

X	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

Regulatory Project Manager Date

Chief, Project Management Staff Date

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

KATI JOHNSON
07/26/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Memorandum

Date: July 23, 2012
From: Karen Davis-Bruno PhD; Pharmacology Supervisor; DMEP
Subject: Supervisory Pharmacology/Toxicology Memo
To: NDA 202-057 Vascepa (icosapent ethyl capsules)/Amarin for hypertriglyceridemia

Reference is made to the Pharmacology/Toxicology Review of NDA 202-057 of June 2012 and the ECAC Meeting Minutes of April 2012 in preparation of this memo

Vascepa (ethyl-EPA) is the ethyl ester of eicosapentaenoic acid, a long chain polyunsaturated omega-3 fatty acid (C20:5). Vascepa was submitted as a 505(b)2 application based on referenced published literature on the reprotoxicity data of Epadel; a Japanese approved ethyl EPA product. A 28-day rat comparative bridging toxicity study with Vascepa compared to an Epadel arm was provided. The results of this study establish comparability between the products which allows for reliance on the published literature with Epadel. The following labeling is recommended based on the results of these studies.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. It is unknown whether VASCEPA can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. VASCEPA should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus.

In pregnant rats given oral gavage doses of 0.3, 1 and 2 g/kg/day icosapent ethyl from gestation through organogenesis all drug treated groups had visceral or skeletal abnormalities including: 13th reduced ribs, additional liver lobes, testes medially displaced and/or not descended at human systemic exposures following a maximum oral dose of 4 g/day based on body surface comparisons. Variations including incomplete or abnormal ossification of various skeletal bones were observed in the 2g/kg/day group at 5 times human systemic exposure following an oral dose of 4 g/day based on body surface area comparison.

In a multigenerational developmental study in pregnant rats given oral gavage doses of 0.3, 1, 3 g/kg/day ethyl-EPA from gestation day 7-17, an increased incidence of absent optic nerves and unilateral testes atrophy were observed at ≥0.3 g/kg/day at human systemic exposure following an oral dose of 4 g/d based on body surface area comparisons across species. Additional variations consisting of early incisor eruption and increased percent cervical ribs were observed at the same exposures. Pups from high dose treated dams exhibited decreased copulation rates, delayed estrus, decreased implantations and decreased surviving fetuses (F2) suggesting multigenerational effects of ethyl-EPA at 7 times human systemic exposure following 4 g/day dose based on body surface area comparisons across species.

In pregnant rabbits given oral gavage doses of 0.1, 0.3, and 1 g/kg/day from gestation through organogenesis there were increased dead fetuses at 1 g/kg/day secondary to maternal toxicity (significantly decreased food consumption and body weight loss).

In pregnant rats given ethyl-EPA from gestation day 17 through lactation day 20 at 0.3, 1, 3 g/kg/day complete litter loss was observed in 2/23 litters at the low dose and 1/23 mid-dose dams by post-natal day 4 at human exposures based on a maximum dose of 4 g/day comparing body surface areas across species.

8.3 Nursing Mothers

Studies with omega-3-acid ethyl esters have demonstrated excretion in human milk. The effect of this excretion is unknown; caution should be exercised when VASCEPA is administered to a nursing mother. In lactating rates, given oral gavage ^{14}C-ethyl EPA, drug levels were 6 to 14 times higher in milk than in plasma.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Carcinogenicity

In the 2-year rat (Wistar) carcinogenicity study there were no drug-related neoplasms in male rats. In female rats there was a statistically significant increase in the incidence of hemangiomas/hemangiosarcomas at the mesenteric lymph node (MLN) at clinically relevant exposures. However, when these vascular tumors were combined across all anatomical sites, statistical significance was not achieved. The increased tumor incidence at this site is considered attributable to the site of systemic absorption of EPA via the lymphatics of the GI tract. The MLN in the rat becomes a site of maximum EPA exposure. Interestingly, the male rat would be anticipated to have maximum EPA exposure at the MLN as well. However there are no drug-related neoplasms observed in the male rats. Exposure differences can not account for this gender difference in neoplastic incidence.

MLN Tumors	0		Icosapent-ethyl 91 mg/kg/d		Icosapent-ethyl 273 mg/kg/d		Icosapent-ethyl 911 mg/kg/d	
Exposure Margin	0		<1X		3X		7X	
	M	F	M	F	M	F	M	F
Hemangioma	1	0	0	0	0	3	5	4
Hemangiosarcoma	4	0	4	0	5	2	7	2
Combined	5	0	4	0	5*	5	12	6*

0=un-dosed control; MLN=mesenteric lymph node; 50 rats/sex/group; Exposure margin relative to 4 g maximum clinical dose $AUC_{0\text{-}24h}$=20,300 ng h/ml; *p<0.01

Published historical control data[1] reports the background rates of MLN hemangiomas combined with hemangiosarcomas of 0.5-7.5% in Wistar rats with a maximum incidence of 3.2% for males and 1.2% for females. Based on the 3-fold higher background rate in males it would be anticipated that the vascular tumor incidence would be higher in male than female rats, but this is not observed. Publications[2] indicate that the Wistar strain of rat is predisposed to the formation of hemangiomas at the MLN. Strain differences in vascular tumor incidence have been reported across rodents and various strains. Rodents are considered more susceptible to hemangiosarcomas than humans although the mechanism is unknown. One potential mechanism that has been proposed by Cohen et al[3] for hemangioma formation in rodents involves hemolysis, resulting in an increase in reactive oxygen species (ROS), recruitment of macrophages, increased cytokines and eventual increased endothelial cell proliferation. The relatively high, localized concentration of ethyl-EPA in the MLN may predispose this region to increased hemolysis. Histopathology findings of increased pigment i.e. heme, erythrophagocytosis,

[1] Reindel, JF et al Mesenteric Lymph Node Hemangiomas of Wistar Rats. Tox Path 1992, 20:268
[2] Cohen SM et al Hemangiosarcoma in Rodents: Mode-of-Action Evaluation and Human Relevance Tox Sci 2009, 111(1):4-8
[3] Ibid

thrombosis and inflammation were observed in the rat which might contribute to the hemangiomas(sarcoma) formation in the rat. There may be strain and species related variability in the release of ROS or in circulating concentrations of anti-oxidants thereby modulating the extent of hemolysis. This is consistent with elevated incidences of hemangiosarcomas observed in male mice treated with hemolytic agents such as 2-butoxyethanol, p-nitroaniline and p-chloroaniline. However this remains a theoretical explanation.

Another variable worth consideration is dietary intake of fat and oil. Normal rat chow has an optimized 5% dietary content of all fats. This is much lower than a healthy human diet of 20-35% total fat intake. Rat chow contains an omega-3 fatty acid content of <0.5% indicating that as a result of ethyl-EPA dosing omega-3 fatty acid exposure in rats was much higher than normal in these series of toxicology studies. This excess exposure to omega-3 fatty acids in this rat study may have resulted in disturbances in fatty acid metabolism. Humans will likely be administered the maximum 4 g/day dose BID, unlike the rat that received a single daily dose. This suggests that humans will need to process a lower concentration of ethyl-EPA relative to the rat at any given dose. Humans are also accustomed to processing diets much higher in fat content relative to the rat.

In the 6-month transgenic mouse study, there were no drug related neoplasms in females. There were skin/subcutis papillomas of the tail in males. The incidence was 0-0-0-1-5 for doses of 0, 0.5, 1, 2, 4.6 g/kg/d respectively. There is an increased incidence of rectal oil leakage with increasing ethyl-EPA dosing resulting in deposition on the skin or fur. This suggests the possibility that this could be a result of a skin interaction with metabolized or oxidized EPA. Histopathology findings at the proximal tail included acanthosis/hyperkeratosis, erosion/ulceration and inflammation consistent with a localized skin irritation effect of the oil. It isn't clear why this does not occur in female mice as well. If these lesions are considered localized oil deposition on the skin near the tail leading to inflammation and proliferative effects, then this is not likely to be clinically relevant in humans.

Histopathology findings in the transgenic mouse included an increase in thrombosis and inflammation in the mesenteric and perimesenteric vein as well as increased pigment in the MLN in both genders of transgenic mice at ≥2 g/kg/d. However, no vascular tumors were observed in contradiction with the 2-year rat bioassay results described above. ECAC reviewed the results of the 2-year rat and 6-month transgenic mouse bioassays. They noted that the increased incidence of mesenteric lymph node thrombosis of the perimesenteric vein as well as ileum mesenteric vein thrombosis and inflammation, both seen in the TgRasH2 mice and the high dose drug exposure at the mesenteric lymph nodes in the rats suggest that the mesenteric lymph node hemangiomas/ hemangiosarcomas in rats are drug-related.

Based on this information the following labeling recommendations are made.

NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In 2-year rat carcinogenicity study with oral gavage doses of 0.09, 0.27, and 0.91 g/kg/day icosapent ethyl respectively males did not exhibit drug-related neoplasms. Hemangiomas and

hemangiosarcomas of the mesenteric lymph node, the site of drug absorption were observed in females at clinically relevant exposures based on body surface area comparisons across species relative to the maximum clinical dose of 4 g/day. Overall incidence of hemangiomas and hemangiosarcomas in all vascular tissues did not increase with treatment.

In a 6-month carcinogenicity study in Tg rasH2 transgenic mice with oral gavage doses of 0.5, 1, 2, and 4.6 g/kg/day icosapent ethyl, drug-related incidences of benign squamous cell papilloma in the skin and subcutis of the tail was observed in high dose male mice. The papillomas were considered to develop secondary to chronic irritation of the proximal tail associated with fecal excretion of oil and therefore not clinically relevant. Drug-related neoplasms were not observed in female mice.

Icosapent ethyl was not mutagenic with or without metabolic activation in the bacterial mutagenesis (Ames) assay or in the *in vivo* mouse micronucleus assay. A chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells was positive for clastogenicity with and without metabolic activation.

In an oral gavage rat fertility study, ethyl-EPA, administered at doses of 0.3, 1, and 3 g/kg/day to male rats for 9 weeks before mating and to female rats for 14 days before mating through day 7 of gestation, increased anogenital distance in female pups and increased cervical ribs were observed at 3 g/kg/day (7 times human systemic exposure with 4 g/day clinical dose based on a body surface area comparison).

There is some prior experience with pharmaceuticals and increased incidences of hemangiosarcomas. Pharmaceuticals that induce hemangiosarcomas appear to have initiating events leading to local tissue hypoxia and macrophage activation. These changes can increase angiogenic factors which can result in dysregulated angiogenesis. Angiogenesis is considered vital for metastasis of tumors in general and in particular for these endothelial derived vascular tumors. Pregabalin can induce macrophage activation and increased angiogenic growth factors in the bone marrow, spleen and liver. These are tissues that are associated with hemangiosarcomas in the mouse[4]. The majority of published literature associated with this proposed mechanism of action is associated with hemangiosarcomas in the mouse. Examples of other pharmaceuticals associated with hemangiosarcomas some of which are marketed include the following:

Pharmaceutical	**Hemangiosarcomas Observed**
PPARγ	Mice ••
PPARαγ	Mice ••
Olanzapine	Mice •
Pregabalin	Mice B6C3F1 and CD-1 strains ••
Entecavir	Mice •
Cidofovir	Hemangioma: rats, mice
Vildagliptin	Mice • Rat•
Dronedarone	Mice•, hemangiomas •• mice
EMLA Cream	Mice ••
Etretinate	Mice •
Pentosan polysulfate sodium	Mice ••

Summary

In a 2-year carcinogenicity study in Wistar rats, females in the high does group (exposure margin 7X the 4 g/day clinical dose) had significantly increased incidence of combined hemangiomas/hemangiosarcomas at the mesenteric lymph node. The incidence of these vascular tumors at all anatomical sites combined was not statistically significant.

[4] Pegg D et al, Hemangiosarcoma in Mice Administered Pregabalin: Analysis of Genotoxicity, Tumor Incidence, and Tumor Genetics Toxicol Sci 2012, 128(1):9-21

Additionally, male rats did not exhibit an imbalance in vascular tumors at any anatomical site. These findings together with an absence of any imbalance in hemangiomas or hemangiosarcomas or combined incidence in any mice (male or female) in the 6-month transgenic mouse model suggests that the finding of increased incidence of hemangiomas and hemangiosarcomas in female rats is of limited clinical significance based on the limited strength of the observed vascular tumor signal.

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/s/

KAREN L DAVIS BRUNO
07/25/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	June 11, 2012
To:	Mary Parks, M.D., Director **Division of Metabolic and Endocrinology Products (DMEP)**
Through:	LaShawn Griffiths, RN, MSHS-PH, BSN Associate Director, Patient Labeling Team **Division of Medical Policy Programs (DMPP)**
	Melissa Hulett, RN, BSN, MSBA Team Leader, Patient Labeling Team **Division of Medical Policy Programs (DMPP)**
From:	Twanda Scales, RN, MSN/Ed. Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling (Patient Package Insert) (PPI)
Drug Name:	VASCEPA (icosapent ethyl)
Dosage Form and Route:	Capsules
Application Type/Number:	NDA 202057
Applicant:	Amarin Pharma Inc.

1 INTRODUCTION

On September 25, 2011 Amarin Pharma Inc. submitted a new drug application (NDA) for VASCEPA (icosapent ethyl), 1g, for the treatment of patients with very high triglycerides (≥500mg/dL).

This review is written in response to a request by the Division of Metabolic and Endocrinology Products (DMEP) for the Division of Medical Policy Programs **(**DMPP) to provide a review the Applicant's proposed Patient Package Insert (PPI) for VASCEPA (icosapent ethyl), 1g, capsules.

2 MATERIAL REVIEWED

- Draft VASCEPA (icosapent ethyl), PPI received on September 25, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on June 7, 2012
- Draft VASCEPA (icosapent ethyl), Prescribing Information (PI) received on September 25, 2011, revised by the Review Division throughout the review cycle, and received by DMPP June 7, 2012

(b) (4)

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible

- ensured that the PPI is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated version of the PPI is appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

8 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) Immediately Following this Page

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/s/

TWANDA D SCALES
06/12/2012

MELISSA I HULETT
06/12/2012

LASHAWN M GRIFFITHS
06/12/2012

505(b)(2) ASSESSMENT

Application Information		
NDA # 202057	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: VASCEPA Established/Proper Name: icosapent ethyl Dosage Form: Capsules Strengths: 1 gram		
Applicant: Amarin Pharmaceuticals Ireland Limited		
Date of Receipt: 9/26/2011		
PDUFA Goal Date: 7/26/2012	Action Goal Date (if different):	
Proposed Indication(s): Adjunct to diet to reduce triglyceride (b) (4) levels in patients with very high (≥500 mg/dL)) triglycerides.		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO X

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Published literature	8.1-Pregnancy 8.3-Nursing Mothers 13.1-Carcinogenesis, Mutagenesis, Impairment of Fertility

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Amarin conducted a 4-week rat comparative toxicity and toxicokinetics study with Vascepa and Epadel. Epadel was cited in the literature and Amarin is relying on that published literature for the above cited sections of the package insert.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES X NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

☐ NO X**

YES

*If "**NO**", proceed to question #5.*
*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

***The sponsor refers to a specific product "Epadel" which is approved in Japan but not the US.*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☐ NO X

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☐ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☐

*If "**YES**", please list which drug(s) and answer question d) i. below.*

*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO X

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO X

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☐ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all*

of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

X No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the

NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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/s/

KATI JOHNSON
06/05/2012

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: June 4, 2012

TO: Kati Johnson, Regulatory Project Manager
Iffat N. Chowdhury, M.D., Medical Officer
Eric Coleman, M.D., Deputy Director
Division of Metabolism and Endocrinology Products

FROM: Jean Mulinde, M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
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SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 202057

APPLICANT: Amarin Pharma, Inc.
DRUG: VASCEPA™ (icosapent ethyl) Capsules, 1 g
NME: No

REVIEW PRIORITY: Standard Review

INDICATION: As an adjunct to diet to reduce triglyceride (b) (4) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia.

CONSULTATION REQUEST DATE: November 29, 2011
INSPECTION SUMMARY GOAL DATE: June 1, 2012
DIVISION ACTION GOAL DATE: July 26, 2012
PDUFA DATE: July 26, 2012

I. BACKGROUND:

VASCEPA™ (AMR101, icosapent ethyl) is a highly purified formulation of ethyl eicosapentaenoic acid (an ethyl ester of an essential fatty acid), which the Applicant has developed for the treatment of patients with very high triglycerides (≥500 mg/dL). The Applicant hypothesizes that icosapent ethyl reduces hepatic very low-density lipoprotein (VLDL) triglyceride synthesis and/or secretion and enhances triglyceride clearance from circulating VLDL particles.

Prior to the hypertriglyceridemia program, the safety and efficacy of icosapent ethyl was studied in central nervous system (CNS) disorders, including Huntington's disease (3 studies), depression (3 studies), schizophrenia (1 study), and age-associated memory impairment (1 study). Icosapent ethyl doses in these studies ranged from 0.5 g/day to 4 g/day, with the majority of patient receiving 2 g/day. Based on data from these studies, as well as data from studies submitted in support of patients with elevated triglycerides (TG), the most frequently occurring adverse events observed (reported in ≥2% of subjects) included diarrhea, nausea, nasopharyngitis, headache, depression, insomnia, fall, and arthralgia. In the two pivotal Phase 3 studies in subjects with hypertriglyceridemia the most common adverse events (reported in ≥3% of subjects) included urinary tract infection, diarrhea, and nausea. Additional serious adverse events of concern (derived from safety data for all studies) included suicide (one subject in CNS study), non-cardiac chest pain, coronary artery disease, aggression, depression, psychotic disorder, overdose, irritability, and subarachnoid hemorrhage.

Based primarily on the outcomes of one pivotal clinical study [Protocol AMR-01-01-0016 (MARINE)], Amarin Pharma, Inc. is seeking approval to also market icosapent ethyl as an adjunctive treatment to diet to reduce triglyceride (b) (4) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia.

The protocol inspected was:

Protocol AMR-01-01-0016, entitled "A Phase 3, Multi-Center, Placebo-Controlled, Randomized, Double-Blind, 12-Week Study with an Open-Label Extension to Evaluate the Efficacy and Safety of AMR101 in Patients with Fasting Triglyceride Levels ≥500 mg/dL and ≤2000 mg/dL" (The MARINE Study)

Study AMR-01-01-0016 was a Phase 3 randomized, double-blind, multicenter, repeat-dose study of icosapent ethyl capsules 2 g daily or 4 g daily compared to placebo as an adjunct to diet to reduce TG levels in subjects with very high TG levels (≥500 mg/dL). The total duration of the study was 58- to 60-weeks, including three treatment periods (6-8 week screening

period, 12 week double-blind treatment period, and 40 week open-label extension period). Once determined to be eligible, subjects were randomized (start of double-blind treatment period) in a 1:1:1 ratio: icosapent ethyl (IPE) 2 gm daily, IPE 4 gm daily, or placebo. During the extension period, all subjects were treated with 4 gm IPE daily. (NOTE: Only data for subjects through the end of the double-blind treatment period was included in the current application.) The study was conducted at 54 clinical investigator sites in the United States, The Netherlands, Finland, Germany, Italy, Ukraine, Russia, India, and South Africa. A total of 229 subjects were randomized into the trial. Subjects were enrolled in the study from December 14, 2009 through October 19, 2010 (Date of final study report: June 15, 2011). The sponsor contracted the following study related responsibilities (b) (4) : project management, clinical monitoring, data management, statistical analysis, and study report preparation. (b) (4) was responsible for clinical laboratory analyses. (b) (4) performed the fatty acid profile assays.

The primary efficacy endpoint for the double-blind treatment period was the percent change in TG from baseline (Week 0, Visit 4) to Week 12 (Visit 7). Safety measurements included assessment of adverse events, clinical laboratory measurements (chemistry, hematology, and urinalysis), 12-lead electrocardiograms (ECGs), blood pressure, and physical examinations.

The clinical investigator sites selected for inspection for Study AMR-01-01-0016 were chosen based on their prior inspectional history, as well as their enrollment, protocol violation, and/or screen to randomization ratio profiles. An inspection of (b) (4) the contract research organization (CRO), to whom the sponsor (Amarin Pharma, Inc.) contracted most study related regulatory requirements, was also inspected to evaluate the adequacy of their conduct of Study AMR-01-01-0016.

II. RESULTS (By Site)

Name of Inspected Entity	Protocol # Site# Subject#	Inspection Date	Final Classification
Harold Bays, M.D. Louisville Metabolic and Atherosclerosis Research Center 3288 Illinois Ave. Louisville, KY 40213	Protocol: AMR-01-01-0016 Site #002 Enrolled: 21 Randomized: 9	December 12-20, 2011	NAI
Alexey Blokhin, M.D. Federal State-Institution "Out-patient Clinic # 3" of Russian Federation President's Management Department 31 Grokholsky lane, 129090 Moscow, Russia	Protocol: AMR-01-01-0016 Site #577 Enrolled: 58 Randomized: 41	May 2012	Pending (Preliminary Classification NAI)

Name of Inspected Entity	Protocol # Site# Subject#	Inspection Date	Final Classification
Andrey Sussekov, M.D. Federal State Institution "Russian Cardiological Research and Production Complex of RoseMedTechnologies" Age-related Problems Department 15A, 3rd Cherepkovskaya str., 121552 Moscow, Russia	Protocol: AMR-01-01-0016 Site #582 Enrolled: 33 Randomized: 21	May 2012	Pending (Preliminary Classification NAI)
(b) (4)	Protocol AMR-01-01-0016	February 1-3, 2012	NAI
	Protocol AMR-01-01-0016	February 7, 2012	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI* = Significant deviations from regulations.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and/or complete review of EIR is pending.

1. **Harold Bays, MD**
   Louisville Metabolic and Atherosclerosis Research Center
   3288 Illinois Ave.
   Louisville, KY 40213
   Site #002

   a) What was inspected:
   For Study AMR-01-01-0016, at this site, 21 subjects were screened, 9 subjects were enrolled, and 8 subjects completed the study. All (screen failures and enrolled) subjects' records were reviewed during the inspection. The record audit included comparison of source documentation and CRFs to NDA line listings with particular attention paid to informed consent documentation, inclusion/exclusion criteria compliance, primary efficacy endpoint data, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated screening and randomization process, clinical laboratory report documentation, protocol deviation reports, concomitant medication usage, test article accountability, financial disclosure reporting, IRB communications and approvals, subject recruitment materials, monitoring visit logs, and sponsor and monitor correspondence to the site. There were no limitations to the inspection.

b) General observations/commentary:
Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 202057 were compared and verified. The investigator's execution of the protocol was found to be adequate. A Form FDA 483, Inspectional Observations was not issued to the clinical investigator.

c) Assessment of data integrity:
The data provided by Dr. Bay's site for Study AMR-01-01-0016 that were submitted to the Agency in support of NDA 202057 appear to be reliable and acceptable for use in support to the pending application.

2. Alexey Blokhin, M.D.
Federal State-Institution
"Out-patient Clinic # 3" of Russian Federation President's Management Department
31 Grokholsky lane, 129090
Moscow, Russia
Site #577

a) What was inspected:
For Study AMR-01-01-0016, at this site, 58 subjects were screened (enrolled), 41 subjects were randomized to study therapy, and 38 subjects completed the study. The record audit included comparison of source documentation and CRFs to NDA line listings with particular attention paid to informed consent documentation, inclusion/exclusion criteria compliance, primary efficacy endpoint data, identification of adverse events, and reporting of AEs in accordance with the protocol. There were no limitations to the inspection.

b) General observations/commentary:
Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 202057 were compared and verified. The investigator's execution of the protocol was found to be adequate. A Form FDA 483, Inspectional Observations was not issued to the clinical investigator.

c) Assessment of data integrity:
The data provided by Dr. Blokhin's site for Study AMR-01-01-0016 that were submitted to the Agency in support of NDA 202057 appear to be reliable and acceptable for use in support to the pending application.

Note: The EIR and associated exhibits for this inspection were not available at the time this CIS was written. The general observations described above are based on review of preliminary information provided by the ORA investigator. An inspection summary addendum will be generated if conclusions change upon final review of the final EIR.

3. **Andrey Sussekov, MD**
Federal State Institution
"Russian Cardiological Research and Production Complex of RoseMedTechnologies"
Age-related Problems Department
15A, 3rd Cherepkovskaya str., 121552
Moscow, Russia
Site #582

   a) **What was inspected:**
   For Study AMR-01-01-0016, at this site, 33 subjects were screened (enrolled), 21 subjects were randomized to study therapy, and 20 subjects completed the study. The record audit included comparison of source documentation and CRFs to NDA line listings with particular attention paid to informed consent documentation, inclusion/exclusion criteria compliance, primary efficacy endpoint data, identification of adverse events, and reporting of AEs in accordance with the protocol. There were no limitations to the inspection.

   b) **General observations/commentary:**
   Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 202057 were compared and verified. The investigator's execution of the protocol was found to be adequate. A Form FDA 483, Inspectional Observations was not issued to the clinical investigator.

   c) **Assessment of data integrity:**
   The data provided by Dr. Sussekov's site for Study AMR-01-01-0016 that were submitted to the Agency in support of NDA 202057 appear to be reliable and acceptable for use in support to the pending application.

Note: The EIR and associated exhibits for this inspection were not available at the time this CIS was written. The general observations described above are based on review of preliminary information provided by the ORA investigator. An inspection summary addendum will be generated if conclusions change upon final review of the final EIR.

4. (b) (4)

   a) **What was inspected:**
   This Contract Research Organization (CRO) inspection was performed to evaluate (b) (4) role in the conduct of Study AMR-01-01-0016. The study sponsor, Amarin Pharma Inc., delegated, by contract, the following study related responsibilities to (b) (4): clinical study site management, clinical

monitoring, pharmacovigilence, ethics committee submissions, regulatory agency submissions, preparation of the study protocol, creation of electronic case report forms, data management, statistical analysis, and medical writing of the study report. During the inspection the FDA investigator focused on the CRO's oversight of the following four clinical investigators: Christine Ballantyne (Site #001, Texas), Harold Bays (Site #002, Kentucky), Alexey Blohkin (Site #577, Russia), and Andrey Sussekov (Site #582, Russia). For these four sites, an in depth review of monitoring reports and monitor communications with the sites was conducted. In addition, the FDA investigator reviewed the CRO's role and responsibilities related to evaluation and selection of clinical investigator sites for participation in the study, GCP and study specific training provided to clinical sites, the study monitoring plan and its implementation, oversight of IRB/IEC submissions, the safety monitoring plan and its implementation, and data collection and handling procedures.

b) General observations/commentary:
CRO records and procedures were clear, and generally well organized. In relation to Study AMR-01-01-0016, the CRO's safety monitoring and procedures, as well as data collection and handling procedures, appeared to be satisfactory. In addition, based on the in depth review of monitoring reports and correspondence for the four noted sites, overall site monitoring appeared adequate. (b) (4) appeared to fulfill sponsor/monitor regulatory requirements that had been designated to them by Amarin Pharma Inc. for Study AMR-01-01-0016. A Form FDA 483 was not issued to the CRO.

c) Assessment of data integrity:
Study AMR-01-01-0016 appears to have been conducted adequately by (b) (4) and the data submitted by the Applicant for Study AMR-01-01-0016 may be used in support of the pending application.

5. (b) (4)

a) What was inspected:
Given the proximity of (b) (4) to its affiliate (b) (4) and because (b) (4) was contracted by Amarin Pharma Inc., to provide centralized clinical laboratory services for Study AMR-01-01-0016, a brief inspection of this facility was conducted in conjunction with the inspection of (b) (4) During the limited inspection of (b) (4) the FDA field investigator verified that the facility was capable of conducting the 13 study related laboratory tests that they were contracted to perform. It was verified that necessary equipment was present on site and that the laboratory was accredited by CLIA and The College of American Pathologists.

b) General observations/commentary:
While this was a limited inspection of (b) (4), no regulatory violations were observed and a Form FDA 483 was not issued to the site.

c) Assessment of data integrity:
The Study AMR-01-01-0016 data provided by (b) (4) that were submitted to the Agency in support of NDA 202057 appear to be reliable and acceptable for use in support to the pending application.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for clinical investigators Dr. Blokhin and Dr. Sussekov, as well as final review of inspectional findings for clinical investigator Dr. Bays, the CRO, (b) (4)., and (b) (4), the Study AMR-01-01-0016 data submitted by the Applicant appear reliable in support of NDA 202057.

The preliminary classifications for the inspections of Dr. Blokhin and Dr. Sussekov are No Action Indicated (NAI).

The final classifications for the inspections of Dr. Bays, (b) (4) are No Action Indicated (NAI).

Note: Observations noted above for the inspections of Dr. Blokhin and Dr. Sussekov are based on preliminary communications with the field investigator for each of the CI inspections; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs for these inspections.

{See appended electronic signature page}

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/s/

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06/04/2012

JANICE K POHLMAN
06/05/2012

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06/05/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label and Labeling Review

Date:	December 23, 2011
Reviewer(s):	Jamie Wilkins Parker, Pharm.D. Division of Medication Error Prevention and Analysis
Division Director	Carol A. Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength(s):	Vascepa (Icosapent Ethyl) Capsules, 1 gram
Application Type/Number:	NDA 202057
Applicant/sponsor:	Amrin Pharmaceuticals Ireland, Ltd.
OSE RCM #:	2011-3562

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis's evaluation of the proposed container labels and insert labeling for Vascepa (Icosapent Ethyl) Capsules for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

The Applicant submitted the proposed labels and labeling for Vascepa Capsules (NDA 202057) on September 26, 2011.

1.2 PRODUCT INFORMATION

Vascepa is an ethyl ester of the omega-3 fatty acid eicosapentaenoic acid (EPA) with a proposed indication of an adjunct to diet to reduce triglyceride (b) (4)) levels in patients with very high (≥ 500 mg/dL) triglycerides. The recommended dose of Vascepa is 4 grams per day (taken as two capsules twice daily) (b) (4) Vascepa will be supplied as (b) (4) 120 capsule trade containers. Vascepa capsules are amber-colored soft-gelatin capsules (b) (4).

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis[1] and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Insert Labeling submitted September 26, 2011
- Trade Container Labels submitted September 26, 2011
- Professional Sample Container Labels submitted September 26, 2011

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 DISCUSSION OF DEFICIENCIES IDENTIFIED

3.1 INSERT LABELING

- The insert labeling contains an error-prone abbreviation throughout the labeling.

3.2 CONTAINER LABELS AND CARTON LABELING

- Trade and Professional Sample Labels
    - The trade and professional sample container labels have improper prominence and location of the strength statement, dangerous abbreviations within the strength statement, improper prominence of the net quantity statement, and do not contain the Rx Only statement on the principal display panel.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling introduce vulnerability due to improper prominence and location of, as well as dangerous abbreviations within the strength statement, and improper prominence of the net quantity statement. We recommend the following:

A. Insert Labeling

1. The error-prone symbol '/' occurs in the insert labeling. This abbreviation appears on the ISMP List of Error Prone Abbreviations, Symbols, and Dose Designations[2]. It has been found to be mistaken as the number 1. Therefore, we request you replace the '/' symbol with the text "per" wherever it may occur.

B. Trade and Professional Sample Labels

1. Relocate, and revise the strength statement to immediately follow the established name as follows:

Vascepa
(Icosapent Ethyl) Capsules
1 gram

2. Additionally, increase the prominence of the strength statement. It currently lacks prominence as stated in 21 CFR 201.15(a)(6), which reads "A word, statement, or other information required by or under authority of the act to appear on the label may lack that prominence and conspicuousness required by section 502(c) of the act by reason, among other reasons, of smallness or style

[2] Institute for Safe Medication Practices, "List of Error-Prone Abbreviations, Symbols, and Dose Designations. www.ismp.org.

of type in which such word, statement, or information appears, insufficient background contrast, obscuring designs or vignettes, or crowding with other written, printed, or graphic matter."

3. Relocate and decrease the prominence of the net quantity statement, as it is currently of greater prominence than that of the strength and established name statements. It should appear away from the strength statement on the principal display panel of the label.

If you have further questions or need clarifications, please contact Margarita Tossa, project manager, at 301-796-3904.

APPENDICES

Appendix A: Trade Container Labels –

Appendix B: Professional Sample Container Labels (4 capsules) –

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/s/

JAMIE C WILKINS PARKER
12/23/2011

CAROL A HOLQUIST
12/23/2011

REGULATORY PROJECT MANAGER
PLR FORMAT LABELING REVIEW

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 202057

Name of Drug: VASCEPA (icosapent ethyl) Capsules, 1 gram

Applicant: Amarin Pharmaceuticals Ireland Ltd.

Labeling Reviewed

Submission Date: September 25, 2011

Receipt Date: September 26, 2011

Background and Summary Description

VASCEPA (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) (b) (4) levels in adult patients with very high (≥ 500 mg/dL) triglycerides.

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" section of this review. Labeling deficiencies are identified in this section with an "X" in the checkbox next to the labeling requirement.

In addition, the following labeling issues were identified:

There should be no periods after numbers for sections and subsections in the Table of Contents and Full Prescribing Information.

Conclusions/Recommendations

All labeling deficiencies identified in the SRPI section of this review and identified above will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies by January 1, 2012. The resubmitted labeling will be used for further labeling discussions.

Regulatory Project Manager	Date
Chief, Project Management Staff	Date

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**
  - ☐ HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
  - ☐ HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
  - ☐ There is no redundancy of information.
  - ☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
  - ☐ A horizontal line must separate the HL and Table of Contents (TOC).
  - ☐ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
  - ☐ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
  - ☐ Section headings are presented in the following order:

• **Highlights Limitation Statement** (required statement)
• **Drug names, dosage form, route of administration, and controlled substance symbol, if applicable** (required information)
• **Initial U.S. Approval** (required information)
• **Boxed Warning** (if applicable)
• **Recent Major Changes** (for a supplement)
• **Indications and Usage** (required information)
• **Dosage and Administration** (required information)
• **Dosage Forms and Strengths** (required information)
• **Contraindications** (required heading – if no contraindications are known, it must state "None")
• **Warnings and Precautions** (required information)
• **Adverse Reactions** (required AR contact reporting statement)
• **Drug Interactions** (optional heading)
• **Use in Specific Populations** (optional heading)
• **Patient Counseling Information Statement** (required statement)

- **Revision Date** (required information)

- **Highlights Limitation Statement**
  - ☐ Must be placed at the beginning of HL, **bolded,** and read as follows: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

- **Product Title**
  - ☐ Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**
  - ☐ The verbatim statement "Initial U.S. Approval" followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**
  - ☐ All text in the boxed warning is **bolded**.
  - ☐ Summary of the warning must not exceed a length of 20 lines.
  - ☐ Requires a heading in UPPER-CASE, **bolded** letters containing the word "**WARNING**" and other words to identify the subject of the warning (e.g.,"**WARNING: LIFE-THREATENING ADVERSE REACTIONS**").
  - ☐ Must have the verbatim statement "***See full prescribing information for complete boxed warning.***" If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**
  - ☐ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
  - ☐ The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, "Dosage and Administration, Coronary Stenting (2.2) -- 2/2010."
  - ☐ For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line ("margin mark") on the left edge.
  - ☐ A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.

☐ Removal of a section or subsection should be noted. For example, "Dosage and Administration, Coronary Stenting (2.2) -- removal 2/2010."

- **Indications and Usage**

☐ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)]." Identify the established pharmacologic class for the drug at:

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm.

- **Contraindications**

☐ This section must be included in HL and cannot be omitted. If there are no contraindications, state "None."

☐ All contraindications listed in the FPI must also be listed in HL.

X List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.

☐ For drugs with a pregnancy Category X, state "Pregnancy" and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

☐ Only "adverse reactions" as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).

☐ For drug products other than vaccines, the verbatim **bolded** statement, "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**" must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

X Must include the verbatim statement: "**See 17 for Patient Counseling Information**" or if the product has FDA-approved patient labeling: "**See 17 for Patient Counseling Information and (insert either "FDA-approved patient labeling" or "Medication Guide")**.

- **Revision Date**

☐ A placeholder for the revision date, presented as "Revised: MM/YYYY or Month Year," must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

☐ The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.

☐ The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.

X All section headings must be in **bold** type, and subsection headings must be indented and not bolded.

☐ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:

8.1 Pregnancy

8.3 Nursing Mothers (not 8.2)

8.4 Pediatric Use (not 8.3)

8.5 Geriatric Use (not 8.4)

X If a section or subsection is omitted from the FPI and TOC, the heading "**Full Prescribing Information: Contents**" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI)

- **General Format**

☐ A horizontal line must separate the TOC and FPI.

☐ The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.

☐ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

☐ Must have a heading, in UPPER CASE, **bold** type, containing the word "**WARNING**" and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.

☐ Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

☐ Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided.

☐ For the "Clinical Trials Experience" subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

☐ For the "Postmarketing Experience" subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

- **Use in Specific Populations**

☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

☐ This section is required and cannot be omitted.

X Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement "See FDA-approved patient labeling (insert type of patient labeling)." should appear at the beginning of Section 17 for prominence. For example:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

APPEARS THIS WAY ON ORIGINAL

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

/s/

KATI JOHNSON
12/12/2011