

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206406Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

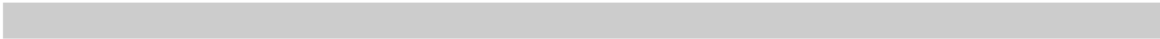
Application Information		
NDA # 206406	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Envarsus XR Established/Proper Name: tacrolimus extended release tablets Dosage Form: extended-release tablets Strengths: 0.75 mg, 1.0 mg and 4.0 mg		
Applicant: Veloxis Pharmaceuticals, Inc.		
Date of Receipt: 12/30/2013		
Original PDUFA Goal Date: 10/30/2014	Action Goal Date (if different):	
NOTE: A Tentative Approval letter issued October 30, 2014, and an approval letter issued July 10, 2015, with the indication proposed in the June 12, 2015, resubmission (see below).		
RPM: Lois Almoza		
Proposed Indication(s):		
Indication Proposed in December 28, 2013, submission (N doc): prophylaxis of organ rejection in patients receiving a kidney transplant		
Indication Proposed in June 12, 2015, Class 1 resubmission: prophylaxis of organ rejection in kidney transplant patients converted from tacrolimus immediate-release preparations in combination with other immunosuppressants		

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

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 by reliance on published literature, or by reliance on a final OTC monograph. *(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 listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 50-708 Prograf® (tacrolimus) capsules Prograf is an immediate release formulation of tacrolimus	Labeling Sections: Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions; Drug Interactions; Use in Specific Populations; Overdosage; Description; Clinical Pharmacology; Non-clinical Toxicology

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 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)

As part of their development program, the Applicant also conducted BA/BE studies comparing their drug with the listed drug.

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 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?

YES NO

If “NO,” proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

- (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 cited reliance on 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
If "NO," proceed to question #10.

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

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Prograf® capsules	050,708	Y (annotated label)

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 final OTC drug monograph?

YES NO
If “YES”, please list which drug(s).

Name of drug(s) described in a final OTC drug 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”).

This application provides for a change in dosage form, from the immediate release capsule formulation (Prograf) to extended release tablet (Envarsus XR).

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 intended for the same route of administration 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), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).

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

*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?

N/A YES NO

*If this application relies only on non product-specific published literature, answer "N/A"
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

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)?

N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"

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):

NDA 50-777, Protopic (tacrolimus) ointment and multiple generic tacrolimus ointments: all patents and exclusivity for Protopic expired]

NDA 50-708, Prograf® (tacrolimus) Capsules and multiple generic tacrolimus capsules: the RLD and generics are all immediate release formulations of tacrolimus. [i.e., all patents and exclusivity for Prograf expired]

NDA 50-709, Prograf® (tacrolimus) injection: all patents and exclusivity for Prograf expired]

NDA 204096, Astagraf XL® (tacrolimus extended release capsules) was submitted by Astellas; and was approved on July 19, 2013 based on new clinical trials. (Astellas was granted 3 years marketing exclusivity that expires July 19, 2016.)

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.

There are no unexpired patents for this product in the Orange Book Database.

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.)

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):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

- (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/

LOIS A ALMOZA
07/10/2015

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for each type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA#	206406
Product Name:	Envarsus XR (tacrolimus extended-release tablets)
PMC #1 Description:	Develop and validate a regulatory X-Ray Powder Diffraction (XRPD) test, with a limit of detection of not more than (b) (4), for determination of crystalline tacrolimus content in tacrolimus extended-release tablets. Revise 3.2.P.5 Drug Product Specification accordingly. Submit a supplemental NDA to add the XRPD testing facility. Add XRPD testing to the on-going drug product stability protocol (first three commercial batches of each strength or next three consecutive commercial batches of each strength and annual stability commitment batches).

PMC Schedule Milestones:	Final Protocol Submission:	12/30/2014
	Study/Trial Completion:	07/30/2015
	Final Report Submission:	10/30/2015
	Other: Interim	04/30/2015

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

To enhance the solubility and dissolution, and hence bioavailability, of tacrolimus,

(b) (4)

(b) (4)

In the original application, the Applicant presented data on crystalline content in a limited number of samples using (b) (4) and X-ray powder diffraction (XRPD) were discussed with the Applicant during the review cycle. Preliminary work identified limitations of (b) (4) but demonstrated potential of XRPD.

Until such time that the Applicant has demonstrated that (b) (4) crystalline form will not occur in the drug product as currently formulated and manufactured, a regulatory test for crystalline content in the drug product will provide additional assurance that the drug product has the requisite quality and bioavailability.

2. Describe the particular review issue and the goal of the study.

The Applicant will develop and validate an XRPD test for crystalline content in the drug product. The test will be performed as part of the regulatory specification for the drug product at release and on stability. An analytical testing facility that will perform the testing will be identified and qualified.

Inclusion of an XRPD test in the regulatory specification will provide additional assurance of the quality and bioavailability of the drug product.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues

Other

Describe the agreed-upon study:

Veloxis will develop and validate a regulatory test for crystalline content in Envarsus XR (tacrolimus extended-release tablets).

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

MARK R SEGCEL
10/24/2014

CELIA CRUZ
10/24/2014

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA#	206406
Product Name:	Envarsus XR (tacrolimus extended-release tablets)
PMC #2 Description:	Develop and validate an X-Ray Powder Diffraction (XRPD) test, with a limit of detection of not more than (b) (4) Add XRPD testing to tacrolimus (b) (4) stability protocol.

PMC Schedule Milestones:	Final Protocol Submission:	12/30/2014
	Study/Trial Completion:	07/30/2015
	Final Report Submission:	10/30/2015
	Other: Interim	04/30/2015

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

To enhance the solubility and dissolution, and hence bioavailability, of tacrolimus, (b) (4)

In the original application, the Applicant presented data on crystalline content in a limited number of samples using (b) (4)

X-ray powder diffraction (XRPD) were discussed with the Applicant during the review cycle. Preliminary work identified limitations of (b) (4) but demonstrated potential of XRPD.

To ensure that complete (b) (4) crystalline tacrolimus content using a validated XRPD will be developed and implemented.

XRPD testing of (b) (4) on stability will provide assurance that material will be (b) (4)

2. Describe the particular review issue and the goal of the study.

The Applicant will develop and validate an XRPD test for crystalline content as (b) (4) tacrolimus (b) (4). Inclusion of an in-process XRPD test will provide additional assurance of the quality and bioavailability of the drug product manufactured with the tacrolimus (b) (4)

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues

Other

Describe the agreed-upon study:

Veloxis will develop and validate ^{(b) (4)} test for crystalline content in tacrolimus ^{(b) (4)} in the manufacture of the drug product.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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NDA#	206406
Product Name:	Envarsus XR (tacrolimus extended-release tablets)
PMC #3 Description:	Evaluate the crystalline content of available legacy batches of tacrolimus (b) (4) and of drug product stability batches by XRPD.

PMC Schedule Milestones:	Final Protocol Submission:	12/30/2014
	Study/Trial Completion:	07/30/2015
	Final Report Submission:	10/30/2015
	Other:	Interim 04/30/2015

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

To enhance the solubility and dissolution, and hence bioavailability, of tacrolimus, (b) (4)
A limited number of samples were previously tested for crystalline content using (b) (4) (b) (4) tablets. An X-ray powder diffraction test for crystalline tacrolimus is under development. This method will then be applied to legacy samples.

2. Describe the particular review issue and the goal of the study.

The Applicant will apply the validated XRPD test (see PMCs #1 and #2) for crystalline content in tacrolimus (b) (4) tablets to samples of previously manufactured materials.

Evaluation of legacy samples of the (b) (4) and finished dosage form will provide additional evidence of the quality of materials previously used to support clinical trials and process development. Testing of legacy samples will provide evidence for the (b) (4) stability of tacrolimus in (b) (4) finished dosage form.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Using the validated XRPD method developed according to PMCs #1 and #2, the Applicant will measure the crystalline content in legacy samples of the (b) (4) and extended-release tablets.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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NDA#	206406
Product Name:	Envarsus XR (tacrolimus extended-release tablets)
PMC #4 Description:	Evaluate conditions that might be expected to promote crystallization of tacrolimus in (b)(4) tablets, including: • Any relationship between (b)(4) and crystalline tacrolimus content in tacrolimus extended-release tablets. • The (b)(4) stability of tacrolimus in (b)(4) tablets under accelerated and stress conditions.

PMC Schedule Milestones:	Final Protocol Submission:	01/30/2015
	Study/Trial Completion:	01/30/2016
	Final Report Submission:	04/30/2016
	Other: Interim	07/30/2015

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

As noted in PMC templates #1, #2 and #3, the potential for (b)(4)

The applicant has not evaluated factors potentially impacting (b)(4) stability using a validated method such as XRPD, which is currently under development by the Applicant.

2. Describe the particular review issue and the goal of the study.

The propensity for (b) (4) and following exposure to accelerated and stress storage conditions.

Identification of conditions that promote crystallization in the MeltDose tacrolimus (b) (4) if any, will provide a basis for further defining appropriate handling and storage conditions, if needed.

A determination that the materials have robust stability with respect to (b) (4) form will support any proposals to reduce or eliminate the frequency of testing for crystalline content.

3. [OMIT – for PMRs only]
4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The Applicant will evaluate conditions that might be expected to promote crystallization of tacrolimus in (b) (4) tablets, such as elevated (b) (4) and exposure to accelerated and stress conditions.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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NDA#	206406
Product Name:	Envarsus XR (tacrolimus extended-release tablets)
PMC #5 Description:	Evaluate the effect of MeltDose manufacturing process parameters on crystalline content of (b) (4) tablets.

PMC Schedule Milestones:	Final Protocol Submission:	01/30/2015
	Study/Trial Completion:	01/30/2016
	Final Report Submission:	04/30/2016
	Other: Interim	07/30/2015

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

To enhance the solubility and dissolution, and hence bioavailability, of tacrolimus, (b) (4)

(b) (4)

A suitable method (XRPD) for determining crystalline content in the MeltDose (b) (4) is being developed by the Applicant. The analytical procedure proposed in the original NDA, (b) (4), was found wanting.

2. Describe the particular review issue and the goal of the study.

Complete (b) (4)

(b) (4)

Such information will support current process

parameters and acceptable variations thereof, or will drive enhanced process controls.

3. [OMIT – for PMRs only]
4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Veloxis will characterize the effects of MeltDose manufacturing process parameters on the crystalline content of (b) (4) tablets using validated XRPD method.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

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/s/

MARK R SEGCEL
10/24/2014

CELIA CRUZ
10/24/2014

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: October 15, 2014

To: Lois Almoza, Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products (DTOP)

CC: Ozlem Belen, MD, MPH, Deputy Director for Safety
DTOP

From: Christine Corser, PharmD, RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Amy Toscano, PharmD, RAC, CPA, Team Leader
OPDP

Subject: **ENVARUSUS XR[®] (tacrolimus extended-release capsules)
NDA #206406**

As requested in DTOP's consult dated October 3, 2014, OPDP has reviewed a proposed (b) (4), which was received via email from DTOP on October 3, 2014. OPDP also referred to the substantially complete proposed draft product labeling (PI), "EnvarsusXR-10-3-14-ToSponsor.doc," that was received via email from DTOP on October 3, 2014, for the review of this (b) (4)

The purpose of the (b) (4) is to (b) (4) Envarsus XR. OPDP offers the following comments:

General Comments

- OPDP notes that the proposed (b) (4) is based on (b) (4). We remind the sponsor that th (b) (4) for Envarsus XR.

Specific Comments

Specific comments on the proposed (b) (4) are included in the attached, clean version of the proposed (b) (4)

Thank you for the opportunity to review and provide comments on the proposed (b) (4). If you have any questions please contact Christine Corser at 6-2653 or Christine.Corser@fda.hhs.gov.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CHRISTINE G CORSER
10/15/2014

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: October 9, 2014

To: Lois Almoza, Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products (DTOP)

From: Christine Corser, PharmD, RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **ENVARBUS XR[®] (tacrolimus extended-release capsules)
NDA #206406**

As requested in DTOP's consult dated March 6, 2014, OPDP has reviewed the draft PI and proposed carton and container labeling for ENVARBUS XR[®] (tacrolimus extended-release capsules) (Envarsus XR).

OPDP reviewed the proposed substantially complete version of the PI titled, "EnvarsusXR-10-3-14-ToSponsor.doc" received via email from DTOP on October 3, 2014. OPDP notes that several sections of the PI are awaiting input/revisions from the drug sponsor (Veloxis Pharmaceuticals, Inc.). OPDP's comments are provided in the attached clean version of the labeling.

OPDP has reviewed the proposed carton and container labeling submitted to FDA on September 26, 2014 and located at:

<\\cdsesub1\evsprod\nda206406\0026\m1\us\114-label\1141-draft-label\carton-envarsus.pdf> and <\\cdsesub1\evsprod\nda206406\0026\m1\us\114-label\1141-draft-label\contain-envarsus.pdf>. OPDP has no comments on the proposed carton and container labeling at this time.

Thank you for the opportunity to review and provide comments on this proposed labeling. If you have any questions please contact Christine Corser at 6-2653 or Christine.Corser@fda.hhs.gov.

23 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CHRISTINE G CORSER
10/09/2014

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

PATIENT LABELING REVIEW

Date: October 08, 2014

To: Renata Albrecht, MD
Director
Division of Transplant and Ophthalmology Products (DTOP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Melissa Hulett, MSBA, MSN, FNP-BC, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Christine Corser, PharmD, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): ENVARUSUS XR (tacrolimus)

Dosage Form and Route: Extended-release tablets, for oral use

Application Type/Number: NDA 206-406

Applicant: Veloxis Pharmaceuticals Inc.

1 INTRODUCTION

On December 28, 2013, Veloxis Pharmaceuticals Inc., submitted for the Agency's review a New Drug Application (NDA 206406) for ENVARSUS XR (tacrolimus) extended-release tablets, for oral use, for the purposed indication of prophylaxis of organ rejection in patients receiving a kidney transplant.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Transplant and Ophthalmology Products (DTOP) on March 06, 2014, and March 06, 2014, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ENVARSUS XR (tacrolimus) extended-release tablets, for oral use.

2 MATERIAL REVIEWED

- Draft ENVARSUS XR (tacrolimus) extended-release tablets MG received on December 30, 2013, and received by DMPP on October 06, 2014.
- Draft ENVARSUS XR (tacrolimus) extended-release tablets MG received on December 30, 2013, and received by OPDP on October 06, 2014.
- Draft ENVARSUS XR (tacrolimus) extended-release tablets Prescribing Information (PI) received on December 30, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on October 06, 2014.
- Draft ENVARSUS XR (tacrolimus) extended-release tablets Prescribing Information (PI) received on December 30, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on October 06, 2014.
- ASTAGRAF XL (tacrolimus) DMPP MG review provided to DTOP on May 14, 2014.

3 REVIEW METHODS

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 MG document using the Verdana font, size 10.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
10/08/2014

CHRISTINE G CORSER
10/08/2014

MELISSA I HULETT
10/08/2014

ADDENDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Addendum: October 3, 2014
Requesting Office or Division: Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number: NDA 206406
Product Name and Strength: Envarsus XR (Tacrolimus) Extended-release Tablets, 0.75 mg, 1 mg, and 4 mg
Submission Date: December 30, 2013
Applicant/Sponsor Name: Veloxis Pharmaceuticals
OSE RCM #: 2014-262-2
DMEPA Primary Reviewer: Rachna Kapoor, PharmD
DMEPA Team Leader: Yelena Maslov, PharmD

1 PURPOSE OF ADDENDUM

Division of Transplant and Ophthalmology Products requested that we review the revised (b) (4) overwrap (Appendix A) around the container for Envarsus XR that was submitted by the Applicant on September 30, 2014 to determine if it is acceptable from a medication error perspective.

2 CONCLUSIONS

We find the (b) (4) overwrap submitted on September 30, 2014 acceptable from the medication error perspective. Thus, we have no additional recommendations regarding container label and carton labeling.

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/s/

RACHNA KAPOOR
10/03/2014

YELENA L MASLOV
10/07/2014

MEMORANDUM

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

DATE: September 30, 2014

TO: Renata Albrecht, M.D.
Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products

Ramesh Sood, Ph.D.
Director,
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

Ethan M. Stier, Ph.D., R.Ph.
Director (Acting)
Division of Bioequivalence II
Office of Generic Drugs

FROM: Arindam Dasgupta, Ph.D.
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Charles Bonapace, Pharm.D.
Chief, GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations
and

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Surveillance inspection of (b) (4)
(b) (4) covering NDA 206-406 (Tacrolimus

(b) (4)

Summary:

At the request of the Division of Bioequivalence II, Office of Generic Drugs (OGD) and Division of New Drug Quality Assessment I, Office of New Drug Quality Assessment (ONDQA), the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted the inspection of the clinical and analy

conducted by

(b) (4)

Additional B

d

nce approach to assess the firm's overall bioanalytical operations and capability to conduct bioequivalence studies. A Summary of inspected studies is provided in **Attachment 1**.

Division of Transplant and Ophthalmology Products (OAP)/
Division of New Drug Quality Assessment I (ONDQA)
NDA 206-406 (Tacrolimus extended release tablets)

Study #: LCP-Tacro 1020

Study Title: "A Two-Way Crossover, Open-Label, Multiple-Dose, Fasting, Bioequivalence Study of LCP Tacro™ 1 mg Tablets (Formulation F) Versus LCPTacro™ 1 mg Tablets (Formulation D) in Normal, Healthy, Non-Smoking Male and Female Caucasian Subjects."

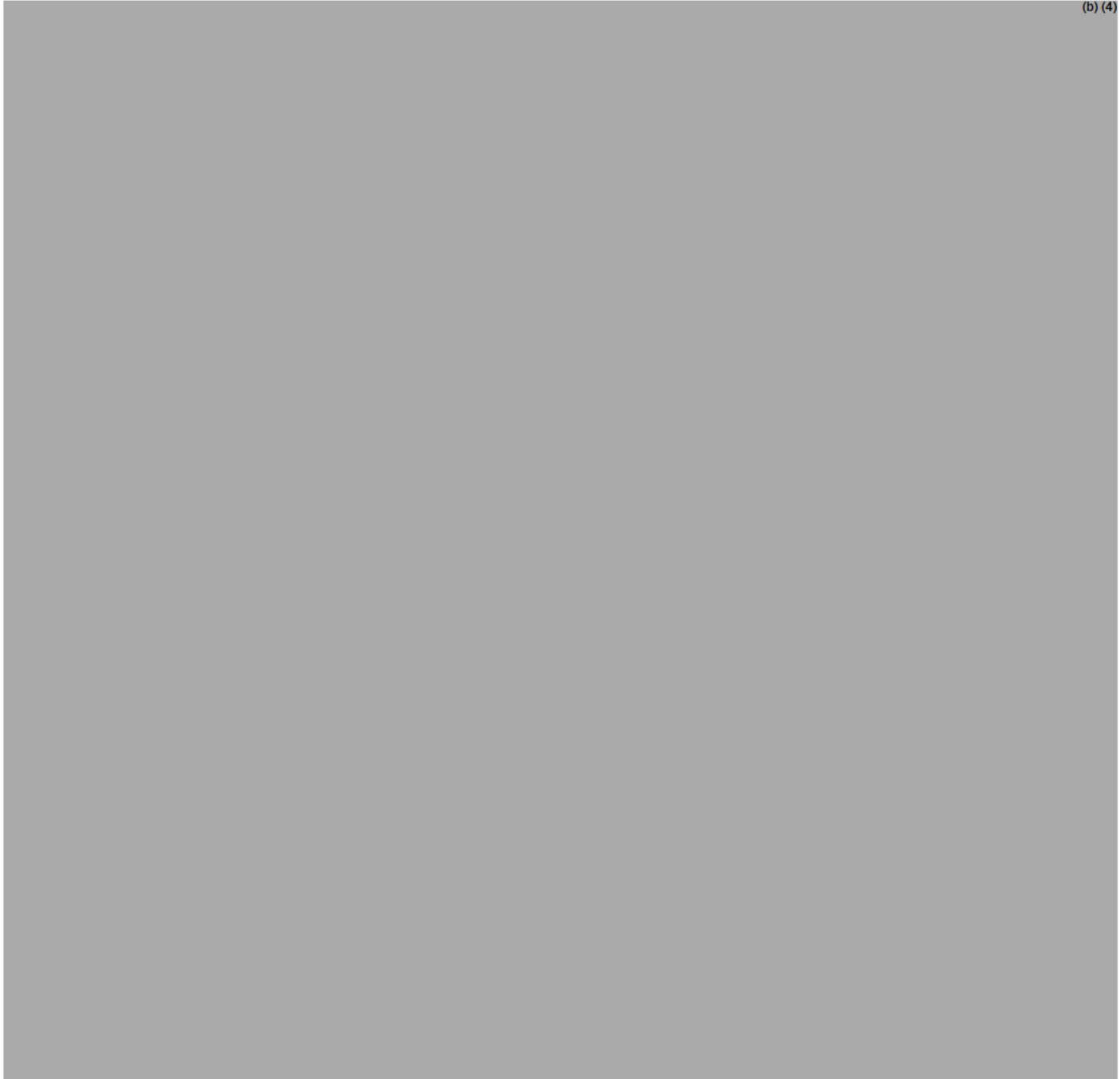
Study #: LCP-Tacro 1023

Study Title: "A Two-Way Crossover, Open-Label, Multiple-Dose, Fasting, Bioequivalence Study of LCP Tacro™ 4 mg Tablets (Formulation G) Versus LCPTacro™ 4 mg Tablets (Formulation F) in Normal, Healthy, Non-Smoking Male and Female Caucasian Subjects."

Study #: LCP-Tacro 1024

Study Title: "The Determination of Tacrolimus in Human Whole Blood by High Performance Liquid Chromatography- Tandem Mass Spectrometry"

(b) (4)



Clinical and Analytical

The clinical [redacted] re
audited at [redacted] (b) (4) by
Comyar Shog [redacted]

[redacted] (b) (4) asgupta Ph.D (Pharmacologist, DBGLPC) during [redacted] (b) (4)
[redacted] (b) (4) The audits included a thorough examination
s and equipment, review of study records in
correspondence, and interviews and discussions with [redacted] (b) (4)

management and staff. As part of global assessment of the firm's bioanalytical operations, several key study components that best represent the firm's bioanalytical operations were selected and audited across the studies. Recent or ongoing studies also selected for audit to gain a better perspective of current bioanalytical operations. DBGLPC audited the studies requested by OAP/ONDQA and OGD using the above surveillance approach.

The ONDQA Biopharm Reviewer had a specific concern on the circumstances of withdrawal of subject 13 from study LCP-Tacro 1023 (NDA 206-406) (Please see **Attachment 2**). Subject 13 also had a pre-dose concentration above the LLOQ in Period I of the study. During the audit, we determined that Subject 13 withdrew from the study due to a family emergency on September 17, 2010 (**Attachment 3**). Samples from subject 13 were analyzed on September 23 (**Attachment 4**) after the subject withdrew from the study. Because the subject withdrew before the analysis of the samples, the pre-dose concentration for subject 13 could not have impacted the subject's withdrawal from the study.

At the conclusion of inspections, no objectionable conditions were observed at the clinical and the analytical sites, and no Form FDA 483 was issued.

Conclusion:

Following review of the inspectional findings, I recommend the following:

- The results from the clinical and bioanalytical portions of the following studies are acceptable for further Agency review.

NDA 206-406

Study Number: LCP-Tacro 1020

Study Number: LCP-Tacro 1023

Study Number: LCP-Tacro 1024

(b) (4)

Arindam Dasgupta Ph.D.

Division of Bioequivalence and GLP compliance
Office of Scientific Investigations

Final Classification:

Clinical and Analytical

NAI:

(b) (4)

FEI:

(b) (4)

CC:

OSI/DBGLPC/Taylor/Bonapace/Haidar/Skelly/Choi/Dasgupta

OSI/DBGLPC/Fenty-Stewart/Nkha/Dejernet/Johnson

CDER/OGD/DB2/Stier/Vehovic

CDER/OND/OAP/DTOP/Albrecht

CDER/OPS/ONDQA/DNDQAI/Ramesh Sood/Zolnik

ORA/PA-FO/LOS-DO/LOS-DIB/Shoghi

Draft: AD 09/10/2014

Edit: CB 09/16/2014

File #

(b) (4)

File #

4)

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE

Program

Sites/

(b) (4)

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/s/

ARINDAM DASGUPTA
09/30/2014

CHARLES R BONAPACE
10/01/2014

WILLIAM H TAYLOR
10/03/2014

ADDENDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Addendum: October 1, 2014
Requesting Office or Division: Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number: NDA 206406
Product Name and Strength: Envarsus XR (Tacrolimus) Extended-release Tablets, 0.75 mg, 1 mg, and 4 mg
Submission Date: December 30, 2013
Applicant/Sponsor Name: Veloxis Pharmaceuticals
OSE RCM #: 2014-262-1
DMEPA Primary Reviewer: Rachna Kapoor, PharmD
DMEPA Team Leader: Yelena Maslov, PharmD

1 PURPOSE OF ADDENDUM

Division of Transplant and Ophthalmology Products requested that we review the (b) (4) overwrap around the container for Envarsus XR to determine if it is acceptable from a medication error perspective. This review also evaluates revised carton labeling and container label (Appendix A) submitted by the Applicant on September 26, 2014.

2 CONCLUSIONS

We find the container labels and carton labeling submitted on September 26, 2014 acceptable from the medication error perspective. Thus, we have no additional recommendations regarding container label and carton labeling.

However, the (b) (4) overwrap does not have any information to identify the product. DMEPA concludes that the (b) (4) overwrap can be improved to include identifying information to promote the safe use of the product.

Thus, DMEPA recommends the following be implemented prior to the approval of this NDA:

A. (b) (4) Overwrap Labeling

- i. At the very least, consider adding the proprietary name, established name, dosage form, strength, an identifying lot or control number, and the name of the manufacturer, packer, or distributor on the (b) (4) overwrap as per the 21 Code of Federal Regulations 201.10(h)(2)(i). This information should be added for identification of the correct product and strength of the product.

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/s/

RACHNA KAPOOR
10/01/2014

YELENA L MASLOV
10/02/2014

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: September 25, 2014

TO: Lois Almoza, Regulatory Project Manager
Ergun Velidedeoglu, M.D., Medical Officer
Joette Meyer, Pharm.D., Medical Team Leader
Division of Transplantation and Ophthalmic Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 206406

APPLICANT: Veloxis Pharmaceuticals

DRUG: Envarsus[®] extended-release tablets [LCP-Tacro (tacrolimus)]

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Prevention of acute allograft rejection in stable adult male and female kidney transplant patients

CONSULTATION REQUEST DATE:	February 4, 2014
CLINICAL INSPECTION SUMMARY DATE:	October 2, 2014
DIVISION ACTION GOAL DATE:	October 28, 2014
PDUFA DATE:	October 30, 2014

I. BACKGROUND:

The Applicant submitted this NDA to support the use of Envarsus[®] for the prevention of acute allograft rejection in stable adult male and female kidney transplant patients.

Two pivotal studies were inspected in support of the indication: LCP-Tacro 3001, entitled “A Phase 3, Open-label, Multicenter, Prospective, Randomized Study of the Efficacy and Safety of Conversion from Prograf[®] Capsules Twice Daily to LCP-Tacro[™] Tablets Once Daily for the Prevention of Acute Allograft Rejection in Stable Kidney Transplant Patients”, and Protocol LCP-Tacro 3002, entitled “A Phase 3, Double-Blind, Double-Dummy, Multi-Center, Prospective, Randomized Study of the Efficacy and Safety of LCP-Tacro[™] Tablets, Once Daily, Compared to Prograf[®] Capsules, Twice Daily, in Combination with Mycophenolate Mofetil for the Prevention of Acute Allograft Rejection in *De Novo* Adult Kidney Transplant Recipients”.

The clinical sites of Drs. Bunnapradist, Budde, and Ciechanowski were selected for inspection because they each conducted both studies and were among the highest enrolling sites.

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ Site #/ # of Subjects (enrolled)	Inspection Dates	Final Classification
Dr. Suphmai Bunnapradist UCLA Medical Center Plaza 200 Medical Plaza, Suite 365C Ronald Reagan UCLA Medical Center 757 Westwood Plaza Los Angeles, CA 90095	LCP-Tacro 3001/ 106/ 22 and LCP-Tacro 3002/ 001/009/ 18	16-24 Apr 2014	NAI
Klemens Budde, M.D. Charite University Clinic Campus Mitte Luisenstrasse 13a Abteilung Nephrologic Ebene 2 Berlin, Germany	LCP-Tacro 3001/ 4991/ 17 and LCP-Tacro 3002/ 049/137/ 46	16-20 Jun 2014	NAI
Kazimierz Ciechanowski , M.D. Pomorski Uniwersytet Medyczny (PUM) AL. Powstancow Wielkopolskich 72 70-111 Szczecin Poland	LCP-Tacro 3001/ 4882/ 27 and LCP-Tacro 3002/ 048/148/ 34	23-27 Jun 2014	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

1. Dr. Suphmai Bunnapradist
UCLA Medical Center Plaza
200 Medical Plaza, Suite 365C
Ronald Reagan UCLA Medical Center
757 Westwood Plaza
Los Angeles, CA 90095

- a. **What was inspected:** At this site for Protocol LCP-Tacro 3001, 31 subjects were screened, 22 subjects were enrolled, and 21 subjects completed the study. For Protocol LCP-Tacro-3002, 27 subjects were screened, 18 subjects were enrolled, and 12 subjects completed the study.

For Protocol LCP-Tacro-3001

The informed consent forms for all subjects were reviewed. The records of all subjects were reviewed with respect to eligibility criteria. The study records of ten subjects were audited. Records reviewed included, but were not limited to, financial disclosure forms, medical histories, laboratory reports, source documents, Case Report Forms (CRFs), the primary efficacy endpoint, biopsy results, adverse event reporting, IRB and monitor correspondence, and test article accountability.

For Protocol LCP-Tacro-3002

The informed consent forms for all subjects were reviewed. The records of all subjects were reviewed with respect to eligibility criteria. The study records of eight subjects were audited. Records reviewed included, but were not limited to, financial disclosure forms, medical histories, laboratory reports, source documents, Case Report Forms (CRFs), the primary efficacy endpoint, biopsy results, adverse event reporting, IRB and monitor correspondence, and test article accountability.

- b. General observations/commentary:** Of the six subjects discontinuing in in Protocol LCP-Tacro-3002, four discontinued due to adverse events. Of these four, two subjects were randomized to treatment with Prograf and the other two to LCP-Tacro. The remaining two subjects were voluntary discontinuations who were randomized to Prograf. A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. Assessment of data integrity:** The studies appear to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Dr. Klemens Budde
Charite University Clinic Campus Mitte
Luisenstrasse 13a
Abteilung Nephrologic Ebene 2
Berlin, Germany

- a. What was inspected:** For Protocol LCP-Tacro 3001, 17 subjects were screened and enrolled with 13 subjects completing the study. For Protocol LCP-Tacro 3002, 47 subjects were screened, 46 subjects were enrolled, and 45 subjects completed the minimum 12 months/endpoint of the study.

For both studies, informed consent forms were reviewed for all subjects. The records of ten subjects for each protocol were reviewed in depth, including but not limited to, medical histories, adverse event reports, laboratory findings, IRB approval, sponsor, monitor and contract research organization (CRO) communications, and test article accountability and storage conditions. The records of these subjects and additional selected subjects were reviewed with respect to treatment, randomization, deaths, graft failure, biopsy-proven acute rejection, subjects lost to follow up, and adverse event reporting.

- b.** General observations/commentary: Of the four subjects not completing Protocol LCP-Tacro 3001, three subjects did not receive the study drug because two subjects withdrew consent and one experienced an adverse event prior to study drug administration. The remaining subject was discontinued for inadvertently taking a commercial form of Prograf. A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c.** Assessment of data integrity: The studies appear to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. Kazimierz Ciechanowski , M.D.
Pomorski Uniwersytet Medyczny (PUM)
AL. Powstancow Wielkopolskich 72
70-111 Szczecin
Poland

- a. What was inspected:** At this site for Protocol LCP-Tacro 3001, 27 subjects were screened and enrolled with 26 subjects completing the study. For Protocol LCP-Tacro 3002, 35 subjects were screened, 34 subjects were enrolled, and 31 subjects completed the study.

For both studies, informed consent forms were reviewed for all subjects. The records of ten subjects per study were reviewed in depth, including but not limited to, medical histories, adverse event reports, laboratory findings, IRB approval, sponsor, monitor and contract research organization (CRO) communications, and test article accountability and storage conditions. The records of these subjects and additional selected subjects were reviewed with respect to treatment, randomization, deaths, graft failure, biopsy-proven acute rejection, subjects lost to follow up, and adverse event reporting.

- b.** General observations/commentary: A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c.** Assessment of data integrity: The studies appear to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigator sites of Drs. Bunnapradist, Budde, and Ciechanowski were inspected in support of this NDA. None of these clinical sites were issued a Form FDA 483, and the final classification of these inspections was No Action Indicated (NAI). The data generated by these clinical sites appear adequate in support of the respective indication.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigation

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/s/

ROY A BLAY
09/25/2014

JANICE K POHLMAN
09/25/2014

KASSA AYALEW
09/25/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	August 26, 2014
Requesting Office or Division:	Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number:	NDA 206406
Product Name and Strength:	Envarsus XR (Tacrolimus) Extended-release Tablets, 0.75 mg, 1 mg, and 4 mg
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Veloxis Pharmaceuticals
Submission Date:	December 30, 2013
OSE RCM #:	2014-262
DMEPA Primary Reviewer:	Rachna Kapoor, PharmD
DMEPA Team Leader:	Yelena Maslov, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed container label, carton labeling, prescribing information, product design, and communication plan for Envarsus XR (Tacrolimus) Extended-release Tablets, NDA 206406, for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Labels and Labeling	D

3 PRODUCT CHARACTERISTICS

The following Table 1 contains Tacrolimus products

Table 1.

	Envarsus XR^{***} (under review)	Prograf Approved 4/8/94	Astagraf XL Approved 7/19/13
NDA number	206406	050708	204096
Active Ingredient	Tacrolimus	Tacrolimus	Tacrolimus
Interchangeability	Not interchangeable with Prograf or Astagraf XL	Not interchangeable with Envarsus XR or Astagraf XL	Not interchangeable with Envarsus XR or Prograf
Indication of Use	Prophylaxis of organ rejection in patients receiving a kidney transplant	Prophylaxis of organ rejection in patients receiving a kidney, liver, or heart transplant	Prophylaxis of organ rejection in patients receiving a kidney transplant
Route of Administration	Oral	Oral	Oral
Dosage Form	Extended-release tablets	Immediate-release capsules	Extended-release capsules
Formulation Differences	LCP-Tacro tablets (MeltDose [®] drug-delivery technology)	Immediate Release product	Extended release hard gelatin capsules
Strengths	0.75 mg 1 mg 4 mg	0.5 mg 1 mg 5 mg	0.5 mg 1 mg 5 mg
Dose and Frequency	(b) (4) mg/kg once daily at the same time	0.1 to 0.2 mg/kg/day in two divided doses	0.15 mg/kg once daily at the same time

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

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The biggest medication error concern related to Envarsus XR tablets is the potential confusion with Prograf and Astagraf XL due to overlap in 1 mg strength (refer to Table 1 to compare the product characteristics). If Envarsus XR is administered instead of Prograf or Astagraf XL and vice versa, potentially serious underdoses and overdoses can occur, which may result in graft rejection. Thus, sufficient measures should be taken in terms of naming, labels, labeling and healthcare provider education to help prevent the confusion.

For this particular product, Veloxis Pharmaceuticals proposes to differentiate this formulation of tacrolimus (i.e., tacrolimus extended-release, LCP-Tacro tablets, using its proprietary MeltDose® drug-delivery technology) from Prograf and Astagraf XL by proposing the following features:

- A use of unique proprietary name (i.e., Envarsus XR);
- Differentiating the dosage form by supplying the product as extended-release tablets versus capsules;
- Use of the frequency of administration statement “Once daily” on the container label and carton labeling;
- Use of different color schemes to highlight the strengths of Envarsus XR;
- Including a warning statement in Envarsus XR’s prescribing information regarding medication errors reported with unintentional substitution of Prograf with Astagraf XL;
- Including a warning statement in Envarsus XR’s prescribing information that it is not interchangeable for, or substitutable with, tacrolimus immediate-release formulations or other extended-release formulations on an equal per dose basis;
- Including a statement in Envarsus XR’s prescribing information and medication guide for the patient to inspect the Envarsus XR medication and make sure it looks the same before taking it;
- Including a statement in Envarsus XR’s prescribing information about conversion from tacrolimus immediate-release formulations to Envarsus XR;
- Inclusion of a (b) (4)

These medication error reducing strategies are acceptable given the fact that development of strength other than 1 mg is not a feasible option at this time. The same strategies were used for Astagraf XL in US and the European Union. So far, we have not identified medication errors related to confusion between Astagraf XL and Prograf. However, to be consistent with Astagraf XL program, we recommend that Veloxis Pharmaceuticals also develop a Dear Pharmacist and Dear Professional Society Letters to ensure further communication and reinforce the information that the three formulations are different and are not interchangeable and warn of the potential for confusion between these products.

We evaluated the proposed labels and labeling and noted that it can be improved to increase the prominence and readability of important information to promote the safe use of the product. We provide recommendations in section 5.1.

5 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the container label and carton labeling can be improved from a safety perspective by increasing the prominence of important information on the label to promote the safe use of the product.

Additionally, DMEPA recommends a Dear Pharmacist and Dear Professional Society Letters for distribution for Envarsus XR to alert pharmacists and transplant specialists for this new extended-release formulation for tacrolimus.

Currently, we have no comments for the (b) (4) or Prescribing Information at this time.

Based on this review, DMEPA recommends the following be implemented prior to the approval of this NDA:

5.1 COMMENTS TO THE APPLICANT

5.1.1 Container Label (All Strengths)

- i. Add the modifier 'XR' to the proprietary name, Envarsus, since the product's name is Envarsus XR.
- ii. Increase the prominence of the established name to ensure that it is displayed with equal prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing features per 21 CFR 201.10(g)(2).
- iii. Add a statement on the principal display panel stating that this product must be dispensed with a Medication Guide per 21 CFR 208.24(d).
- iv. Add the National Drug Code (NDC) number to the top panel and the principal display panel of the container label. As per the 21 Code of Federal Regulations 207.35 (b)(3), the NDC number should appear prominently in the top third of the principal display panel.
- v. The established name should include the finished dosage form as recommended in the Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.¹ It should be written as follows:

¹ 2013 Draft Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>

Envarsus XR
(Tacrolimus)
Extended-release Tablets

Currently, part of your established name will be on [REDACTED] (b) (4) and will not be visible right away as it is located closer to the end of the label. Thus, we recommend placement of the established name as above.

- vi. Decrease the prominence of the company logo as it is almost as prominent as the proprietary name of the product. As per the Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors² the most prominent information on the label should be the proprietary and established names.
- vii. Consider increasing the prominence of the strength by using more intense color to ensure adequate legibility of this very important information.
- viii. Increase the prominence of the statement “Swallow tablet whole. Do not chew, divide, or crush tablet” by bolding the font and placing this information prior to the statement “Dosage: See Package Insert for Dosage Information”. We recommend this revision to help identify the correct technique of product administration.
- ix. Decrease the prominence of the net quantity by removing the [REDACTED] (b) (4) around it and decreasing its font size. Currently, although your net quantity is located off to the side, it is still more prominent than the strength of the product because it is [REDACTED] (b) (4). Thus, the confusion between the strength and net quantity can occur.

5.1.2 Carton Labeling (All Strengths)

- i. See A.i through A.vii and revise carton labeling accordingly.
- ii. Increase the prominence of the statement “Swallow tablet whole. Do not chew, divide, or crush tablet” by bolding the font.
- iii. Decrease the prominence of the net quantity by removing [REDACTED] (b) (4) its font size, and moving above the proprietary name or away from the “ONCE DAILY” statement. As currently presented, the net quantity is more prominent than the strength of the product.

² 2013 Draft Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Envarsus XR that Veloxis Pharmaceuticals submitted on January 23, 2014.

Table 2. Relevant Product Information for Envarsus XR	
Active Ingredient	Tacrolimus
Indication	Prophylaxis of organ rejection in patients receiving a kidney transplant
Route of Administration	Oral
Dosage Form	Extended-release tablets
Strength	0.75 mg, 1 mg, and 4 mg
Dose and Frequency	(b) (4) mg/kg by mouth once daily at the same time
How Supplied	30 and 100 count bottles
Storage	Store at 25°C (77°F); excursions permitted to 15°C – 30°C (59°F – 86°F)

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on May 7, 2014 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.² A gap search was completed from a previous post marketing medication error review on tacrolimus.

Table 3: FAERS Search Strategy	
Date Range	July 4, 2013 to May 1, 2014
Drug Names	Tacrolimus [active ingredient] Tacrolimus anhydrous [active ingredient]
MedDRA Search Strategy	Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Quality Issues (NEC)[HLT]

B.2 Results

From our gap search we identified 85 cases, of which 84 cases were excluded for the following reasons.

- Cases not related to tacrolimus capsules and/or to medication errors involving label and labeling (n=16)
- Adverse event not related to a medication error (n=2)
- Foreign case (n=43)
- Concomitant medication (n=2)
- Product quality issue (n=5)
- Duplicate case (n=1)
- Inappropriate preparation of medication (not relevant to this review) (n=3)
- Wrong technique (not relevant to this review) (n=2)
- Wrong dose, overdose (not relevant to this review) (n=6)
- Wrong dose, underdose (not relevant to this review) (n=4)

² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

Following exclusions described above, 1 medication error case remained for our detailed analysis.

- Wrong drug (n=1)
 - This case involved a patient who was prescribed tacrolimus 0.5 mg (3 tablets) twice daily. The pharmacy dispensed Flomax (tamsulosin) 0.4 mg (3 tablets) three times daily. The prescription bottle was labeled as tacrolimus but filled with tamsulosin. The outcome is unknown. The labels and labeling for Envarsus XR are clearly differentiated from that for tamsulosin. Additionally, the dosage form for Envarsus XR are tablets and tamsulosin are capsules.

B.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the case relevant for this review.

Case Number	Version	Manufacturer Control Number
10018342	1	None

B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:Drive Med Err Consults Completed on June 2, 2014 using the term, tacrolimus, to identify reviews previously performed by DMEPA.

C.2 Results

A proprietary name review was completed on April 15, 2014 for Envarsus XR under the same NDA 206406 (OSE RCM#2014-16828). There were several reviews completed for tacrolimus under the NDA 204096. They include a proprietary name review on November 19, 2012 for Advagraf (b) (4) a proprietary name review on April 4, 2013 for Graceptor XL ((b) (4) a proprietary name review on May 30, 2013 for Astagraf XL (OSE RCM#2013-897), a label, labeling and packaging review on June 17, 2013 for Astagraf XL (OSE RCM#2012-2550 and 2012-2748), and a label and labeling review on February 3, 2014 for Astagraf XL (OSE RCM#2012-2550-1).

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APPENDIX D. LABELS AND LABELING

D.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,³ along with postmarket medication error data, we reviewed the following Envarsus XL labels and labeling submitted by Veloxis Pharmaceuticals on January 23, 2014.

- Container Label
- Carton Labeling
- Package Insert (no image included)
- Medication Guide (no image included)
-  (b) (4) (no image included)

D.2 Label and Labeling Images



³ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

RACHNA KAPOOR
08/26/2014

YELENA L MASLOV
08/26/2014

LUBNA A MERCHANT
08/26/2014

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 # 206406 BLA# N/A	NDA Supplement #: S- N/A BLA Supplement # N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: Envarsus (under review by OSE) Established/Proper Name: tacrolimus Dosage Form: extended-release tablets Strengths: 0.75 mg, 1.0 mg, and 4.0 mg		
Applicant: Veloxis Pharmaceuticals, Inc. Agent for Applicant (if applicable): N/A		
Date of Application: December 28, 2013 Date of Receipt: December 30, 2013 Date clock started after UN: N/A		
PDUFA Goal Date: October 30, 2014	Action Goal Date (if different): N/A	
Filing Date: February 28, 2014	Date of Filing Meeting: February 11, 2014	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed indication(s)/Proposed change(s): prophylaxis of organ rejection in patients receiving a kidney transplant		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</i>		
Review Classification:	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted ☐ Pediatric Rare Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? ☒ N/A	Resubmission after refuse to file? ☒ N/A	
Part 3 Combination Product? N/A <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)	

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ☐ 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): N/A				
List referenced IND Number(s): 75250				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	☒	☐		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>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.</i>	☒	☐		
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)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	☒	☐	☐	Review Priority:S
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	☐	☒		
<i>If yes, explain in comment column.</i>			X	
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>	☐	☐	X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status <i>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.</i>		Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required Note: Applicant initially paid User Fee with intent noted in Application to request refund at later date due to their orphan drug designation. A request for the refund was submitted on, January 21, 2014 and the request was granted as of March 11, 2014.			
<i>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.</i>		Payment of other user fees: ☒ 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?		☐	☒	☐	
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)].		☐	☒	☐	
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)]?		☐	☒	☐	
<i>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 505(b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on any drug product containing 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:					
Application No. N204096	Drug Name Astagraf XL	Exclusivity Code NDF		Exclusivity Expiration July 19, 2016	
<i>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 314.108(b)(2). Unexpired, 3-</i>					

<i>year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>				
Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</i>	☐	☒		Prograf is approved for kidney transplantation but does not have Orphan Exclusivity in this indication.
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)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	☐	☒	☐	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested (b) (4) <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	☐	☒	☐	Requested (b) (4) 7-year orphan drug exclusivity in submission received December 30, 2013, letter dated December 20, 2013.
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	☐	☒	☐	
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)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	☐	☐	☒	
Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? (<i>Original 351(a)BLAs/BLA supplements only</i>) <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement if exclusivity has not yet been granted. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	☐	☐	☒	

Format and Content	
<i>Do not check mixed submission if the only electronic component</i>	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic)

<i>is the content of labeling (COL).</i>	☒ 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).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
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: ☒ 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 #	☐	☐	☒	
Forms and Certifications				
<i>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.</i>				
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)].	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	Additional facility information was submitted on

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

An information request regarding establishments, based on information provided in the December 28, 2013, submission, was sent to the applicant on January 8, 2014.				January 10, 2014 & January 14, 2014, by the Applicant per FDA request made on January 8, 2014.
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)?	☒	☐	☐	Submitted in original submission on December 28, 2013.
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)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	☒	☐		Submitted in original submission on December 28, 2013.
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	☒	☐		
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>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].</i> <i>Note: Debarment Certification should use wording in FD&C Act 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..."</i>	☒	☐	☐	
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? <i>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)</i>	☒	☐	☐	

<i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>				
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)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	☐	☐	☒	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>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.</i>	☐	☒		
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	☐	☐	☒	
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? <i>If no, request in 74-day letter</i> NOTE: The submission dated December 28, 2013 included a partial waiver in addition to a pediatric plan. However, pediatric studies are not needed as this product has orphan drug designation, per letter dated December 20, 2013 from Office of Orphan Products Development. The active moiety or principal molecular structural features of the drug and not the formulation of the drug is designated.	☒	☐	☐	See "NOTE"
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)? <i>If no, request in 74-day letter</i>	☐	☐	☒	
<u>BPCA (NDAs/NDA efficacy supplements only):</u> Is this submission a complete response to a pediatric Written	☐	☒		

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	☒	☐	☐	Proprietary name not in original submission. Submitted on January 23, 2014 by Applicant.
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	☐	☒	☐	
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	☒	☐		
Is the PI submitted in PLR format? ⁴	☒	☐		
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? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☐	☐	☐	OPDP consult sent March 6, 2014
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	☐	☐	☒	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	OSE-DMEPA and DMPP-PatientLabeling

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

				Team consulted on March 6, 2014.
OTC Labeling	☒ 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? <i>If no, request in 74-day letter.</i>	☐	☐	☒	
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	☐	☐	☒	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	☐	☐	☒	
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) <i>If yes, specify consult(s) and date(s) sent:</i>	☒	☐	☐	OSI/DGCPC Consult: Request for Clinical Inspections archived February 4, 2014.
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): February 16, 2010 <i>If yes, distribute minutes before filing meeting</i>	☒	☐		End-of-Phase 2 meeting
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): August 7, 2013 <i>If yes, distribute minutes before filing meeting</i>	☒	☐		There were 2 separate Pre-NDA meetings on August 7, 2013. One meeting was with DTOP, and the other was with ONDQA.
Any Special Protocol Assessments (SPAs)? Date(s): May 14, 2010 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	☒	☐		Special Protocol Assessment submitted March 31, 2010 - No Agreement letter issued on May 14, 2010.

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 11, 2014

BLA/NDA/Supp #: 206406

PROPRIETARY NAME: Envarsus (under review by OSE)

ESTABLISHED/PROPER NAME: tacrolimus

DOSAGE FORM/STRENGTH: extended-release tablets, 0.75 mg, 1.0 mg and 4.0 mg

APPLICANT: Veloxis Pharmaceuticals, LLC.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): for prophylaxis or organ rejection in patients receiving a kidney transplant

BACKGROUND: Veloxis Pharmaceuticals, LLC (Veloxis) submitted this NDA on December 28, 2013, and it was received electronically on December 30, 2013. An addendum to Form FDA 356h was received on January 10, 2014 after an information request was made via e-mail on January 8, 2014, requesting information for all API facilities (and/or drug intermediate facility) and Drug Product facilities. The request for proprietary name review was also submitted and received on January 23, 2014. Veloxis submitted additional information on February 12, 2014, after a request for information was made via e-mail on February 4, 2014, requesting datasets and analysis scripts. Information requests sent on February 14, 2014 which requested additional Clinical Pharmacology/Pharmacometrics and Clinical information was partially responded to by Veloxis on February 27, 2014. Veloxis committed via telephone to submit the rest of the response no later than March 31, 2014.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Lois Almoza	Y
	CPMS/TL:	Diana Willard	Y
Cross-Discipline Team Leader (CDTL)	Joette Meyer		Y
Clinical	Reviewer:	Ergun Velidedeoglu	Y
	TL:	Joette Meyer	Y

Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	Shukal Bala	Y
	TL:		
Clinical Pharmacology	Reviewer:	Gerlie Gieser	Y
	TL:	Philip Colangelo	Y
Biostatistics	Reviewer:	Hongling Zhou	Y
	TL:	Yan Wang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Aaron Ruhland	Y
	TL:	Lori Kotch	Y
Product Quality (CMC)	Reviewer:	Mark Seggel	Y
	TL:		
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Bryan Riley	Y
	TL:		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies): BA studies and the applicant also conducted their own efficacy and safety trials.	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO
• Per reviewers, are all parts in English or English translation?	☒ YES ☐ NO

If no, explain:	
Electronic Submission comments List comments:	☒ Not Applicable
CLINICAL	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE
Comments:	☐ Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no, explain:	☒ YES ☐ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA , include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>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</i>	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
Abuse Liability/Potential Comments:	☒ 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:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE
Comments:	☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY Comments: Clinical pharmacology study site(s) inspections(s) needed?	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
	☐ YES ☒ NO
BIOSTATISTICS Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology (for sterile products)</u> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments:	☐ Not Applicable ☒ YES ☐ NO

<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? Comments:	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> Comments:	☐ Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Renata Albrecht, M.D. Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS	
☐	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 OMPQ (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
☐	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	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 in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

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

/s/

LOIS A ALMOZA
03/12/2014

DIANA M WILLARD
03/12/2014