CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203791Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 203791 SUPPL # S-000 HFD # 530

Trade Name Sitavig

Generic Name Acyclovir Buccal Tablet

Applicant Name Bioalliance Pharma SA

Approval Date, If Known 04/12/2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

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d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

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NDA#	18603	INJECTABLE; INJECTION (Discontinued)
NDA#	18604	OINTMENT; TOPICAL
NDA#	18828	CAPSULE; ORAL
NDA#	19909	SUSPENSION; ORAL
NDA#	20089	TABLET; ORAL
NDA#	21478	CREAM; TOPICAL

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

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1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

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(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

BA2005/21/02: A Randomised, Double-Blind, Single dose, One-Day Early Administration, Multicentre Study comparing the Efficacy and Safety of Acyclovir LauriadTM 50 mg muco-adhesive buccal tablet to matching Placebo, in the Treatment of Herpes Labialis in Immunocompetent Patients.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

BA2005/21/02: YES ☐ NO ☒

YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

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b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

BA2005/21/02: A Randomised, Double-Blind, Single dose, One-Day Early Administration, Multicentre Study comparing the Efficacy and Safety of Acyclovir LauriadTM 50 mg muco-adhesive buccal tablet to matching Placebo, in the Treatment of Herpes Labialis in Immunocompetent Patients.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 BA2005/21/02: !

IND # 77812 YES ☒ ! NO ☐

! Explain:

Investigation #2 !

IND # YES ☐ ! NO ☐

! Explain:

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(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Sohail Mosaddegh
Title: Regulatory Project Manager
Date: 04/11/2013

Reference ID: 3291808

Name of Office/Division Director signing form: Jeffrey Murray, MD, MPH
Title: Deputy Director, Division of Antiviral Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

Reference ID: 3291808

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

/s/

SOHAIL MOSADDEGH
04/11/2013

JEFFREY S MURRAY
04/11/2013

1.3.3 Debarment Certification

BioAlliance Pharma 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 NDA for acyclovir Lauriad™ 50 mg, Buccal Tablet.

February 8th, 2012

Judith Greciet, Pharm. D.
CEO
BioAlliance Pharma
49 Boulevard du Général Martial Valin
75015 PARIS - FRANCE

Date

Countersigned by:

Digitally signed by James Carter
DN: cn=James Carter, o=Regulatory Compliance Initiatives, ou=Principal, email=jcarter@regulatorycomp.com, c=US
Date: 2012.02.02 04:42:37 -08'00'

Jim Carter, Ph.D.
Principal, Regulatory Compliance Initiatives
Regulatory Compliance Initiatives, Inc.
PO Box 95651
Las Vegas, NV 89193
U.S. Agent for BioAlliance Pharma

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 203791 BLA #	NDA Supplement # S-000 BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Sitavig Established/Proper Name: Acyclovir Buccal Tablet Dosage Form: tablet		Applicant: Bioalliance Pharma SA Agent for Applicant (if applicable):
RPM: Sohail Mosaddegh		Division: Division of Antiviral Products

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Zovirax capsule (NDA 18828)

Provide a brief explanation of how this product is different from the listed drug.

Sitavig is a locally acting Buccal tablet, Zovirax capsule is used orally.

☐ This application does not reply upon a listed drug.
☒ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☒ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 04/12/2013	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☒ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☒ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☒ N/A (no paragraph IV certification) ☐ Verified

Version: 1/27/12

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

Reference ID: 3292604

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[4]	04/12/2013
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s)04/12/2013
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	04/09/2013
• Original applicant-proposed labeling	03/12/2012
• Example of class labeling, if applicable	

[4] Fill in blanks with dates of reviews, letters, etc.

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❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	04/09/2013
• Original applicant-proposed labeling	03/12/2012
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	04/09/2013
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	Acceptable letter: 09/21/2012 Reviews: 09/21/2012, 11/13/2012, 03/05/2013
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 05/17/2012 ☒ DMEPA 11/20/2012 ☒ DMPP/PLT (DRISK) 10/11/2012 & 03/08/2013 ☒ ODPD (DDMAC) 10/10/2012 & 03/13/2013 ☐ SEALD ☐ CSS ☒ Other reviews Non-clinical – 03/20/1013
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	RPM Filing Review/Memo of Filing Review – 05/15/2012 ☐ Not a (b)(2) 04/11/2013 ☐ Not a (b)(2) 04/12/2013
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

Reference ID: 3292604

❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 03/06/2013 If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	03/15/2012, 04/05/2012, 04/24/2012, 05/09/2012, 05/24/2012, 06/05/2012, 06/20/2012, 06/28/2012, 07/11/2012, 11/28/2012 07/25/2012, 08/15/2012, 10/03/2012, 10/11/2012, 11/01/2012, 11/09/2012, 11/09/2012, 12/07/2012, 01/10/2013, 02/26/2013, 03/08/2013, 03/15/2013, 03/22/2013
❖ Internal memoranda, telecons, etc.	None
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 04/08/2010, 05/26/2011
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 04/10/2013
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 12/20/2012, 03/28/2013
PMR/PMC Development Templates *(indicate total number)*	☐ None 1
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See CDTL Review
• Clinical review(s) *(indicate date for each review)*	Filing review: 05/29/2012 Combined clinical/stats:

[6] Filing reviews should be filed with the discipline reviews.

Reference ID: 3292604

	12/03/2012, 03/21/2013
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See 12/03/2012 clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested inspection summary: 12/05/2012, letters: 09/05/2012, 12/04/2012, 02/26/2013
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None Filing review: 04/27/2012 Application Review: 11/16/2012, 03/20/2013
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None Filing Review: 05/16/2012 Combined clinical/stats Application Review: 12/03/2012, 03/21/2013, 04/10/2013
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None Filing Review: 6/04/2012 Application Review: 12/07/2012
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None

Reference ID: 3292604

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None Filing Review: 04/24/2012 Application Review: 12/06/2012, 03/20/2013
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None Filing Review: 05/04/2012 Application Review: CMC 12/07/2012, 04/10/2013 Biopharm 12/11/2012
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	see product quality review dated 12/07/2012
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

Reference ID: 3292604

❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: 04/09/2013 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Reference ID: 3292604

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

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

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

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

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

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

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

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

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

Reference ID: 3292604

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/s/

SOHAIL MOSADDEGH
04/12/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

Date: **March 23, 2013**

NDA: **203791**

Drug: **Sitavig, Acyclovir buccal tablets**

To: **James Carter, US Agent**

Sponsor: **BioAlliance Pharma**

Subject: **USPI, PPI, IFU, Blister Label and Carton Labeling comments**

Please refer to your NDA 203791, submitted March 12, 2012. Please see the attached proposed labeling and refer to email sent to you on March 15, 2013 with CMC/Product Labeling comments. Please submit the USPI, PPI, and IFU as a single document.

Please provide revised labeling by 10 AM, March 26, 2013.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
03/22/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

Date: **March 15, 2013**

NDA: **203791**

Drug: **Sitavig, Acyclovir buccal tablets**

To: **James Carter, US Agent**

Sponsor: **BioAlliance Pharma**

Subject: **USPI, PPI, IFU, Blister Label and Carton Labeling comments**

Please refer to your NDA 203791, submitted March 12, 2012 and to your proposed USPI submitted March 07, 2013. Please see the attached Instructions for Use (IFU), PPI, and PI. The instructions for use in PI and PPI/IFU should be the same and need to be supported by the protocol instructions or instructions given to subjects at the onset of the trial. Please provide the requested supporting documentation or where to locate this information in the NDA.

Please use the attached PPI and IFU for any additional edits; use the same format (including the font, bulleting, indentation, and line spacing). Using our attached document will ensure specifically that the formatting changes are preserved. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

We have the following comments:
CMC/Product Labeling:

1. Delete (b) (4) from the description section of the package insert
2. Recommend the storage statement on the carton and on the blister as follows:

   "Store at 20 to 25°C (68 to 77°F) [see USP controlled room temperature]; excursions between 15 and 30°C (59-86°F) permitted at room temperature."

   If the space is insufficient:

   "Store at 20 to 25°C (68 to 77°F)."

3. The physical layout of the blister package and the carton are not completely clear from the submitted information. Please provide the updated blister package and the carton, or an accurate model.

Please provide revised labeling by March 22, 2013.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
03/15/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

Date: **March 08, 2013**

NDA: **203791**

Drug: **Sitavig, Acyclovir buccal tablets**

To: **James Carter, US Agent**

Sponsor: **BioAlliance Pharma**

Subject: **USPI, Blister Label and Carton Labeling comments**

Please refer to your NDA 203791, submitted March 12, 2012 and to your proposed USPI submitted March 07, 2013. Please see the attached revised USPI and the following comments/requests:

A. General Comment

- The current presentation of the net quantity for the blister and the carton as well as the packaging for the blister is confusing. The net quantity statement does not provide a clear presentation of how many tablets are actually in the blister or the carton. In addition, having two empty pockets is misleading and may cause patients to think there is something wrong with their package if they try to open and see nothing in them. This may result in patients throwing the packaging away and pose a risk of occurrences of dose omission medication errors. We recommend you consider re-designing your blister packaging to minimize this risk of confusion; however, we recognize that at this advanced stage of product development, it may not be feasible for you to re-design the packaging. Therefore, if you are unable to revise your blister packaging, we recommend improved directions for patients on the blister label. We provide recommendations in section C below.

B. Blister Label and Carton Labeling

- Ensure that the established name is at least half the size of the proprietary name. Ensure the established name has 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).
- Revise the proprietary name from all uppercase (TRADENAME) to title case (Tradename) for improved readability.
- Ensure that there is a barcode on the label per 21 CFR 201.25.
- Ensure that the manufacturer information and statement of the place of business are included per 21 CFR 201.1(h)(1).

C. Blister Label

- Ensure that the print on the back of the blisters is not printed directly on the foil backing. Black print directly on foil will not provide sufficient contrast for readability. Additionally, the dimpling on the foil may obscure the print.
- Revise the net quantity statement to read "1 tablet".
- Revise the "pill-off" statement to read "peel-off".
- Given the small size of the blister label, ensure the directions for patients on how to access the single tablet are printed large enough to allow for improved readability.
- In order to avoid patient confusion regarding the two empty pocket ' (b) (4) on the blister packaging, we recommend including a step (e.g. between steps 1 and 2) that shows that these should be discarded and do not contain medicine.

D. Carton Labeling

- Revise the net quantity statement to say "2 blisters, each blister contains one 50 mg buccal tablet". Additionally, on the principal display panel, move the net quantity statement to the upper right corner away from the statement of strength.
- Place the dosage form statement (Buccal Tablets) immediately next to the active ingredient statement (Acyclovir). Additionally, ensure the same font is utilized for both the active ingredient and the dosage form.
- Revise the usual dosage statement to the following, "See package insert for dosing and administration information."
- Ensure that the storage requirements are present on the back panel.

E. Blister Packaging

- Consider revising the packaging such that there are no empty pockets on the blister. This may help with confusion so that patients will not think that they have not received any medication in their blister by peeling or breaking the wrong side.

Please provide a response to the USPI edit by March 13, 2013 and to the above Blister Label and Carton Labeling by March 20, 2013.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
03/08/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

Date: **February 26, 2013**

NDA: **203791**

Drug: **Sitavig, Acyclovir buccal tablets**

To: **James Carter, US Agent**

Sponsor: **BioAlliance Pharma**

Subject: **Labeling, PMC, and pediatric plan comments**

Please refer to your NDA 203791, submitted March 12, 2012. Please see the attached proposed labeling and the following comments/requests:

1. Labeling:
   a. Section 12 of the USPI was modified:

(b) (4)

2. Post marketing commitment:
   DAVP is requesting a post marketing commitment to study the effectiveness of Sitavig in an African American population in order to obtain more information applicable to the US market.

3. Pediatric Plan:
   Please submit your revised pediatric plan to include a partial waiver request for ages 6 years and under and a partial deferral for the 6-17 year olds. Your pediatric plan should

cover ages 6-17 years and can be conducted (b) (4)

Please provide a response to the above by March 06, 2013.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
02/26/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203791

REVIEW EXTENSION – MAJOR AMENDMENT

BioAlliance Pharma
c/o Regulatory Compliance Initiatives, Inc.
Attention: Jim Carter, PhD
US Agent
PO Box 95651
Las Vegas, NV 89193

Dear Dr. Carter:

Please refer to your March 12, 2012 New Drug Application (NDA), submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for SITAVIG® (acyclovir) Buccal Tablet, 50 mg.

On January 04, 2013, we received your unsolicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is April 12, 2013.

In addition, in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017," the timeline for communicating labeling changes and/or postmarketing requirements/commitments, provided in our May 24, 2012, filing communication letter, no longer applies and no new timeline will be provided.

If you have any questions, call Sohail Mosaddegh, PharmD, Regulatory Project Manager, at (301) 796-4876 or (301) 796-1500.

Sincerely yours,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

JEFFREY S MURRAY
01/10/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203791 **DISCIPLINE REVIEW LETTER**

BioAlliance Pharma
c/o Regulatory Compliance Initiatives, Inc.
Attention: Jim Carter, PhD
US Agent
PO Box 95651
Las Vegas, NV 89193

Dear Dr. Carter:

Please refer to your March 12, 2012 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SITAVIG® (acyclovir) Buccal Tablet, 50 mg.

Our review of the clinical and statistical sections of your submission is complete, and we have identified the following deficiencies:

Issue 1: (b) (4) claim for (b) (4)

(b) (4)

(b) (4)

The following trial design and analyses issues led to our conclusions and are presented below:

(b) (4)

(b) (4)

Issue 2: Claim to (b) (4)

(b) (4)

Issue 3: Claim (b) (4)

(b) (4)

Issue 4: Adolescents (b) (4)

(b) (4)

Issue 5: Dose selection and drug delivery method

At the pre-NDA meeting and throughout our review, we questioned the dose selection and delivery method. Specifically, (b) (4) lead to a greater difference in TTH? Although you imply acyclovir is delivered mostly from licking of the lips, we do not have convincing evidence of the delivery mechanism to the site of action. Therefore, we needed to rely on robust clinical data demonstrating efficacy in one or more trials.

Other deficiencies:

- The Phase 3 trial enrolled 95% Caucasians; therefore, our ability to conduct analyses based on race was limited.
- When using one trial to demonstrate efficacy, we look for consistency among subgroup analyses. However, results for TTH analyses by study drug application (within 1 hour or greater of appearance of prodromal symptoms) and tablet adhesion times (< 6 hours, 6-12

hours and > 12 hours) did not show consistent results compared to the overall population. These finding again question the robustness of the trial results.

We have determined that the identified deficiencies preclude discussion of labeling changes and/or postmarketing requirements/commitments at this time.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Sohail Mosaddegh, Regulatory Project Manager (301) 796-4876 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Kim Struble, PharmD
Medical Team Lead
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KIMBERLY A STRUBLE
12/07/2012

Cuff, Althea

From: James E. Carter [jcarter@regulatorycomp.com]
Sent: Tuesday, November 27, 2012 2:15 PM
To: Cuff, Althea
Subject: Re: NDA 203791 Information Request

Thanks Althea,

I will take care of the request.

Is Sohail still our Project Manager or did he move?

Best Regards,

Jim
--
James E. Carter, Ph.D.
Regulatory Compliance Initiatives, Inc.
PO Box 95651
Las Vegas, NV 89193

Ph. 702 914 0798
Fx. 702 269 9341

On 11/27/12 10:49 AM, Cuff, Althea wrote:

> Please refer to your NDA 203791, submitted March 12, 2012. We have the following comments/requests:
>
> Provide a revised drug product specification which does not contain the footnote for (b) (4) This is consistent with the understanding reached in the May 26, 2011 Pre-NDA meeting; see Meeting Minutes dated June 9, 2011.
>
> Please confirm receipt of this e-mail. We are requesting a response by December 3, 2012.
>
> Thanks,
>
> ***Althea Cuff, MS***
> ***Regulatory Health Project Manager***
> ***Food & Drug Administration, CDER***
> ***Office of New Drugs Quality Assessment II***
> ***301-796-4061***

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/s/

ALTHEA CUFF
11/28/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

Date: **November 9, 2012**

NDA: **203791**

Drug: **Sitavig, Acyclovir buccal tablets**

To: **James Carter, US Agent**

Sponsor: **BioAlliance Pharma**

Subject: **CMC information request**

Please refer to your NDA 203791, submitted March 12, 2012. We have the following comments/requests:

1. Based on the provided dissolution data from your clinical and primary stability batches, we recommend the following dissolution acceptance criteria at release and on stability. Remember that in setting the dissolution acceptance criteria, you need to consider the mean data at each time point (not individual data) and sometimes you may have to proceed to L2 or L3 stages.

Dissolution acceptance Criteria for Acyclovir Buccal Tablets	
Time Point (hr)	% Drug Dissolved
1	(b) (4)
5	
12	

   Please implement the above recommended acceptance criteria and send us the updated specifications table for your drug product.

2. Please update Section 3.2.P.8.2 by including a Post-approval Stability Protocol to study two additional batches manufactured at commercial scale. We recommend that the stability protocol be similar to the protocol used for the primary stability batches (only one of which was manufactured on commercial scale).

Please submit your response by November 16, 2012.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
11/09/2012

From: Mosaddegh, Sohail
Sent: Friday, November 09, 2012 10:13 AM
To: 'jcarter@regulatorycomp.com'
Subject: : Question Clarification NDA 203791 - Sitavig

Hello:
In response to your question:
Boutolleau's report does not state the treatment which patients had received. It only states that "HSV clinical isolates were mainly obtained from immunocompromised patients (HIV-1 infected patients and transplant recipients) suffering from various HSV-induced diseases."

Please identify the HSV-1 and HSV-2 isolates listed in Table 2 and Table 3 (Page 9-10) in the Boutolleau report, which were obtained from patients who had not previously received acyclovir, provide the range, and median EC50 values and number of isolates tested for HSV-1 and for HSV-2.

Sohail Mosaddegh, Pharm.D.
Lieutenant Commander, USPHS
Regulatory Health Project Manager
FDA/CDER/OND/OAP/Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6377
Silver Spring, MD 20993-0002
Phone: (301) 796-4876
Fax: (301) 796-9883
Email: Sohail.Mosaddegh@FDA.HHS.GOV

From: James E. Carter [mailto:jcarter@regulatorycomp.com]
Sent: Tuesday, November 06, 2012 11:52 AM
To: Mosaddegh, Sohail
Subject: Question Clarification NDA 203791

Hi Sohail,

BioAlliance is seeking clarification --

The range values that we indicated in the labeling come from Zovirax labeling and are also referenced in publications. Publications do not report median and do not identify clinical isolates that have not been exposed to acyclovir. Therefore we would like clarification on the question from FDA. Do they refer to Boutolleau's report No. ba2011-21-00-bou-001 on "In vitro evaluation of the antiviral activity towards herpes

simplex viruses of a mucoadhesive gingival tablet delivering acyclovir" and provided in Sequence 0000?

Best Regards,

Jim
--
James E. Carter, Ph.D.
Regulatory Compliance Initiatives, Inc.
PO Box 95651
Las Vegas, NV 89193

Ph. 702 914 0798
Fx. 702 269 9341

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/s/

SOHAIL MOSADDEGH
11/09/2012
Virology comments

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

Date: **November 1, 2012**

NDA: **203791**

Drug: **Sitavig, Acyclovir buccal tablets**

To: **James Carter, US Agent**

Sponsor: **BioAlliance Pharma**

Subject: **Virology information request**

Please refer to your NDA 203791, submitted March 12, 2012 and to your proposed Microbiology section of the labeling in the October 19, 2012 submission. We have the following comments/requests:

Please provide the range and median EC_{50} values and number of acyclovir susceptible herpes simplex virus type 1 (HSV-1) and herpes simples virus type 2 isolates (HSV-2) tested. Please include only those clinical isolates that have not been exposed to acyclovir.

Please identify the source of these data and respond by November 08, 2012.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
11/01/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

Date: **October 11, 2012**

NDA: **203791**

Drug: **Sitavig, Acyclovir buccal tablets**

To: **James Carter, US Agent**

Sponsor: **BioAlliance Pharma**

Subject: **Packaging comments**

Please refer to your NDA 203791, submitted March 12, 2012. We have the following comments/requests:

Please clarify the packaging for Sitavig. Does it contain 1 tablet per blister card and 2 blisters per carton? Also, please provide rationale for the two empty blisters on the blister card that appear to get discarded.

Please provide a response by COB October 19, 2012.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
10/11/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203791

DEFICIENCIES PRECLUDE DISCUSSION

BioAlliance Pharma
c/o Regulatory Compliance Initiatives, Inc.
Attention: Jim Carter, PhD
US Agent
PO Box 95651
Las Vegas, NV 89193

Dear Dr. Carter:

Please refer to your March 12, 2012 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SITAVIG® (acyclovir) Buccal Tablet, 50 mg.

We also refer to our May 24, 2012, letter in which we notified you of our target date of October 08, 2012 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals And Procedures – Fiscal Years 2008 Through 2012."

As part of our ongoing review of your application, we have identified deficiencies that preclude discussion of labeling and postmarketing requirements/commitments at this time.

This notification does not reflect a final decision on the information under review.

If you have any questions, call Sohail Mosaddegh, Regulatory Project Manager (301) 796-4876 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Kim Struble, PharmD
Medical Team Lead
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KIMBERLY A STRUBLE
10/03/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 203791

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

BioAlliance Pharma
c/o Regulatory Compliance Initiatives, Inc.
PO Box 95651
Las Vegas, NV 89193

ATTENTION: James Carter, Ph.D.
Principal, Regulatory Compliance Initiatives
US Agent for BioAlliance Pharma

Dear Dr. Carter:

Please refer to your New Drug Application (NDA) dated and received March 12, 2012, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Acyclovir Buccal Tablets, 50 mg.

We also refer to your correspondence dated June 25, 2012, and received June 26, 2012, requesting review of your proposed proprietary name, Sitavig. We have completed our review of the proposed proprietary name, Sitavig and have concluded that it is acceptable.

The proposed proprietary name, Sitavig, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. Additionally, if **any** of the proposed product characteristics as stated in your June 26, 2012, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Sohail Mosaddegh at 301-796-4876.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

AZEEM D CHAUDHRY
09/20/2012

CAROL A HOLQUIST
09/21/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

Date: **August 15, 2012**

NDA: **203791**

Drug: **Sitavig, Acyclovir buccal tablets**

To: **James Carter, US Agent**

Sponsor: **BioAlliance Pharma**

Subject: **CMC comments**

Please refer to your NDA 203791, submitted March 12, 2012. We have the following comments/requests:

1. In your Acyclovir DS specification (section 3.2.S.4.1), please revise the [redacted] (b) (4) content limit from NMT [redacted] (b) (4)% to [redacted] (b) (4)% as indicated in the manufacturer's Certificate of Analysis.

2. Please describe the critical quality attributes of Acyclovir 50 mg buccal tablets.

3. A detailed manufacturing flow diagram is provided in Section 3.2.P.3.3 in the submission. It includes [redacted] (b) (4) Please identify the critical in-process parameters.

4. Provide available data on the following:
   a. [redacted] (b) (4).
   b. [redacted] (b) (4)

5. DMF deficiency letters were issued to the holder of DMF [redacted] (b) (4) on July 11, 2012, and August 15, 2012.

Please respond to the above by August 25, 2012.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research

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/s/

SOHAIL MOSADDEGH
08/15/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

Date: **July 25, 2012**

NDA: **203791**

Drug: **Sitavig, Acyclovir buccal tablets**

To: **James Carter, US Agent**

Sponsor: **BioAlliance Pharma**

Subject: **Virology comments to SDN 09 (SN 008, 07/16/12) NDA 203791**

We refer to your Viral Load Report-Study BA2005/21/02 submitted on July 16, 2012 in response to our request of June 29, 2012. We have following comments for data presented in Excel spreadsheet (Page 10):

1. Please provide baseline (prior to acyclovir Lauriad tablet application) saliva HSV-1 viral load (DNA copies/mL and titer) for patients listed in the Excel spreadsheet (Page 10).

2. Please provide acyclovir concentrations for saliva samples for which HSV DNA copies/mL and titers were determined.

3. Please provide time in hours after acyclovir Lauriad tablet application when saliva samples were collected for the HSV viral load determination for patients listed in the Excel spreadsheet (Page 10).

4. There seems to be repetition of data for patients from center LIP402 in the Excel spreadsheet (Page 10). Please confirm or provide explanation.

5. Please provide a summary and interpretation of results on the saliva acyclovir concentrations and HSV-1 DNA copies/ml and titers presented in Viral Load Report-Study BA2005/21/02.

Please respond to the above by August 07, 2012.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
07/25/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203791 **INFORMATION REQUEST**

BioAlliance Pharma
c/o Regulatory Compliance Initiatives, U.S. Agent
Attention: James E. Carter, Ph.D., Principal
PO Box 95651
Las Vegas, NV 89193

Dear Dr. Carter:

Please refer to BioAlliance Pharma's New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sitavig (acyclovir) Buccal Tablets.

We are reviewing the Biopharmaceutics section of BioAlliance Pharma's submission and have the following comments and information requests. We request a prompt written response by July 20, 2012, in order to continue our evaluation of your NDA.

1) Submit data for models and justification for the appropriateness of the models (on Pages 40 to 43 in Section 3.2.P.2). Submit the statistical method for estimating parameters and precisions of the estimation.

2) Clearly define what condition (medium, pH, etc.) was used to generate the in-vitro dissolution data used to correlate with in-vivo data. Also define what method you are proposing as the Regulatory dissolution method for your proposed product.

3) Submit a proper statistical assessment criteria for profile comparison of in vivo data.

4) Submit the normal linear-scale plot for Figures 25, 26, and 27 (in Section 3.2.P.2).

5) We wish to notify you that a DMF Deficiency letter has been issued to the holder of DMF (b) (4) dated July 11, 2012.

To facilitate prompt review of your response, please also provide an electronic courtesy copy of your response to both Jeannie David, Regulatory Project Manager in the Office of New Drug Quality Assessment (Jeannie.David@fda.hhs.gov), and Sohail Mosaddegh, Regulatory Project Manager the Office of New Drugs (Sohail.Mosaddegh@fda.hhs.gov).

If you have any questions regarding this CMC letter, call Jeannie David at (301) 796-4247.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

STEPHEN MILLER
07/11/2012
For R. Madurawe

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

Date: **June 28, 2012**

NDA: **203791**

Drug: **Sitavig, Acyclovir buccal tablets**

To: **James Carter, US Agent**

Sponsor: **BioAlliance Pharma**

Subject: **Virology comments to NDA 203791**

We refer to your March 12, 2012 submission.

1. Please provide a complete virology study report on viral load and acyclovir saliva concentrations for subjects enrolled in study BA2005/21/02. In your report, please include detailed descriptions of the assays used for the quantification of HSV-1 titer/HSV-1 DNA in saliva samples. If this information is present in your submission, please provide its location.

2. If you have submitted a Pediatric Investigation Plan (PIP) to the European Medicines Agency; then, please submit a copy to the NDA.

Please submit the requested information to your NDA by July 09, 2012.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
06/28/2012

-----Original Message-----
From: Mosaddegh, Sohail
Sent: Wednesday, June 20, 2012 3:40 PM
To: 'jcarter@regulatorycomp.com'
Subject: NDA 203791 -(Sitavig) -revised pediatric plan and resistance info

(b) (4)

. Please reconcile the ages and resubmit.
Thanks

Sohail Mosaddegh, Pharm.D.
Lieutenant Commander, USPHS
Regulatory Health Project Manager
FDA/CDER/OND/OAP/Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6377
Silver Spring, MD 20993-0002
Phone: (301) 796-4876
Fax: (301) 796-9883
Email: Sohail.Mosaddegh@FDA.HHS.GOV

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/s/

SOHAIL MOSADDEGH
06/20/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 77,812

MEETING MINUTES

BioAlliance Pharma
c/o Regulatory Compliance Initiative
US Agent for BioAlliance Pharma
Attention: James E. Carter, Ph.D., Principal
P.O. Box 95651
Las Vegas, Nevada 89193

Dear Dr. Carter:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for acyclovir buccal tablets, 50 mg.

We also refer to the Chemistry, Manufacturing and Controls **(CMC) Type B, pre-NDA** meeting between representatives of your firm and the FDA on May 26, 2011. The purpose of the meeting was to discuss the CMC data to support the submission of a new drug application (NDA) for the proposed acyclovir buccal tablets, 50 mg.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jeannie David, Regulatory Health Project Manager, at (301) 796-4247.

Sincerely,

{See appended electronic signature page}

Stephen P. Miller, Ph.D.
CMC Lead, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

ENCLOSURES:
FDA Meeting Minutes
Sponsor Slides

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	CMC Pre-NDA
Meeting Date and Time:	May 26, 2011, 10:00 AM – 11:00 AM EST
Meeting Location:	FDA, Silver Spring, MD
Application Number:	IND 77,812
Product Name:	Acyclovir Buccal Tablets, 50 mg
Indication:	Treatment of Herpes Labialis
Sponsor/Applicant Name:	BioAlliance Pharma
Meeting Chair:	Stephen P. Miller, Ph.D., CMC Lead, Branch V
Meeting Recorder:	Jeannie David, M.S., Regulatory Health Project Manager

FDA ATTENDEES

1. Tapash Ghosh, Ph.D., Biopharmaceutics Reviewer, Office of New Drug Quality Assessment (ONDQA)
2. Bala Shanmugam, Ph.D., Review Chemist, ONDQA
3. Stephen P. Miller, Ph.D., CMC Lead, ONDQA
4. Rapti D. Madurawe, Ph.D., Branch Chief, ONDQA
5. Jessica Cole, Ph.D., Product Quality Microbiology Reviewer, New Drug Microbiology Staff (NDMS)
6. Irene Z. Chan, Pharm.D., BCPS, Team Lead, DMEPA
7. M. Regina Alivisatos*, Medical Officer, Division of Antiviral Products (DAVP)
8. Kimberly Struble, Pharm.D., Clinical Team Leader, DAVP
9. Amalia Himaya, Regulatory Project Manager, DAVP
10. Jeannie David, M.S., Regulatory Health Project Manager, ONDQA

SPONSOR ATTENDEES

1. Pierre Attali, Chief Operating Officer, BioAlliance Pharma
2. Céline Buffangeix, Pharm.D., Project Manager, BioAlliance Pharma
3. James E. Carter, Ph.D., Principal, Regulatory Compliance Initiatives (U.S. Agent)
4. Dominique Costantini, M.D., V.P. Product Development, BioAlliance Pharma
5. Michel Forest, Pharm.D., V.P. Quality Assurance, BioAlliance Pharma
6. John Koleng, Ph.D., R.Ph, Associate, Regulatory Compliance Initiatives (U.S. Agent)
7. Delphine Lucas, Pharm.D., Regulatory Affairs Director, BioAlliance Pharma

*attendance by teleconference

1.0 BACKGROUND

BioAlliance Pharma requested a Type B pre-NDA Chemistry, Manufacturing, and Controls (CMC) meeting, letter dated March 25, 2011, to discuss the CMC data to support the submission of a new drug application (NDA) for the proposed acyclovir buccal tablets, 50 mg. The submission of the NDA is planned for Q3 2011. A separate, clinical pre-NDA meeting for this IND was held between BioAlliance Pharma and the Division of Antiviral Products on April 8, 2010 (meeting package dated March 5, 2010, and received March 8, 2010, and FDA meeting minutes dated April 29, 2010).

The Type B pre-NDA CMC briefing package was received on May 2, 2011. The FDA provided BioAlliance Pharma with preliminary comments to address the questions in the package on May 20, 2011. BioAlliance Pharma acknowledged receipt of the preliminary comments and requested the meeting focus on Questions 5, 3 and 6, in that order.

BioAlliance Pharma provided slides and responses to the FDA preliminary comments in preparation for the meeting. The FDA preliminary responses, BioAlliance responses, and the official minutes captured during the May 26, 2011, meeting discussion are provided below.

2.0 DISCUSSION

Q1. Following the Division's recommendations, BioAlliance Pharma has modified the debossing of the tablets and proposes "AL21".

Can the Agency confirm that the use of "AL21" is acceptable?

FDA Response:

As the Applicant, it is your responsibility to determine that the markings and appearance of the tablets conform to the requirements in 21CFR 206. To assist you there are websites available such as the Product Identification System at DailyMed.nlm.nih.gov and CDER DRUG INFO (DRUGINFO@fda.hhs.gov). This is not an all inclusive list of available resources. The evaluation of the tablet appearance is a review issue, but at this time, FDA has no reason to believe the proposed tablet markings are unacceptable.

BioAlliance Pharma Response:

No further comments.

Meeting Discussion:

BioAlliance Pharma clarified that the proposed proprietary name, (b) (4) has been submitted to the Agency and that the proposed "AL21" embossing will remain the same.

Reference ID: 2958616

Q2. The proposed specifications for Acyclovir Lauriad™ 50 mg, Mucoadhesive Buccal Tablet are presented in the briefing document (i.e. appearance, identification, acyclovir assay, uniformity of dosage by mass variation, (b) (4) adhesion, dissolution, impurity and microbiological purity).

Does the Agency agree that the proposed specifications are adequate for NDA submission?

FDA Response:

The proposed tests for the drug product specification are acceptable. Please note that the acceptance criteria will be evaluated during review to determine its acceptability and hence we are unable to comment on the values proposed.

Regarding the specifications for the dissolution test, the proposed values for the 1 hour and 12 hour time points are adequate. However for the 5 hours time point, please refer to our response for Q3.

While the current microbiology specification appears adequate for filing purposes, additional information should be submitted in the NDA. At the time of NDA submission, the drug product specification should include microbiological testing for each commercial batch. Your proposed specification indicates that Microbiological Purity will be assessed on the (b) (4) full-scale production batches and then on every (b) (4) batch. This is not acceptable based on the available data.

If you intend to pursue reduced microbiological testing in the future you will need to provide data demonstrating that microbiological specifications are met over an extended time period. Submit evidence demonstrating adequate microbiological control of critical raw materials, the manufacturing environment, critical processing steps, and any in-process control parameters that may affect product quality microbiology. As submitted, some stability studies trend towards increased microbial recovery over time, where at time zero there were no organisms detected for either TAMC or TYMC but later time points indicate recovery of organisms. The microbiological characteristics of your product throughout expiry should be understood before considering reduced testing. The request for reduced microbiological testing may be submitted in a Prior Approval CMC supplement. If after review, these data are deemed adequate to support decreased microbiological release testing, then microbiological testing may be moved to the stability program.

BioAlliance Pharma Response:

BioAlliance Pharma agrees to include microbiology testing for each commercial batch at this time. When more data become available BioAlliance Pharma will submit a prior approval supplement to reduce testing to one every tenth batch.

Meeting Discussion:

No discussion occurred.

Reference ID: 2958616

Q3. Reference is made to the Division's dissolution testing comments of January 28, 2011 and relating to the specification range at the middle 5 hour time point. Acyclovir Lauriad™ is a mucoadhesive buccal tablet designed to release the active substance locally, at the site of infection with early and extended concentrations greater than the IC50 for herpes simplex virus, and with minimal systemic exposure. These concentrations allow for a prolonged inhibition of the virus and therefore circumvent the poor intracellular half-life of acyclovir triphosphate (the active metabolite).

BioAlliance Pharma, therefore, considers that a dissolution specification range of (b) (4) at 5 hours should be adequate for Acyclovir Lauriad™ similar to that applied to its product Oravig™ (NDA 022404) that has been previously approved for the local treatment of oropharyngeal candidiasis exhibiting early and high salivary concentrations and minimal systemic exposure.

Does the Agency agree with this approach?

FDA Response:

No, we do not agree. Based on the available data, we still believe that your product should be able to meet a dissolution specification range of ± (b) (4) at 5 hours. The data show that your product will pass the recommended ± (b) (4)% boundaries (i.e., few individual values are outside the ± (b) (4)% boundaries at Stage I and most likely the product will pass Stage II testing).

Please note that we could accept your proposed range of ± (b) (4)% for the 5 hours time point, if you provide data from an in-vivo BE study showing that batches with dissolution values at the two extremes (i.e., (b) (4)% and (b) (4)%) are bioequivalent. Also, please note that wider dissolution specifications are acceptable if they are supported with a properly validated IVIVC model.

In the event that you cannot meet the recommended dissolution specifications and BE testing is not possible, wider specifications could be considered with appropriate data and justification.

BioAlliance Pharma Response:

Would the Agency consider a wider specification at approval of the product (± (b) (4)%) with a commitment to tighten the specifications post-approval after manufacture of (b) (4) commercial batches?

Meeting Discussion:

The FDA acknowledged the difficulty to generate an IVIVC. However, the data submitted to date do support ± (b) (4)% for the dissolution specification range at 5 hours at the time of NDA submission, and the Agency does not agree with the wider specification (± (b) (4)%) proposed. The Agency indicated that BioAlliance Pharma could highlight stability trends in the NDA dataset, and this would be reviewed. The FDA prefers to have the specification set at the time of approval, and would

reconsider the specification based on data from future manufactured batches through a prior approval supplement.

BioAlliance Pharma requested feedback on the following additional question: does the specification mean have to agree with the available dissolution data, or can knowledge of the manufacturing process be used to suggest a different target (± (b) (4)%)? The Agency agreed to provide a response as a Post-Meeting Comment (see Section 5.0 below).

Q4. During process scale up (b) (4) (b) (4) (b) (4) This decrease did not impact the in vitro release and adhesion properties of the tablets. According to the *Guidance for Industry SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation,* this is a level 2 change. In vitro data will be provided in the briefing package and the NDA to indicate the sameness of the product following this minor formulation change.

Does the Agency agree with this approach?

FDA Response:

Yes, your proposed approach is acceptable.

BioAlliance Pharma Response:

No further comments.

Meeting Discussion:

No discussion occurred.

Q5. BioAlliance is transferring product manufacturing from (b) (4) which has produced the clinical batches, to Farméa, which will be the commercial manufacturer. It has been demonstrated that finished tablets manufactured by Farméa are similar to those manufactured in the clinical batches, especially regarding in vitro release and adhesion properties of the tablets. BioAlliance considers that these data, which will be presented in the briefing document and submitted in the NDA, are sufficient to support the transfer of manufacturing from (b) (4) to Farméa.

Does the Agency agree with this approach?

FDA Response:
No, we do not agree. This site change is considered a Level 3 change and based on the SUPAC-MR guidance the following information is needed to demonstrate sameness of the products manufactured at these two facilities.

Chemistry documentation
- *As per SUPAC-MR guidance.*

Dissolution documentation
- *A multipoint dissolution profile using application/compendial test conditions.*

Bioequivalence documentation
- *A single-dose bioequivalence study. The bioequivalence study may be waived in the presence of an established in vitro/in vivo correlation.*

However, if the plasma concentrations are too low to be measured and do not result in a meaningful PK profile, the Agency will consider your proposal based on multi- point dissolution profiles in several media.

BioAlliance Pharma Response:

Acyclovir Lauriad™ 50 mg is for local treatment. The efficacy of the product is not related to plasma concentrations which are generally below the IC_{50} and markedly delayed. In contrast, saliva concentrations are meaningful to efficacy because they are rapidly above the IC50 (in less than half an hour) for a sustained period of time. In addition, saliva concentrations are dependent on saliva flow which is highly variable within and between subjects.

Therefore a meaningful PK profile cannot be established, and neither a bioequivalence study nor an IVIVC are relevant.

BioAlliance therefore proposes a multi-point dissolution profile comparison in different media in the limited pH range of saliva (pH 6 to 7) to support site transfer from (b) (4) to Farméa. In addition, dissolution profile comparison at pH 4 is also proposed.

Supportive slides are provided herewith.

Meeting Discussion:

BioAlliance Pharma presented Slides 1 - 2 to explain why neither a bioequivalence study nor an IVIVC are relevant to the acyclovir buccal tablet product, and requested that the Agency consider multi-point dissolution testing to support the manufacturing site transfer. BioAlliance Pharma stated that since the drug delivery is mainly local and would depend on the saliva flow, there is inherent variability that is therefore difficult to correlate and produce a predictable plasma profile.

The FDA requested that BioAlliance Pharma provide the data to support the argument that the observed variability would make PK comparison infeasible. Specifically, provide the existing raw PK data and the standard deviation at each timepoint, for each of the 12 subjects presented in Slide 1. ***[Addition of FDA Post-Meeting Comment: Upon review of these data, the Agency will***

Reference ID: 2958616

***comment on the feasibility of generating in-vivo data to compare products manufactured at two different sites. In case PK study appears infeasible and]* the multi-media comparison is acceptable, the Agency also requested that BioAlliance Pharma provide dissolution profile data in simulated saliva fluid in addition to the dissolution data in pH 4.0, 6.0 and 7.0.**

BioAlliance Pharma agreed to provide the requested data, and intends to submit this data to the IND prior to NDA submission. BioAlliance Pharma clarified that they would use the data from at least 2 reference batches from (b) (4) (the development and clinical trial material manufacturing site) and 3 reference batches from Farméa (the intended commercial manufacturing site).

[Addition of FDA Post-Meeting Comment: For the chemistry data to support the site transfer, FDA requests that the NDA include Certificates of Analysis or Batch Analyses for drug substance lots used in the clinical studies, and supporting stability data to show comparability between the two drug product manufacturing sites.]

Q6. In the pre-NDA briefing package submitted March 5, 2010, BioAlliance Pharma indicated that stability studies under ICH conditions would be provided on 3 commercial batches in (b) (4) blisters. Instead, BioAlliance Pharma plans to submit these data on 2 pilot scale batches (i.e. (b) (4) tablets/batch) and 1 commercial scale batch (i.e. (b) (4) tablets) in the NDA.

BioAlliance Pharma, therefore, proposes to provide the following stability data at the time of NDA submission:

- Primary stability data of the proposed commercial product in an (b) (4) blister manufactured and placed on stability at the proposed commercial site (Farméa). Stability data will be available at time of submission on 2 pilot scale batches and 1 commercial scale batch up to 6 months under accelerated and long-term conditions.
- Supportive stability data on product containing (b) (4) magnesium stearate, manufactured using the same (b) (4) blister and the same process as the proposed commercial product, and placed on stability at the proposed commercial manufacturing site (Farméa) and available up to 6 months under accelerated (40°C/75% RH) conditions and 24 months under long-term (25°C/60% RH) conditions.

BioAlliance Pharma considers that these data would be sufficient to support the NDA submission.

BioAlliance Pharma also plans to provide the Division with up to 12 months stability data during the NDA review and commits to provide these data no later than 6 months into the NDA review. With these data, BioAlliance Pharma plans to propose a shelf-life of 24 months for the product.

Does the Agency agree with this approach?

FDA Response:

Primary stability data from 2 pilot batches and 1 commercial batch is acceptable.

At the time of NDA submission, we expect minimally, 12-months of stability data under long-term storage conditions, and at least 6-months data from accelerated conditions (and intermediate conditions, if needed).

To be able for us to comply with internal review timelines and PDUFA dates, we cannot commit to reviewing stability data submitted during the review. However we will attempt to evaluate stability updates that are submitted within the first 3 months of the review cycle.

Also, with respect to microbiology testing, please refer to our response to Question 2.

BioAlliance Pharma Response:

At time of NDA submission (expected in September 2011) BioAlliance Pharma will be able to provide 6 months data under accelerated conditions on the 3 primary stability batches. BioAlliance Pharma will also be able to provide 9 months of stability data for the 2 pilot scales batches and 12 months of stability data for the commercial scale batch under long-term conditions. Finally, BioAlliance Pharma will be able to provide 12 months of stability data on the pilot scale batches within 3 months of the review cycle (i.e. in December 2011).

Meeting Discussion:

The Agency stated that they prefer 3 primary stability batches with 12 months of data at the time of NDA submission. This will critical to review of the proposed 24 month expiry. The review of additional data submitted during the first 3 months of NDA review will depend on the resources available at that time. The Agency indicated that they are willing to consider an alternate proposal for the extent of stability data provided at NDA submission, based on justification of patient need provided prior to the NDA submission.

Q7. BioAlliance Pharma is in the process of conducting child-resistant testing on the primary packaging for Acyclovir Lauriad™ 50 mg, Mucoadhesive Buccal Tablet ([redacted] (b) (4) blisters). The results of this test may not be available at time of submission. BioAlliance Pharma commits to provide the results during the review process and no later than 6 months into the NDA review.

Can the Agency confirm that the absence of these results and the child-resistant certificate in the NDA will not constitute a Refuse to File?

FDA Response:

Not having the certification for child-resistant at the time of submission will not constitute Refuse to file. We recommend that the certificate be submitted no later than 3-months into the NDA review.

BioAlliance Pharma Response:

If not available at submission, BioAlliance Pharma commits to provide the certificate no later than 3 months into the NDA review.

Meeting Discussion:

No discussion occurred.

Q8. Milk Protein Concentrate (MPC) is a component of Oravig® (miconazole) 50 mg, buccal tablet (NDA 22-404) approved April 16, 2010. The excipient is not yet listed in the FDA inactive ingredients guide (IIG).

Can BioAlliance Pharma expect that MPC will be in the IIG listing by the time Acyclovir Lauriad™ 50 mg MBT NDA is filed (projected 3Q2011)? Can BioAlliance Pharma reference the amount approved in the IIG or approved in NDA 22-404 to support the use of this excipient in Acyclovir Lauriad™ 50 mg ABT?

FDA Response:

We are not able to comment on the timeline for listing of MPC in the FDA inactive ingredients guide.

Yes, if you are using the same MPC supplier as for NDA 22-404 you may reference the approved NDA 22-404 to support the use of the excipient. Please note that in addition to providing reference to the NDA, you should submit specification, certificate of analysis and any other appropriate information to support the quality of the excipient. If you are using a different MPC supplier, then please provide adequate information to support its use (similar to MPC information provided in NDA 22-404).

We would like to remind you to please provide a Letter of Authorization to enable review of MPC for your NDA.

BioAlliance Pharma Response:

No further comments.

Meeting Discussion:

No discussion occurred.

Reference ID: 2958616

3.0 PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

BioAlliance Pharma Response:

BioAlliance Pharma will follow 21 CFR 201.56 and 201.57 and available guidelines for the proposed Prescribing Information. This proposed Prescribing Information will be provided in Section 1.14.1 of the NDA.

Meeting Discussion:

No discussion occurred.

4.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, the Division of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

BioAlliance Pharma Response:

BioAlliance Pharma will provide facilities information in Section 1.1 of the NDA as an attachment to Form FDA 356h.

Meeting Discussion:

No discussion occurred.

5.0 POST-MEETING COMMENTS

From Q3 Meeting Discussion: Does the specification mean have to agree with the available dissolution data, or can knowledge of the manufacturing process be used to suggest a different target (± (b) (4)%)?

FDA Post-Meeting Comment:

The sponsor needs to set dissolution specification (both mean and range) based on available data from all commercial batches at the time of NDA submission for the Agency to review. If it deviates from what has been proposed in the IND phase, the deviation needs to be justified based on the dissolution data. However, the sponsor should follow the principal of setting dissolution specifications for modified release products.

6.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Submit PK data to support that the observed variability with the buccal tablets would make PK comparison infeasible.	BioAlliance Pharma	Prior to NDA submission
If multi-media comparison is acceptable, submit dissolution profile data in simulated saliva fluid.	BioAlliance Pharma	Prior to NDA submission
Provide the dissolution data for pH 4.0, 6.0, 7.0.	BioAlliance Pharma	Prior to NDA submission
Provide Post-Meeting Comment on question raised during the meeting (Section 5.0 above).	FDA	Completed

7.0 ATTACHMENTS AND HANDOUTS

Slides were provided by BioAlliance Pharma.

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 2958616

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/s/

JEANNIE C DAVID
06/09/2011

STEPHEN P MILLER
06/09/2011

Emailed to MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

Date:	**May 30, 2012**
NDA:	**203791**
Drug:	**Sitavig, Acyclovir buccal tablets**
To:	**James Carter, US Agent**
Sponsor:	**BioAlliance Pharma**
Subject:	**Template**

TEMPLATE FOR SUBMITTING HSV/CMV RESISTANCE DATA

One dataset combines patient data, endpoint data, genotypic data, and phenotypic data. There are a number of ways datasets can be subdivided (i.e., by clinical study, baseline isolates or virologic failure isolates) and this should be discussed with the division before submission.

For each study, we recommend constructing datasets as SAS transport files containing the information below.

- Please include one record (row) per patient per isolate (*e.g.*, baseline, failure, and other timepoints).
- Please include data in columns (with suggested column headings shown below)[1] on all isolates.
- Genotypic data should be provided on the corresponding record for each patient isolate for baseline isolates and the endpoint isolates of virologic failures in treatment studies.[2] For prophylaxis studies, genotypic data should be provided on the corresponding record for each patient isolate and the endpoint isolate of failures.
- Datasets should contain 2 rows above the reference amino acid sequence. The first row should contain the percent identity for each amino acid position of the target protein based upon available databases. The databases and number of sequences used should be identified. The second row should identify all polymorphic amino acids at each amino acid position occurring at >1% in decreasing order of occurrence. The reference sequence used (e.g. AD169) should be identified.
- Phenotypic data should be provided on the corresponding record for each patient isolate for baseline isolates and the endpoint isolates of virologic failures and discontinuations [2] For prophylaxis studies, phenotypic data should be provided on the corresponding record for each patient isolate and the endpoint isolate of failures

[1] In the SAS transport files, column headings can be given abbreviated column names to fit the SAS format. A description of column names should be provided in the submission.
[2] Treatment and endpoint samples should be collected when the patient is still on study agent.

The specific criteria for defining virologic failures should be discussed with the division and may include multiple primary and secondary protocol endpoints. The endpoints for clinical virologic and resistance outcome analyses should be consistent.

Information to Include with Suggested Column Headings[1]

I. Patient Data:

- Patient identification number (ID number should be unique for all studies)
- Isolate (*e.g.*, baseline, Week 1, Week 2, Discontinuation, *etc.* Multiple isolates should be numbered.)
- Date of isolate
- Date of HSV/CMV disease (where applicable)
- Study day (number of days since the patient started the study agent)
- Previous therapeutic agents where available
- Treatment group
- Censored for analysis (yes or no)
- Resistance Analysis Population (yes or no)
- Last Time on Prophylaxis (active or placebo)
- Last Day on Active Prophylaxis

II. Endpoint Data:

- HSV/CMV DNA (copies/mL) at baseline (viral loads <LLOQ should be listed as "<LLOQ value" and >ULOQ should be listed as "<LLOQ value" or ">ULOQ", not left blank)
- HSV/CMV DNA (copies/mL) at predefined timepoints (e.g., Week 1 and Week 2) , one column for each timepoint including baseline, i.e. the viral load throughout the course of the study is provided for each sample
- HSV/CMV DNA (copies/mL) at other times (e.g., loss of virologic response or discontinuation due to adverse event)
- Endpoint assessment (e.g., mean log change in viral load from baseline, *etc.*)
- Please indicate if data were censored for reasons other than virologic failure (e.g., discontinuation due to adverse event)
- Outcome (i.e. responder, virologic failure, HSV/CMV disease, discontinuation while suppressed, discontinuation before achieving viral suppression)
- Reason for discontinuation (i.e., adverse event, pregnancy, etc.) or failure (*i.e.*, never suppressed, rebound)
- HSV/CMV DNA (copies/ml) from additional timepoints may be included.

III. Genotypic Data:[3]

- Genotype for the UL97, UL54 and other targets, one amino acid per column with the wild-type (WT) amino acid as column heading. Changes from WT standard sequence indicated (i.e., blanks indicate no change). Missing data should be indicated with a hyphen.

[3] Genotypic data should be provided for baseline isolates of all patients and the endpoint isolates of virologic failures and discontinuations in all treatment studies.

- Column with total number of substitutions in the relevant protein per patient isolate (for baseline and endpoint isolates). Please discuss with the Division in advance for agreement on the specific substitutions to include

Table A1 highlights how genotype information should be displayed, but does not include all the column headings suggested above.

Table A1. Example of Genotype Information Display

Patient #	Isolate	V-82	N-83	I-84	I-85	G-86	R-87	N-88	L-89	L-90	# Substitutions
(% identity)		100	100	100	100	100	100	95	100	100	
(polymorphic AA)		V	N	I	I	G	R	N, S	L	L	
001	BL							S		M/L	2
001	WK48			V				S		M	3
002	BL	A/T		V				D		M	4
002	WK48	T		V						M	3
003	BL	T		V							2
004	BL			V						M	2

BL = baseline
WK48 = Week 48 for investigational agent

IV. Phenotypic Data:[4]

1. Information on the Investigational Agent

- Baseline EC_{50} value for investigational agent
- Baseline EC_{50} value of reference strain for investigational agent
- Fold resistant change of baseline EC_{50} value compared to EC_{50} value of reference strain of investigational agent
- EC_{50} value at time of endpoint assessment or failure for investigational agent
- Fold change in EC_{50} value at time of endpoint assessment or failure compared to reference strain for investigational agent
- Fold change in EC_{50} value at time of endpoint assessment or failure compared to baseline for investigational agent
- Replication capacity (if available)

Table A2 highlights how phenotype information should be displayed, but does not include all the column headings suggested above.

Table A2. Example of Phenotype Information

		Other Agents in the Same	Other Agents Outside

[4] Phenotypic data should be provided for baseline isolates and the endpoint isolates of virologic failures and discontinuations. In treatment-experienced studies, it is recommended that baseline phenotypic data be obtained for all patients when the biological cutoff is small relative to reductions in susceptibility found in resistant virus.

Sample	Agent X				Class*		Agent Class*	
	EC_{50} value Agent X	Ref strain EC_{50} value Agent X	Δ resis from ref Agent X	Δ resis from BL Agent X	Δ resis from ref Agent Y	Δ resis from BL Agent Y	Δ resis from ref Agent A	Δ resis from BL Agent A
Baseline								
Endpoint								

Agent X = candidate agent

Δ resis = fold resistance change, e.g.: $\frac{EC_{50} \text{ value of sample with Agent X}}{EC_{50} \text{ value of reference (or baseline) strain with Agent X}}$

ref strain = reference strain (or WT)

Endpoint = predefined timepoint for endpoint assessment (e.g., week 24, week 48, failure or discontinuation)

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/s/

SOHAIL MOSADDEGH
06/05/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203791

FILING COMMUNICATION

BioAlliance Pharma
c/o Regulatory Compliance Initiatives, Inc.
Attention: Jim Carter
US Agent
PO Box 95651
Las Vegas, NV 89193

Dear Mr. Carter:

Please refer to your New Drug Application (NDA) dated and received on March 12, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for SITAVIG® (acyclovir) Buccal Tablet, 50 mg.

We also refer to your amendments dated May 07, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is January 12, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by October 8, 2012.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information by June 15, 2012:

CLINICAL

1. Your submitted pediatric study has proposed study ages that are not consistent with your deferral/waiver. Please realign your waiver/deferral to be consistent with your proposed pediatric study ages.

VIROLOGY

2. Please submit HSV resistance data in DAVP Resistance Template Format.

3. Please provide a complete description of assays used for genotypic and phenotypic analyses (Boutolleau report) in addition to the gene sequences and amino acid substitutions identified in HSV resistant clinical isolates.

CMC

4. Please submit individual data from all 10 batches in an electronic format in support of the proposed dissolution specifications; only summary data are found in the submission.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

HIGHLIGHTS OF PRESCRIBING INFORMATION

1. The date of the initial U.S. approval should be bolded (eg. **1982**).

2. Reformat the WARNINGS AND PRECAUTIONS section to ensure that the title and at least one line of text remain together.

3. Under USE IN SPECIFIC POPULATIONS, remove the (b) (4) (b) (4) information.

FULL PRSCRIBING INFORMATION: CONTENTS*

4. Section headings must be in bold type and should appear in upper-case letters. For example, change “Indications and Usage” to “INDICATIONS AND USAGE”, please see comment number nine.

5. Although the subsection headings were indented, consider using the formatting provided below:

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Basic Dosing Information
2.2 Administration Instructions
3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity

FULL PRESCRIBING INFORMATION

6. Use consistent spacing when separating the headings from the text or subsection. Please see the spacing used for sections 1, 10, and 11 versus the other sections.

7. Section 17's heading should be followed by the following statement:
   - See FDA-approved patient labeling (Patient Information).

8. If the package insert and patient package insert are separate documents, the manufacturer information must appear at the end of the PI.

PATIENT LABELING

9. Change the title of this section from "[redacted] (b) (4)" to "Patient Information".

We request that you resubmit labeling that addresses these issues by June 15, 2012. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Sohail Mosaddegh, PharmD, Regulatory Project Manager, at (301) 796-4876 or (301) 796-1500.

Sincerely yours,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

JEFFREY S MURRAY
05/24/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

Date: **May 09, 2012**

NDA: **203791**

Drug: **Sitavig, Acyclovir buccal tablets**

To: **James Carter, US Agent**

Sponsor: **BioAlliance Pharma**

Subject: **Comments to NDA 203791**

We refer to your March 12, 2012 submission. We have the following requests/comments:

1. Please clearly identify by name and NDA number all of the listed drugs (referenced products) on which you are basing your 505b2 application. In addition to the specific sections of labeling which have already been attributed to specific drugs and NDAs, please provide similar attribution for each section of your submission. You can use the following table if preferred.

Name and NDA of referenced products	Information provided (e.g., pharmacokinetic data)

2. Please update your 356h form to add all of the listed drugs by name, dosage form, and holder of approved application. Also please list all INDs, NDAs, and DMFs as appropriate on the Cross References section of form 356h; as a reminder please delete IND (b) (4) and add IND 77,812.

3. Further as oral acyclovir is not approved for the treatment of HL, please provide a scientific "bridge" to demonstrate that reliance on the Agency's finding of safety and/or efficacy for the listed drug(s) is scientifically justified.

Please submit the requested information to your NDA by May 16, 2012.

Sohail Mosaddegh, Pharm.D.
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
05/09/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

Date: **April 24, 2012**

NDA: **203791**

Drug: **Sitavig, Acyclovir buccal tablets**

To: **James Carter, US Agent**

Sponsor: **BioAlliance Pharma**

Subject: **Comments to NDA 203791**

We refer to your March 12, 2012 submission.

1. Please submit the executable SAS programs used to generate analysis datasets from SDTM datasets for study BA2005/21/02;

2. Please submit the subgroup analyses of primary efficacy and safety results by gender, racial, and geriatric subgroups or provide the location in the NDA submission for these analyses.

Please submit the requested information by May 04, 2012.

Sohail Mosaddegh, Pharm.D.
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
04/24/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

Date: **April 05, 20122**

NDA: **203791**

Drug: **Sitavig, Acyclovir buccal tablets**

To: **James Carter, US Agent**

Sponsor: **BioAlliance Pharma**

Subject: **Comments to NDA 203791**

We refer to your March 12, 2012 submission. After initial review of your submission we did not find the information needed to fully address PREA. Your submission included a request for deferral of pediatric studies for subjects (b) (4) years of age. Pediatric study deferral requests must be accompanied by a pediatric plan. Your pediatric plan should contain elements that allow the Agency to determine whether the plan is sufficient to provide adequate data for dosing, safety, and efficacy for use in the appropriate pediatric populations. The minimum requirements for a pediatric plan:

- Description of the planned or ongoing studies
- Timeline for completion of studies that includes
  - the date the protocol will be submitted,
  - the date the studies will be completed, and
  - the date the studies will be submitted

Please submit the requested information by April 11, 2012.

Sohail Mosaddegh, Pharm.D.
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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SOHAIL MOSADDEGH
04/05/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203791

NDA ACKNOWLEDGMENT

BioAlliance Pharma
c/o Regulatory Compliance Initiatives, Inc.
Attention: Jim Carter
US Agent
PO Box 95651
Las Vegas, NV 89193

Dear Mr. Carter:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: SITAVIG® (acyclovir) Buccal Tablet, 50 mg

Date of Application: March 12, 2012

Date of Receipt: March 12, 2012

Our Reference Number: NDA 203791

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 11, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have any questions, call me at 301-796-4876 or 301-796-1500.

Sincerely,

{See appended electronic signature page}

Sohail Mosaddegh, Pharm.D.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SOHAIL MOSADDEGH
03/15/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

IND 77,812

MEETING MINUTES

BioAlliance Pharma
c/o Regulatory Compliance Initiative
US Agent for BioAlliance Pharma
Attention: James E. Carter, Ph.D., Principal
P.O. Box 95651
Las Vegas, Nevada 89193

Dear Dr. Carter:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Acyclovir Lauriad® 50mg Mucoadhesive Buccal Tablet (MBT).

We also refer to the meeting between representatives of your firm and the FDA on April 8, 2010. The purpose of the meeting was to discuss and determine if the current clinical data is adequate to support a 505(b)(2) NDA submission for Acyclovir Lauriad® 50 mg MBT.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Amalia Himaya, Regulatory Project Manager, at 301-796-3391 or the Division's main number at 301-796-1500.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	April 8, 2010
TIME:	10:00 – 11:00 AM EST
MEETING CATEGORY:	Type B, Pre-NDA
APPLICATION:	IND 77,812
DRUG NAME:	Acyclovir Lauriad® 50mg Mucoadhesive Buccal Tablet (MBT)
INDICATIONS:	Treatment of recurrent oro-facial herpes (b) (4) (b) (4)
SPONSOR:	BioAlliance Pharma
MEETING CHAIR:	Kimberly Struble, Pharm.D.
MEETING RECORDER:	Amalia Himaya

FDA ATTENDEES:

1. Jeffrey Murray, M.D., M.P.H., Deputy Director, Division of Antiviral Products (DAVP)
2. Kimberly Struble, Pharm.D., Medical Team Leader, DAVP
3. Yodit Belew, M.D., Medical Officer, DAVP
4. Anita Bigger, Ph.D., Pharmacology/Toxicology Reviewer, DAVP
5. Julian O'Rear, Ph.D., Virology Team Leader, DAVP
6. Lalji Mishra, Ph.D., Virology Reviewer, DAVP
7. Kellie Reynolds, Pharm.D., Clinical Pharmacology Deputy Director, Division of Clinical Pharmacology 4 (DCP4)
8. Shirley Lu, Ph.D., Clinical Pharmacology Reviewer, DCP4
9. Fraser Smith, Ph.D., Acting Biometrics Team Leader, Division of Biometrics IV(DBIV)
10. Thomas Hammerstrom, Ph.D., Biometrics Reviewer, DBIV
11. Dorota Matecka, Ph.D., Acting Chemistry, Manufacturing, and Controls (CMC) Team Leader, Division of Pre-Marketing Assessment II(DPAII)
12. Karen Winestock, Chief Project Management Staff, DAVP
13. Amalia Himaya, Regulatory Project Manager, DAVP
14. Linda Onaga, Regulatory Project Manager, DAVP
15. Marion Droute, Intern, DAVP
16. Camille Bossard, Intern, DAVP

EXTERNAL CONSTITUENT ATTENDEES (BioAlliance Pharma):

1. Caroline Lemarchand, Pharm.D., Ph.D., CMC Director
2. Pierre Attali, M.D., Chief Medical Officer
3. (b) (4) Statistician Consultant (b) (4)
4. (b) (4) Professor, Dermatology, (b) (4)
5. Delphine Lucas, Pharm.D., Regulatory Affairs Director
6. James E. Carter, Ph.D., Principal, Regulatory Compliance Initiatives

BACKGROUND:

BioAlliance Pharma is developing Acyclovir Lauriad® mucoadhesive buccal tablet (MBT) for the treatment of recurrent oro-facial herpes and (b) (4) (b) (4) Acyclovir is currently marketed and available as generic and brand name products in various formulations. For the treatment of herpes labialis, available formulations are acyclovir tablet, capsule, oral suspension, or cream. BioAlliance Pharma plans to introduce Acyclovir Lauriad® MBT as a new proprietary delivery system allowing for a rapid and prolonged release of an active substance in the patient's buccal cavity with a once daily application.

BioAlliance Pharma plans a 505(b)(2) application based on the extensive historical evidence of the safety and efficacy of acyclovir in the United States and abroad for over 20 years for the treatment of herpes labialis. The clinical program developed and conducted by BioAlliance Pharma includes a pharmacokinetic trial (BA2004/21/01) that evaluated the salivary and plasma pharmacokinetic parameters of acyclovir following a single application of Acyclovir Lauriad 50 mg or 100 mg MBT compared to a single dose of acyclovir 200 mg oral tablet in 12 healthy volunteers. One Phase 3 clinical trial (BA2005/21/02) was conducted to demonstrate the efficacy and safety of Acyclovir Lauriad 50 mg in patients with herpes labialis. The results of these studies, in addition to references from literature, will form the basis of the 505(b)(2) NDA application.

BioAlliance Pharma requested a pre-NDA meeting and submitted the meeting package on February 9, 2010 and March 8, 2010, respectively. DAVP provided BioAlliance Pharma with preliminary comments to address questions in the package including additional comments on April 2, 2010. BioAlliance Pharma responded to the DAVP comments on April 7, 2010 and requested the meeting focus on Questions 2 and 3.

MEETING OBJECTIVE:

To discuss and determine if the current clinical data is adequate to support a 505(b)(2) NDA.

DISCUSSION:

BioAlliance Pharma's questions are in bold and DAVP's preliminary comments are in italic identified as "*DAVP Response*." BioAlliance Pharma's response to preliminary comments is identified as "**BioAlliance Pharma Response**" and the April 8, 2010 meeting is identified as "**Meeting Discussion**" highlighted in gray.

Meeting Discussion:
BioAlliance Pharma is in agreement with DAVP's preliminary comments to the following questions: Questions 1, 4, 5, 6, and 7. For Question 4, BioAlliance Pharma proposes to revise the indications to "treatment of herpes labialis (b) (4), DAVP agrees with the general concept of the newly proposed indications, but the exact wording will be a review issue.

Q2: **The phase 1 clinical trial in healthy adult volunteers showed that the pharmacokinetic and pharmacodynamic data were linear between 50 mg and 100 mg acyclovir Lauriad® MBT following a single application. Dramatically high acyclovir concentrations in saliva and lip samples were obtained rapidly and were sustained for more than 24 hours, targeting a mucosal reservoir.**

Does the agency agree that these clinical data support the single application of a 50 mg dose?

DAVP Response: The clinical data to support the single application of a 50 mg dose come from the Phase 3 trial. Although the 50 mg dose may have shown clinical activity, the treatment effect appears to be modest (approaching 1/2 day). It is not certain that a single dose of 50 mg represents the optimal dose. Studies using higher doses or multiple doses with 50 mg could produce a larger treatment effect.

BioAlliance Pharma Response: Two aspects are being raised by the Division: the dose and the duration of treatment.

Regarding the dose:
Acyclovir Lauriad® 50 mg MBT was designed as a local treatment providing early and extended release of the active substance. The objective was to achieve high acyclovir concentrations in saliva and low acyclovir plasma concentrations, below the IC_{50}. The 50 mg dose met these objectives with local concentrations markedly over the IC_{50} (22.5 ng/mL) and markedly over those obtained after a single administration of acyclovir 200 mg tablet (Zovirax®) (11,700-fold higher for saliva). High acyclovir concentrations in saliva were observed for more than 24 hours. In contrast, after a single application of Acyclovir Lauriad® 50 mg MBT, plasma concentrations were low and generally below the IC_{50} for HSV-1.

The 100 mg dose did not provide any advantages over the 50 mg dose for a local treatment. Acyclovir concentrations in saliva were higher and more prolonged than those observed with the 50 mg dose, making it a good candidate for a local treatment. However, acyclovir plasma concentrations were over the IC_{50} for several hours and up to 24 hours post-dosing. AUC was only slightly lower than that of 200 mg oral tablet (Zovirax®). Thus, it cannot be considered as a local treatment and may have a mixed systemic and local effect. Our goal was to develop an effective and convenient local treatment with none, or negligible systemic effect.

Local tolerance was expected to be better with the 50 mg dose than with the 100 mgdose. Based on these data it was considered that the 50-mg dose was the most appropriate for a local treatment.

Multiple dosing:
HSV can be detected in mucosa, in herpes lesions, and also in saliva. The amount of virus is highest at the lesion onset, particularly at the papule and vesicle stages, and diminishes as the lesion matures. Knowledge on viral load and lesion development have evolved over time recognizing that an early high dose antiviral treatment has been found to maximize treatment effect. Famciclovir and valacyclovir have demonstrated efficacy with this treatment approach. The rational for the application of a single dose of Acyclovir Lauriad® 50 mg MBT is based on the same pathophysiology of labial herpes. Acyclovir Lauriad® is particularly well adapted for this approach as well as for a single application providing high and prolonged (over 24 hours) acyclovir concentrations in saliva. The application of Acyclovir Lauriad® for more than one day is not substantiated by the pathophysiology of the disease. Finally, the magnitude of the effect on herpes lesions observed in the phase 3 Study is comparable to that observed with the other local agents.

The administration of higher doses or multiple doses may produce a larger effect. However, the compliance to multiple-dose treatment may not be as good as a single application and may impact the efficacy and justifies a single dose local treatment.

Meeting Discussion:
DAVP does not have convincing evidence of the delivery mechanism of Acyclovir Lauriad® to the site of action. Although BioAlliance Pharma explained acyclovir is delivered mostly from licking of the lips and provided evidence that acyclovir concentrations in saliva are greater than IC_{50}, DAVP is not convinced using saliva concentrations to choose the 50 mg dose is optimal. Acyclovir exposure/response relationship is unclear for efficacy and based on the trial results, the optimal duration is also unclear. For example, are the dosing duration and delivery optimal or just enough to give some sense of preliminary activity in comparison to other oral or topical agents? To clarify these uncertainties, DAVP needs to rely on robust clinical data.

BioAlliance Pharma may consider exploring a [redacted] (b) (4) of Acyclovir Lauriad®. DAVP is not concerned about the risk of resistance development because it is unlikely that the proposed doses of Acyclovir Lauriad® will lead to significant systemic exposures. However, if herpes lesions recur or do not heal, DAVP may request resistance data for a subset of herpes lesions. Development of resistance may be signified by recurrence of lesions harboring viruses different than original, wild-type lesion.

Q3: **BioAlliance Pharma has conducted a Phase 1 pharmacokinetics/ pharmacodynamic study and a Phase 3 study in immunocompetent patients with herpes labialis. Results of the randomised, double blind, placebo-controlled Phase 3 trial in 775 patients showed that the administration of a single dose of Acyclovir Lauriad® 50 mg MBT within 1 hour after the occurrence of prodromal symptoms significantly reduced the time to healing of the primary**

vesicular lesion (p=0.043), and significantly increased by 38.4% the number of herpes episodes not progressing to the vesicular stage (aborted episodes, p=0.045). In addition, acyclovir Lauriad® 50 mg MBT significantly reduced the overall duration of the herpes episode (p=0.006), the duration of symptoms (e.g. pain, tingling) (p=0.059) and symptom intensity (P=0.008) as compared to placebo. A single application of acyclovir Lauriad® 50 mg reduced the number of patients with at least one recurrence of herpes episode [166/253 (65.6%) in the acyclovir Lauriad® 50 mg MBT, 191/262 (72.9%) in the placebo group] in the 9 months following the single application of treatment and the median time to recurrence was delayed by 37 days in the acyclovir group as compared to the placebo group (p=0.055). The safety of acyclovir Lauriad® did not differ from that of a matching placebo.
BioAlliance Pharma believes that these results support the filing of a 505(b)(2) NDA.

Does the Agency agree that the completed clinical development program is adequate to support filing of an NDA?

DAVP Response: We agree that submission of a 505(b)(2) application is appropriate. In the NDA submission please clearly describe the information on which you relied to support the NDA.

Discussion regarding adequacy for filing of NDA

Before determining the appropriateness of submitting one Phase 3 trial to support an NDA for herpes labialis we have the following points and requests for additional analyses. The Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biologic Products, sections II.C.1.d states where the relationship between blood concentration and response is not well understood and the PK of the new dose, regimen or dosage form differ from the previous one, clinical efficacy data will likely be necessary to support effectiveness of a new regimen. In this case, a single additional efficacy study should ordinarily be sufficient. Of note, whether to rely on a single adequate and well-controlled trial is inevitably a matter of judgment. Whether related trials are capable of substantiating a single trial of a new use is a matter of judgment and depends on the quality and outcomes of the trials and the degrees of relatedness to the new use.

The guidance also references "statistically very persuasive findings and a very low p-value" for a single trial. Further, the trial results must be robust to various sensitivity analyses and consistent across subgroups. Additionally statistically persuasive evidence of an effect on more than one endpoint enhances the weight of evidence for a single trial to support the NDA.

While the guidance does not specify a specific p-value, previous communications with you have specified that a single Phase 3 study would require that the treatment difference between drug and placebo be significant at $p<0.001$ or that you demonstrate activity of your drug by conducting two adequate studies that are significant at $p<0.05$. We are reconsidering the previous advice; however, we need your responses to the following. We would appreciate if you could send the requested results prior to the April 8, 2010 meeting.

We consider the following as the primary analyses. Please submit the results of these analyses in your response. Please also provide these primary analyses stratified by race. In previous communications you state if either date is missing then TTH is missing. In your response please describe how missing data was handled.

A non-primary lesion (whether vesicular or non-vesicular) should not be included in any of the analyses requested below. Your protocol defined non-primary lesions as "those developed in addition to and/or in 1 or more days after the primary lesion and that are located at least 1 cm far from the primary lesion. Aborted lesions are not included in this parameter".

1. *Duration of episode (DOE): For patients who experienced a vesicular lesion, duration of episode is the time from the treatment initiation to the healing of primary lesions (loss of crust). For patients whose primary lesions were not vesicular in nature, duration of episode is the time from the treatment initiation to the return to normal skin or to the cessation of symptoms whichever comes last. If hour is missing for either treatment initiation or the endpoint but both dates are recorded then DOE is number of days (end date – start date) multiplied by 24. If either date is missing then DOE is missing.*

2. *Time to Healing of Vesicular Lesions: For patients who experienced a vesicular lesion, time to healing is the time from the treatment initiation to the healing of primary lesions (loss of crust). If hour is missing for either treatment initiation or the endpoint but both dates are recorded then DOE is number of days (end date – start date) multiplied by 24. If either date is missing then TTH is missing.*

We also request the results from the following four sensitivity analyses. These results can better inform a decision to submit an NDA based on the completed Phase 3 trial or if another Phase 3 trial is needed.

1. *Duration of episode (DOE): For patients who experienced a vesicular lesion, duration of episode is the time from the treatment initiation to the healing of primary (loss of crust). For patients whose primary lesions were not vesicular in nature, duration of episode is the time from the treatment initiation to the return to normal skin or to the cessation of symptoms whichever comes last. If hour is missing for either treatment initiation or the endpoint but both dates are recorded then DOE is number of days (end date – start date) multiplied by 24. If either date is missing and the subject is in the Acyclovir Lauriad arm then DOE is the longest observed time to healing of any subject. If either date is missing and the subject is in the placebo arm then DOE is calculated as follows: if the subject has a vesicular lesion, then DOE is the median DOE for subjects with vesicular lesions in the placebo arm; if the subject does not have a vesicular lesion, then DOE is the median DOE for subjects without vesicular lesions in the placebo arm.*

2. *Time to Healing of Vesicular Lesions: For patients who experienced a vesicular lesion, time to healing is the time from the treatment initiation to the healing of primary lesions (loss of crust). If hour is missing for either treatment initiation or the endpoint but both dates are recorded then DOE is number of days (end date – start date) multiplied by 24. If either date is missing and the subject is in the Acyclovir Lauriad arm then TTH is the longest observed time to healing of any subject with vesicular lesions. If either date is*

missing and the subject is in the placebo arm then TTH is the median TTH in the placebo arm.

3. *Duration of episode (DOE): For patients who experienced a vesicular lesion, duration of episode is the time from the treatment initiation to the healing of primary lesions (loss of crust). For patients whose primary lesions were not vesicular in nature, duration of episode is the time from the treatment initiation to the return to normal skin or to the cessation of symptoms whichever comes last. If hour is missing for either treatment initiation or the endpoint but both dates are recorded then DOE is number of days (end date – start date) multiplied by 24. If either date is missing then DOE is calculated as follows: if the subject has a vesicular lesion, then DOE is the median DOE for subjects with vesicular lesions in the placebo arm; if the subject does not have a vesicular lesion, then DOE is the median DOE for subjects without vesicular lesions in the placebo arm.*

4. *Time to Healing of Vesicular Lesions: For patients who experienced a vesicular lesion, time to healing is the time from the treatment initiation to the healing of primary lesions (loss of crust). If hour is missing for either treatment initiation or the endpoint but both dates are recorded then DOE is number of days (end date – start date) multiplied by 24. If either date is missing then TTH is the median TTH in the placebo arm.*

We recommend you do not submit an application for (b) (4) (b) (4) (b) (4) *at this time. To support such an indication,* (b) (4) (b) (4) *(Please also note section III. Documentation of the quality of evidence supporting effectiveness claim in the guidance document.)*

BioAlliance Pharma Response:

(b) (4)

(b) (4)

(b) (4)

We agree not to submit an application for (b) (4) (b) (4)

Meeting Discussion:

DAVP reiterates its previous communication with BioAlliance Pharma that a single Phase 3 trial would require the treatment difference between drug and placebo be significant at $p < 0.001$ or demonstrate activity of drug by conducting two adequate studies that are significant at $p < 0.05$. For 505 (b)(2) applications, DAVP is willing to accept a single trial provided the results were both statistically significant and clinically meaningful. Although the p-value of Acyclovir Lauriad® appears significant, DAVP questions the clinical significance. The benchmark for clinically meaningful results based on other topical treatments for herpes labialis is at least ½ day for TTH endpoint. The TTH results as presented are less than ½ day difference between Acyclovir Lauriad® and placebo. DAVP is uncertain if a greater difference in TTH could have been achieved with higher doses or more frequent or longer dosing. From the data provided to date, DAVP recommends BioAlliance Pharma conduct an additional trial.

BioAlliance Pharma mentioned a reporting error in the numbers provided for the placebo mean TTH in the response sent to DAVP on April 7, 2010. The correct value is 7.55 ± 0.19 (not 7.30 ± 0.18) while the placebo median TTH of 7.30 is correct. Regardless, the difference in TTH is still less than ½ day. Again DAVP reiterated a second trial is needed. DAVP states the TTH for the currently marketed oral products is approximately 1 day or longer. BioAlliance Pharma may be at a competitive disadvantage for Acyclovir Lauriad® compared to other approved products.

In turn, BioAlliance Pharma states Acyclovir Lauriad® is competitive against other existing drug products because it can (b) (4) (b) (4) (b) (4) (b) (4) BioAlliance Pharma can choose to submit an NDA for treatment of herpes labialis; however, approvability in the first review cycle is questionable.

BioAlliance Pharma considers the data robust. Although the data may not have been analyzed correctly as patients were excluded, there was an overall consistent improvement and that consistent finding across the many endpoints evaluated suggest that the data are robust. DAVP disagrees because having an internal consistency among the endpoints only reflects the correlations between the endpoints and does not signify robustness of the data. In addition, DAVP mentions that even if there is an overall trend towards improvement, not all the results had statistical or clinical significance. Therefore, an additional trial is needed to confirm the findings. BioAlliance Pharma asked if conducting a second trial, which show the same results, help in proving the results are not "by chance". DAVP mentions that generally,

two trials can be averaged showing consistent performance in regards to treatment effect; however, as stated by Dr. Hammerstrom, statistical significance still needs to be demonstrated.

BioAlliance Pharma further mentions that the effectiveness of their drug product has been demonstrated by measurement of acyclovir concentrations in saliva. DAVP considers this speculative as the method of saliva measurement is more proof-of-concept. Rather, clinical outcome should be supported by clinical endpoint (primary) and pharmacokinetic parameters (secondary). DAVP also mentions there are 505(b)(2) applications and generic drugs that don't solely rely on bioequivalence trial but also rely on additional clinical trials. DAVP again reiterates if (b) (4) (b) (4)

BioAlliance Pharma also clarified the definition of "missing data." In the data submitted in the meeting package, BioAlliance Pharma defined missing data as those patients who did not heal by day 13 after initiation of treatment; thus, these subjects were excluded from the TTH analysis. Therefore, out of the 521 patients (mITT), 34 patients were excluded from the THH analysis although these patients were followed up to day 13. DAVP requested these subjects be considered censored and included in the analysis. The Kaplan-Meier analysis sent to DAVP on April 7, 2010 captured these subjects as censored and only 10 patients were considered as missing data. From the figure above (Kaplan-Meier) showing proportion of patients not healed over time, DAVP points out the median difference between the two treatments groups is getting closer together. DAVP considers this a review issue in addition to the p-value.

BioAlliance Pharma stated one advantage of Acyclovir Lauriad® is safety. From published data, 10-20% of patients using other available drug products complain of various adverse events such as local irritation and headache. DAVP cannot assess Acyclovir Lauriad®'s safety in comparison to other drugs because there is no risk comparison data available. Although it has the potential for clinical benefit, DAVP cannot provide a definitive conclusion unless a second trial is conducted.

BioAlliance Pharma asked DAVP if a TTH of longer than 0.5 day, based on current data, would be considered clinically efficacious? DAVP strongly recommended BioAlliance Pharma perform the analyses as requested by DAVP. If these analyses are robust, statistically significant and clinically meaningful (> 1/2 day treatment benefit), then an NDA submission based on one trial may be appropriate. DAVP is willing to discuss the preliminary results from the requested analyses with BioAlliance Pharma before a final determination about NDA submission is made. However, DAVP strongly recommended again a second trial is likely needed for the NDA filing and the second trial can help support the (b) (4) indication it is also seeking.

BioAlliance Pharma answers DAVP's inquiry regarding the amount of time Acyclovir Lauriad® fully dissolves and stays on. Acyclovir Lauriad® fully dissolves in about 18-24

hours and dislodges about 10% of the time. BioAlliance Pharma also references a miconazole study with a dislodgement rate of 5% allowing for a reapplication of a second tablet within the first six hours of initial dislodgement. BioAlliance Pharma also confirms there is no data on viral DNA level of lesions.

DECISIONS (AGREEMENTS) REACHED:

1. Acylovir Lauriad® MBT qualifies as a 505 (b)(2) application. Although BioAlliance Pharma has enough data to file, approvability of this NDA is questionable because, although the TTH difference between Acylovir Lauriad® MBT and placebo is statistically significant, the difference is less than ½ day and less than other approved topical products. Unless the requested analyses show both statistical significance and clinical significant (> ½ treatment benefit) then a second trial is strongly recommended.

2. DAVP is in agreement with the concept of the following proposed indications and acknowledges this will be a review issue: *Treatment of herpes labialis and* [redacted] (b) (4)

ACTION ITEMS:

1. BioAlliance Pharma will resubmit its data analyses including additional analyses requested by DAVP in its preliminary comments sent on April 2, 2010. Analyses will be based on the parameters agreed upon in the meeting and as defined in the DAVP preliminary comments. A single Phase 3 trial is considered acceptable if the efficacy data are both clinically meaningful and statistically significant (i.e., improvement in TTH ≥ 0.5 day and p-value considerably smaller than 0.05).

2. BioAlliance Pharma needs to perform an additional trial to support clinical efficacy for the proposed indication of [redacted] (b) (4) This additional trial should:

   [redacted] (b) (4)

3. If BioAlliance Pharma decides to explore [redacted] (b) (4) [redacted] (b) (4) of Acyclovir Lauriad® and if a subset of subjects develop persistent or recurrent lesions, then DAVP may request resistance data for a subset of herpes lesions.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-77812	GI-1	BIOALLIANCE PHARMA	ACYCLOVIR LAURIAD 50MG BIOADHESIVE BUC T

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

/s/

JEFFREY S MURRAY
04/29/2010