

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022205Orig1s000

OTHER REVIEW(S)

SEALD Director Sign-Off Memo and Labeling Review

Product Trade Name (Non-Propriety Name)	GIAZO (balsalazide disodium) tablets, for oral use
Application Number/Supplement Number	NDA 22205
Type of Application	Resubmission Class 2
Indication	Treatment of mildly to moderately active ulcerative colitis in male patients 18 years of age and older
Applicant	Salix Pharmaceuticals, Inc.
Office/Division	ODE III/DGIEP
Division Project Manager	Kevin Bugin, MS, RAC
Submission Date	August 3, 2011
PDUFA Goal Date	February 3, 2012
SEALD Review Date	February 3, 2012
SEALD Labeling Reviewer	Jeanne M. Delasko, RN, MS
SEALD Director	Laurie B. Burke, RPh, MPH

This memo confirms that a Study Endpoints and Labeling Development (SEALD) review of final agreed-upon prescribing information (USPI) determined that there are **NO** outstanding labeling issues in the USPI. This determination follows active engagement throughout the review process between the Division and the SEALD Labeling Team concerning labeling regulations (21 CFR 201.56 and 201.57), labeling guidances, and best labeling practices. The 46-item Selected Requirements for Prescribing Information (SRPI) checklist contains a subset of these policies that apply to all approved USPIs. At this time, no SRPI deficiencies were found (see below for the SRPI checklist).

This memo also confirms that because there are no outstanding SRPI issues in the USPI, the SEALD Director has **NO OBJECTION** to the approval of the USPI at this time.

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

Only identified deficiencies are checked (no checks means no deficiencies).

Highlights (HL)

- **General comments**

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

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

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

- **Highlights Limitation Statement**

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

- **Product Title**

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

- **Initial U.S. Approval**

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

- **Boxed Warning**

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

- **Recent Major Changes (RMC)**

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

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product] is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

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

- **Revision Date**

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

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

- **General Format**

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

- **Contraindications**
 - For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**
 - Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.
 - For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”
 - For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

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

- **Use in Specific Populations**
 - Subsections 8.4 Pediatric Use and 8.5 Geriatric Use (not needed for “peds only” indications) are required and cannot be omitted.

- **Patient Counseling Information**
 - This section is required and cannot be omitted.
 - Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling ... (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:
 - “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/

JEANNE M DELASKO
02/03/2012

ERIC R BRODSKY
02/03/2012
I agree.

Eric Brodsky, SEALD labeling team leader, signing for Laurie Burke, SEALD Director.

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

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

Memorandum

Date: April 12, 2010

To: Roland Girardet, Regulatory Project Manager
Division of Gastroenterology Products (DGP)

From: Kathleen Klemm, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Lisa Hubbard, Professional Group Leader
Shefali Doshi, Regulatory Review Officer
Robert Dean, DTC Group Leader
Wayne Amchin, Regulatory Health Project Manager
DDMAC

Subject: NDA 022205

DDMAC labeling comments for GIAZO (balsalazide disodium) tablets

In response to DGP's January 14, 2010, consult request, DDMAC has reviewed the draft package insert (PI) for GIAZO (balsalazide disodium) tablets. DDMAC's comments on the PI are based on the proposed draft marked-up labeling titled "Package Insert Working Copy.doc" that was modified in the e-room on April 8, 2010, at 8:48am.

DDMAC's comments on the PI are provided directly in the marked-up document attached (see below).

Thank you for the opportunity to comment on this proposed material.

If you have any questions regarding the PI, please contact Kathleen Klemm at 301.796.3946 or Kathleen.Klemm@fda.hhs.gov.

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

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22205

ORIG-1

SALIX
PHARMACEUTICA
LS INC

BALSALAZIDE DISODIUM
TABLETS

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/s/

KATHLEEN KLEMM

04/12/2010



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

Date: April 1, 2010

To: Donna Griebel, MD, Director
Division of Gastroenterology Products

Through: Melina Griffis, RPh, Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol A. Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Irene Z. Chan, Pharm.D., BCPS, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Giazio (Balsalazide Disodium) Tablets, 1.1 gram

Application Type/Number: NDA 022205

Applicant: Salix Pharmaceuticals, Inc.

OSE RCM #: 2010-199

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1 INTRODUCTION

This review responds to a request dated January 26, 2010, from the Division of Gastroenterology Products for evaluation of revised labels and labeling for Giazio (Balsalazide Disodium) Tablets.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the revised labels and labeling submitted January 21, 2010, in comparison to the previously reviewed labels in OSE Review 2007-1800 dated May 20, 2008. We used Failure Mode and Effects Analysis (FMEA) in our evaluation to identify areas of vulnerability that can lead to medication errors.

3 CONCLUSIONS AND RECOMMENDATIONS

We acknowledge the Applicant addressed some, but not all, of the recommendations made by DMEPA in OSE Review 2007-1800 dated May 20, 2008. These other revisions need to be addressed prior to approval. In addition, we note other areas of vulnerability that can lead to confusion and result in medication errors. We provide comments to the Division, including recommendations for the insert labeling, in Section 3.1. We provide recommendations for the container labels and carton labeling in Section 3.2 that aim at reducing the risk of medication errors. We request these revisions be implemented prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project manager, Nitin Patel, at 301-796-5412.

3.1 COMMENTS TO THE DIVISION

A. FULL PRESCRIBING INFORMATION

1. Section 3 Dosage Forms and Strengths

Consider including the shape of the tablet for identification purposes.

2. Section 16 How Supplied/Storage and Handling

See comment A1 above.

3. Section 17 Patient Counseling Information

Consider including the statement "Patients should be instructed to take GIAZO with food."

3.2 COMMENTS TO THE APPLICANT

A. GENERAL COMMENTS FOR ALL CONTAINER LABELS AND CARTON LABELING

1. As currently presented, the established name appears in a very thin font that is difficult to read. In accordance with 21 CFR 201.10 (g)(2), ensure that the established name is printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

2. The dosage form should be presented in the same font as the established name. Remove the bolding from “tablets” and match the font to that of the established name (see comment A.1 above).
3. The product strength is not easy to identify on the proposed labels and labeling. Relocate the strength so that it appears directly below the established name and increase its size to ensure its prominence is greater than that of the net quantity statement.
4. Assure that there is a space between the numerical value and the unit of measure designation in the strength to avoid crowding and confusion (e.g. 1.1 g versus the current 1.1g).

B. PROFESSIONAL SAMPLE CARTON (b)(4) (6 COUNT SAMPLE)

As currently presented, the Applicant does not provide any directions of use for the (b)(4). We request you include a statement that explains the intended use of the (b)(4). If there is not enough room on the (b)(4) consider printing this statement on the attached carton labeling. Ensure the statement does not distract from the proprietary name, established name, or strength presentation.

C. PROFESSIONAL SAMPLE CONTAINER LABEL (6 COUNT SAMPLE)

The 6 count sample is a unit-of-use package; therefore, include the following statement on the side panel to ensure patients self administer this medication correctly: “Take this medication with food.” To provide room for this statement and to minimize crowding the side panel, remove the information (b)(4)

D. RETAIL CONTAINER LABELS AND PROFESSIONAL SAMPLE CONTAINER LABELS (180 COUNT BOTTLES)

The 180 count bottle can be dispensed as a unit-of-use bottle. Please assure this bottle utilizes child-resistant closures to comply with the Poison Prevention Packaging Act of 1970.

E. RETAIL CONTAINER LABELS AND PROFESSIONAL SAMPLE CONTAINER LABELS (6 COUNT, 180 COUNT, AND 500 COUNT BOTTLES)

1. The (b)(4) used to differentiate the net quantity on the principle display panel is inappropriately applied. As currently presented, the (b)(4) affords the net quantity a greater prominence than the product name and strength. Remove the (b)(4) on the principle display panel to allow room to address comment A.3 above. Once you remove the (b)(4) change the white text to black to improve readability.
2. Minimize the manufacturer’s name and logo on the principle display panel. As currently presented, this information is in larger font than that of the established name and strength presentation.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22205	ORIG-1	SALIX PHARMACEUTICA LS INC	BALSALAZIDE DISODIUM TABLETS

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/s/

IRENE Z CHAN
04/01/2010

MELINA N GRIFFIS
04/01/2010

DENISE P TOYER
04/01/2010

CAROL A HOLQUIST
04/01/2010

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: December 10, 2008

TO: Roland Girardet, Regulatory Project Manager
Chris Leptak, M.D., Medical Officer
Division of Gastroenterology Products

FROM: Khairy Malek, M.D., Ph.D./Roy Blay, Ph.D.
Good Clinical Practice Branch 1
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA #: 22-205

APPLICANT: Salix Pharmaceuticals, Inc.

DRUG: Giazio (balsalazide disodium) Tablets

NME: No

THERAPEUTIC
CLASSIFICATION: Standard

INDICATIONS: Treatment of mild to moderately active ulcerative colitis in patients
18 years or older.

CONSULTATION
REQUEST DATE: August 27, 2008

DIVISION ACTION
GOAL DATE: November 30, 2008

PDUFA DATE: December 31, 2008

I. BACKGROUND:

The protocol inspected was #BZUC3003, entitled “A Multicenter, Randomized, Double-Blind Actively-Controlled, Parallel-Group Trial to Evaluate the Safety and Efficacy of a new Tablet Formulation and Dosing Regimen of Balsalazide Disodium 3.3 g BID Versus Mesalamine (5-ASA) AS Asacol 0.8 gm TID In Mildly to Moderately Active Ulcerative Colitis”.

II. RESULTS (by Site):

Name of CI, Location	Protocol #: and # of Subjects:	Inspection Date	Final Classification
Richard N. Hansen, M.D. Arapahoe Gastroenterology, PC 1001 South Park Drive Littleton, CO 80120	BZUC3003: 16 subjects:	24 Nov-10 Dec 2008	Pending. Interim classification is VAI.
Thomas V. Nowak, M.D. Community Clinical Research Center 1622 N. Madison Avenue Anderson, IN 46011	BZUC3003: 11 subjects:	2-4 Dec 08	Pending. Interim classification is NAI.

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;

The Establishment Inspection Report (EIR) has not been received from the field and complete review of EIR is pending.

1. Richard N. Hansen, M.D.
Arapahoe Gastroenterology, PC
1001 South Park Drive
Littleton, CO 80120

- a. **What was inspected:** 20 subjects were screened, 16 were enrolled, and 14 completed the study. Signed consent forms were present for all subjects. The records of eight subjects were reviewed in depth, including but not limited to verification of the primary and secondary endpoints, adverse event reporting, concomitant medications, and drug accountability
- b. **General observations/commentary:** The Form FDA 1572, Statement of Investigator, omitted the name of one participating physician, and subject 84320 did not have a serum pregnancy test at study completion as required by protocol.
- c. **Assessment of data integrity:** Data appear acceptable in support of the respective application.

Observations noted above are based on communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

2. Thomas V. Nowak, M.D.
Community Clinical Research Center
1622 N. Madison Avenue
Anderson, IN 46011

- a. **What was inspected:** 16 subjects were screened for the study with 11 enrolling and 9 completing the study. The study records, including consent forms, for all 16 subjects were reviewed in depth. Medical histories were reviewed including documentation of the presence of ulcerative colitis, in addition to study documentation of sigmoidoscopies, colonoscopies, laboratory analyses, and physical examinations.
- b. **General observations/commentary:** Primary and secondary endpoints were verified by comparison of source documents with case report forms (CRFs) and line listings. Study diaries were present in all subject files. No regulatory violations were noted.
- c. **Assessment of data integrity:** Data appear acceptable in support of the relevant application

Observations noted above are based on communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Receipt and review of the EIRs for the above sites are pending. An addendum to this clinical inspection summary will be forwarded to the review division should there be any observations of clinical and regulatory significance discovered after reviewing the EIRs.

The data generated by the clinical sites of Drs. Hansen and Nowak appear acceptable in support of the respective application.

{ See appended electronic signature page }

Roy Blay, Ph.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/s/

Roy Blay
12/11/2008 12:34:56 PM
CSO

Constance Lewin
12/11/2008 12:56:48 PM
MEDICAL OFFICER

NDA REGULATORY FILING REVIEW (Including Memo of Filing Meeting)

NDA # 22-205 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Giazio
Established Name: balsalazide disodium
Strengths: 1.1 gm

Applicant: Salix Pharmaceuticals, Inc.
Agent for Applicant (if applicable):

Date of Application: July 16, 2007
Date of Receipt: July 17, 2007
Date clock started after UN:
Date of Filing Meeting: August 27, 2007
Filing Date: September 17, 2007
Action Goal Date (optional): March 17, 2008 User Fee Goal Date: May 17, 2008

Indication(s) requested: Treatment of mildly to moderately active ulcerative colitis in patients 18 years of age and older.

Type of Original NDA: (b)(1) (b)(2)
 AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. 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). If the application or efficacy supplement is a (b)(2), complete Appendix B.*

Review Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
 Waived (e.g., small business, public health)

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain: Salix was granted 3 year exclusivity on December 20, 2006 for Colazal (balsalazide disodium) Capsules, 750 mg

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO

Salix has the orphan indication for balsalazide disodium capsules in the pediatric patient population

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:

- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as a partial electronic submission).

1. This application is a paper NDA YES

2. This application is an eNDA or combined paper + eNDA YES
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

Does the eNDA, follow the guidance? N/A
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments: SPL and labeling only submitted in electronic format

3. This application is an eCTD NDA. YES

If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, 3 Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO
- PDUFA and Action Goal dates correct in tracking system? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: IND 38,492

- Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.
Salix submitted the tradename after the original submission

- End-of-Phase 2 Meeting(s)? Date(s) 8/5/2005 NO

If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s) Date(s) 4/27/2007 NO
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) _____ NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
Tradename not submitted in original application, but submitted on _____ . Consult sent
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA YES NO

If Rx-to-OTC Switch or OTC application: N/A

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO

- If EA submitted, consulted to EA officer, OPS? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
 - If a parenteral product, consulted to Microbiology Team? N/A YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 27, 2007

NDA #: 22-205

DRUG NAMES: Giazio (balsalazide disodium) Tablets, 1.1 gm

APPLICANT: Salix Pharmaceuticals, Inc.

BACKGROUND: This NDA is for a new formulation and strength of the active moiety, balsalazide disodium. Balsalazide disodium is currently marketed by Salix as Colazal Capsules, 750 mg. Salix has proposed a new tradename, Giazio, for this formulation, and have identified the indication as for the treatment of mildly to moderately active ulcerative colitis in patients 18 years of age and older.

ATTENDEES:

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	Fathia Gibril
Secondary Medical:	
Statistical:	Mike Welch
Pharmacology:	Ke Zhang
Statistical Pharmacology:	
Chemistry:	Maria Ysern
Environmental Assessment (if needed):	
Biopharmaceutical:	Jane Bai
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
OPS:	
Regulatory Project Management:	Kristen Everett
Other Consults:	

Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL FILE REFUSE TO FILE

- Clinical site audit(s) needed? YES NO
If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

- Biopharm. study site audits(s) needed? YES NO

PHARMACOLOGY/TOX N/A FILE REFUSE TO FILE

- GLP audit needed? YES NO

CHEMISTRY FILE REFUSE TO FILE

- Establishment(s) ready for inspection? YES NO

- Sterile product? YES NO

If yes, was microbiology consulted for validation of sterilization? YES NO

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. Convey document filing issues/no filing issues to applicant by Day 74.

Kristen Everett
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

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

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

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

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

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

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

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

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

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

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

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

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) YES NO

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product? YES NO

If "Yes" contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.
- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES NO

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

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

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

If “No,” to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

If “Yes,” to (c), proceed to question 7.

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE’s Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

If “No,” to (c), list the pharmaceutical alternative(s) and contact your ODE’s Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES NO

If “No,” skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”).

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES NO

11. Is the application for a duplicate of a listed drug whose only difference is YES NO

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES NO

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

- Not applicable (e.g., solely based on published literature. See question # 7)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES NO

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A YES NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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

/s/

Kristen Everett
4/17/2008 02:45:46 PM
CSO

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: 4/1/2008

TO: Kristen Everett, Regulatory Project Manager
Fathia Gibril, M.D., Medical Officer

FROM: Khairy Malek, M.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: # 22-205

APPLICANT: Salix Pharmaceuticals, Inc.

DRUG: Giazio (balsalazide disodium) tablets 1100 mg

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATIONS: 1. Treatment of mild to moderate Ulcerative Colitis

CONSULTATION REQUEST DATE: October 18, 2007

DIVISION ACTION GOAL DATE: May 16, 2008

PDUFA DATE: May 16, 2008

1. BACKGROUND:

Balsalazide disodium is a pro-drug of mesalamine that is approved in the US for the treatment of mildly to moderately active ulcerative colitis. The regimen used is three

capsules 3 times a day. The new NDA is a new tablet formulation and dosing regimen to provide balsalazide disodium in a more convenient dosing regimen consisting of three tablet twice daily for the treatment of mildly to moderately active ulcerative colitis. The current protocol BZUC3002 is intended to assess the clinical safety and effectiveness of the more convenient regimen compared to placebo for this purpose.

The sites inspected were chosen because of the number of subjects at these sites.

There was one protocol used at the 3 sites which is protocol BZUC3002, entitled: “A Multicenter, Randomized, Double-Blind Placebo-Controlled Trial to Evaluate the Safety and Efficacy of a New Tablet Formulation and Dosing Regimen of Balsalazide Disodium 3.3 g BID Versus Placebo in Mildly to Moderately Active Ulcerative Colitis”

II. RESULTS (by Site):

Name of CI	City and State	Protocol	Inspection Dates	Final Classification
Dennis Riff, M.D.	Anaheim, CA	BZUC3002	1/24-2/4/08	VAI
Shahriar Sedghi, M.D.	Macon, GA	Same	1/22/08	VAI
Mark Lamet, M.D.	Hollywood, FL	Same	2/5-2/8/08	NAI

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

Pending = Preliminary classification based on information in 483; EIR has not been received from the field and complete review of EIR is pending.

1. Dennis Riff, M.D.-Site #216, Anaheim, CA

- What was inspected: The field investigator reviewed the records of all subjects in the trial (21 subjects). There was no limitation to the inspection.
- General observations/commentary:
Review of the records revealed protocol violations:

Two subjects (#02 and 11) had their flexible sigmoidoscopy/colonoscopy done 15 and 12 days, respectively, before randomization instead of the 3-7 day period allowed by the protocol.

Subject #12’s stool specimen required at screening to rule out ova, parasites and C. difficile was described as improper by the lab. The subject was enrolled without repeating the test.

Subject #18 was enrolled while using 325 mg ASA. The upper limit of the allowed dose is 162 mg.

Quality of life questionnaire required by the protocol to be completed before Visit 1, at Visit 3 and end of the study was not always completed as required. Subjects #5, 13, 14 and 16 missed one of the questionnaires.

These violations will not affect the validity of the data, and the data from this site can be used in support of the NDA

2. Shahriar Sedghi, M.D.-Site 547, Macon, GA

- What was inspected: At this site 13 subjects were randomized and 9 subjects completed the study. The 4 discontinued subjects: one placebo subject (#26) was non-compliant; one placebo subject (#19) was discontinued due to an adverse event (AE), 2 Giazio subjects (#5 and 15) were discontinued due to lack of efficacy. The field investigator reviewed the records of all subjects in the study. There was no limitation to the inspection.
- General Observations/Commentary:
The inspection revealed one protocol violation: Two subjects on the study took prohibited medications. Subject #13 took Colazal, and #25 took Pepto-Bismol.

These violations would not affect the validity of the data. The data from this site can be used in support of the NDA.

3. Mark Lamet, M.D.-Site #675-Hollywood, FL.

- What was inspected: At this site 13 subjects were randomized and 8 subjects completed the study. The field investigator reviewed the records of all subjects in the study. There were 5 early withdrawals; 4 withdrew because of low creatinine clearance, and one withdrew due to an AE. Five out of 8 had clinical improvement, 4 in the Giazio group and 1 in the placebo group.
- General Observations/Commentary:

The inspection revealed no violation of the federal regulations.

The data from this study can be used in support of the NDA.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from these 3 sites can be used in support of the NDA.

{ See appended electronic signature page }

Khairy Malek, M.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

Constance Lewin, M.D., M.P.H.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations
Office of Compliance

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

/s/

Constance Lewin

4/3/2008 01:55:47 PM

MEDICAL OFFICER

Entered into DFS on behalf of Dr. Khairy Malek.

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Gastroenterology Products

Application Number: 22-205

Name of Drug: GIAZO (balsalazide disodium) tablets, 1.1 g

Applicant: Salix Pharmaceuticals, Inc.

Material Reviewed:

Submission Date(s): July 16, 2007
November 16, 2007

Receipt Date(s): July 18, 2007
November 16, 2007

Submission Date of Structure Product Labeling (SPL): July 16, 2007

Type of Labeling Reviewed: Word

Background and Summary

Salix Pharmaceuticals, Inc., submitted NDA 22-205 on July 16, 2007. The proposed indication for this NDA is the treatment of mildly to moderately active ulcerative colitis in patients 18 years of age and older.

The labeling text for this pending NDA was submitted in Structured Product Labeling (SPL) format, along with the proposed package insert in Physician's Labeling Rule format (PLR) using the approved format of Colazal on July 16, 2007. These were submitted along with the original NDA. The 4-month Safety Update submitted November 16, 2007 contained updated labeling information but no updates to the SPL format.

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in your proposed labeling.

1. Highlights

- a **Initial U.S. Approval** - The verbatim statement “Initial U.S. Approval” followed by the four-digit year in which FDA initially approved a new molecular entity...
 - The active ingredient balsalazide disodium was first approved as Colazal NDA 20-610 on July 18, 2000¹.
- b Font is currently in 10 point font but must be in 8 point font.
 - Highlights, excluding the boxed warning, must be limited in length to one-half page (e.g., would fit on one-half page if printed on 8.5” x 11 paper, single spaced, 8 point type with ½ inch margins on all sides, in a two-column format)
- c Inconsistent bulleting under headings. Because each heading only contains one item, no bullets are needed; either choose to bullet every subheading or remove bullets.
 - If there are multiple subheadings, each subheading must be preceded by a bullet point. [Best Practices].

2. Table of Contents

- Change 13.2 subsection title from (b)(4) to “Animal Toxicology and/or Pharmacology”.

3. Full Prescribing Information

- Remove bold from body systems in subsection 6.1, and from subsection 16. All headings and subheadings must be highlighted by bold type that prominently distinguishes the headings and subheadings from other labeling information. Therefore, for other labeling information, use bold type sparingly; and use another method for emphasis such as italics or underline. [Best Practices].
- In subsection 6.1 Clinical Studies Experience, include the following statement (or appropriate modification) preceding presentation of adverse reactions from clinical trials: “Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.” (Word copy only; SPL format contains this statement).

¹ http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=020610&TABLE1=OB_Rx

Recommendations

Please address the identified deficiencies/issues and re-submit labeling by February 22, 2008. This updated version of labeling will be used for further labeling discussions.

Heather Buck
Regulatory Project Manager
Division of Gastroenterology Products

Supervisory Comment/Concurrence:

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products

Drafted: HB 1/24/08

Revised/Initialed: BKS 1/30/08

Finalized: HB 1/31/08

Filename: CSO Labeling Review Template (updated 1-16-07).doc

RPM LABELING REVIEW

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

/s/

Heather G Buck
1/31/2008 04:26:49 PM
CSO

Brian Strongin
1/31/2008 04:57:12 PM
CSO

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Pharmacokinetics of balsalazide, mesalamine and N-acetyl aminosalicylic acid should be evaluated in patients with and without concomitant antibiotics administration. The regimen for the selected antibiotics should be adequate to result in alteration of gut-flora.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: A placebo-controlled clinical trial in female patients with active ulcerative colitis to assess the efficacy of an eight week course of Giazio therapy for the treatment of active disease in this patient population.

PMR/PMC Schedule Milestones: Final protocol Submission Date: 01/2013
Study/Clinical trial Completion Date: 06/2015
Final Report Submission Date: 12/2012
Other: _____

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

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Since Giazio is approved only for male patients with mildly to moderately active UC and women are significantly represented among all patients with UC, we request a placebo-controlled clinical trial in female UC patients to assess effectiveness of Giazio in the treatment of this patient population.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Review of BZUC3002, the one placebo-controlled study, demonstrated efficacy in men only as female patients treated with placebo responded better than those treated with Giazio. The outcome of this additional trial would help to address the effectiveness of Giazio in the treatment of women with UC.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A placebo-controlled clinical trial in female UC patients to assess effectiveness of Giazio in the treatment of this patient population. The design of this trial could include three treatment arms for comparison: Giazio, the Applicant's marketed product Colazal, and placebo. We recommend an eight week course of treatment.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
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 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
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- Other
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5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
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PMR/PMC Development Coordinator:

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(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: NDA 22205/Giazo (balsalazide disodium)

PMR/PMC Description: A single- and repeated-dose pharmacodynamics and pharmacokinetics trial of Giazo tablets administered orally to pediatric patients ages 12 years to less than 17 years with mildly to moderately active ulcerative colitis to support pediatric labeling

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>06/2013</u>
	Study/Trial Completion:	<u>06/2015</u>
	Final Report Submission:	<u>12/2015</u>
	Other:	<u>MM/DD/YYYY</u>

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

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
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- **Which regulation?**

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Continuation of Question 4

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PMR/PMC Development Coordinator:

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

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