

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022205Orig1s000

OTHER ACTION LETTER(s)



NDA 022205

COMPLETE RESPONSE

Salix Pharmaceuticals, Inc.
Attention: Benjamin Burgin, RAC
Senior Manager, Regulatory Affairs
1700 Perimeter Park Drive
Morrisville, NC 27560

Dear Mr. Burgin:

Please refer to your new drug application (NDA) dated July 16, 2007, received July 17, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for GIAZO (balsalazide disodium) tablets, 1.1 g.

We acknowledge receipt of your submissions dated August 16, 2007, September 21, 2007, November 16, 2007, November 21, 2007, November 30, 2007, December 22, 2007, February 15, 2008, February 20, 2008, March 6, 2008, March 10, 2008, March 20, 2008, March 24, 2008, May 19, 2008, June 30, 2008, August 19, 2008, September 8, 2008, September 19, 2008, October 28, 2008, November 11, 2008, January 7, 2009, February 3, 2009, April 7, 2009, October 26, 2009, January 21, 2010, February 16, 2010, April 2, 2010, April 6, 2010, April 9, 2010, April 14, 2010, April 16, 2010, April 21, 2010 and April 26, 2010.

The October 26, 2009, submission constituted a complete response to our December 22, 2008, action letter.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

FACILITY INSPECTIONS

During a recent inspection of the Nexgen Pharma Inc. manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

LABELING

We note that the carton and container labeling submitted on April 14, 2010, and the package insert submitted on April 26, 2010, are acceptable; however, we reserve final comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(1)(1)(i)] in structured product

labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Roland Girardet, Regulatory Project Manager, at (301) 796- 3827.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and research

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/

DONNA J GRIEBEL

04/27/2010



NDA 22-205

COMPLETE RESPONSE

Salix Pharmaceuticals, Inc.
ATTENTION: David Dobrowski
Director, Regulatory Affairs
1700 Perimeter Park Drive
Morrisville, NC 27560

Dear Mr. Dobrowski:

Please refer to your new drug application (NDA) dated July 16, 2007, received July 17, 2007, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Balsalazide Disodium Tablets, 1100 mg.

We acknowledge receipt of your amendments dated August 16, September 21, November 16, November 21, November 30, and December 22, 2007, and February 15, February 20, March 6, March 10, March 20, March 24, June 30, August 19, October 28, and November 11, 2008.

The June 30, 2008, amendment constituted a complete response to our May 16, 2008, action letter.

We also acknowledge receipt of your amendment dated September 19, 2008. This submission was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

In our Approvable letter dated May 16, 2008, responding to your original submission of NDA 22-205, we determined that your single placebo-controlled study, Study BZUC3002, was inadequate as a single study to support effectiveness of balsalazide disodium (BD) tablets, because it did not demonstrate a statistically persuasive finding of treatment effect and there was a lack of consistency of treatment effect between men and women. The observed efficacy of BD tablets in the study was largely driven by a subpopulation, namely, males. When compared to placebo response rates, the treatment effect of BD tablet therapy was superior to placebo in male patients (37% difference, $p < 0.001$), but the treatment effect was clinically and statistically insignificant in females (-4% difference, (b) (4)). As stated in the Approvable letter, future approval of BD tablets for the treatment of mildly to moderately active UC would be dependent upon the review of an additional adequate and well-controlled study that would demonstrate evidence of effectiveness.

In response to the Approvable action, you submitted a Complete Response for NDA 22-205 with the additional Phase 3, active-comparator study, Study BZUC3003. Upon review of this study, we conclude that several deficiencies still remain, and the data submitted are inadequate for an Approval action at this time. The deficiencies are as follows:

CLINICAL AND STATISTICAL

1. Inadequate Justification of the (b) (4) Non-Inferiority for Study BZUC3003

Your non-inferiority (NI) margin was not appropriately justified. In support of the (b) (4) NI margin, you cite input from clinicians with experience in the treatment of active ulcerative colitis (UC) and make reference to several studies in the published literature. You conducted a meta-analysis of 16 placebo-controlled trials (between years 1967 to 1989), of which 11 studies were for induction in UC. All these studies included patients with mildly to severely active UC.

However, we do not agree that all these studies support your choice of the (b) (4) NI margin. The choice of NI margin should be based on data from placebo-controlled studies of the active control (Asacol 2.4 g/day) in the same patient population and with the same endpoints as currently being studied. Only one study (Sninsky et al.) of the 11 you cited exemplifies the appropriate choice of a reference trial for NI margin assessment as outlined in the ICH E10 Guidance. Although not identical in efficacy endpoint selection, Study BZUC3003 and the Sninsky article used analogous composite disease activity indices for efficacy determination.

The Sninsky article reports that the six-week combined treatment outcomes of patients classified as “in remission” or “improved” were: 10/44 (23%) patients in the Asacol 2.4 g/day treatment arm and 21/43 (49%) patients in the placebo treatment arm achieved clinical improvement (an endpoint similar to the primary efficacy endpoint assessment in Study BZUC3003). Thus, a treatment effect for Asacol (Asacol treatment response minus placebo treatment response) can be estimated as 26%, with a 95% Confidence Interval of (6%, 45%). According to the ICH E10 Guidance, “The margin chosen for a non-inferiority trial cannot be greater than the *smallest effect size that the active drug would be reliably expected to have* compared with placebo in the setting of the planned trial.” Following Agency statistical practice, that *smallest* effect is estimated as 50% of the lower confidence bound, which would be 3% based on the Sninsky study. Thus, as judged from your reference literature, the study that adheres acceptably to the ICH E10 criteria results in a substantially lower NI margin (3%) than the margin (b) (4) used in your study. The choice of a 3% NI margin is also supported by a study used for Agency approval of Asacol.

2. Inability of the Results of Study BZUC3003 to Address the Deficiencies of the May 16, 2008, Approvable Letter

With the NI margin taken to be 3%, Study BZUC3003 fails to demonstrate non-inferiority of BD tablets compared to Asacol. Therefore, Study BZUC3003 cannot be considered to provide additional evidence of the efficacy of BD tablets. Because Study BZUC3003 fails to provide evidence of efficacy, a gender sub-analysis of this study does not contribute information to resolve the question about the differences between men and women regarding the efficacy of BD tablets. Further, without a placebo comparison, this study cannot provide reliable estimates of the treatment effect, and, consequently, cannot convincingly address questions about the difference in treatment effect between men and women. Therefore, the deficiencies identified in the May 16, 2008, Approvable letter have not been addressed by Study BZUC3003 and your Complete Response submission, and those deficiencies remain to be resolved.

Future approval of BD tablets for the treatment of mildly to moderately active UC will be dependent upon the review of additional efficacy data from an adequate and well-controlled study that demonstrates substantial evidence of effectiveness and has the ability to resolve the questions about differences between men and women regarding the treatment effect of BD tablets in active UC. Before initiating such a study, we recommend that you obtain input from us regarding the study design.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
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3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
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 5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
 6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
 7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
 8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (<http://www.fda.gov/cder/guidance/2125fnl.htm>).

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Roland Girardet, Regulatory Project Manager, at (301) 796-3827.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.

Director

Division of Gastroenterology Products

Office of Drug Evaluation III

Center for Drug Evaluation and Research

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/s/

Donna Griebel

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NDA 22-205

Salix Pharmaceuticals, Inc.
Attention: Benjamin Burgin, RAC
Senior Manager, Regulatory Affairs
1700 Perimeter Park Drive
Morrisville, NC 27560

Dear Mr. Burgin:

Please refer to your new drug application (NDA) dated July 16, 2007, received July 17, 2007, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Giazio (balsalazide disodium) Tablets, 1100 mg.

We acknowledge receipt of your submissions dated August 16, September 21, November 16, November 21, November 30, and December 22, 2007, and February 15, February 20, March 6, March 10, March 20, and March 24, 2008.

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to resolve the following:

Your placebo controlled study is not adequate as a single study to support the effectiveness of balsalazide tablets for treatment of mildly to moderately active ulcerative colitis because it did not demonstrate a statistically persuasive finding of treatment effect and because there was a lack of consistency of treatment effect between men and women, subsets that were equally represented in this study.

The issuance of an approval is dependent upon the review of an additional adequate and well controlled study that demonstrates that balsalazide tablets are effective in treating mildly to moderately active ulcerative colitis.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
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 6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
 7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with the Division of Gastroenterology Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Heather Buck, Regulatory Project Manager, at (301) 796-1413.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Division Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Donna Griebel

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