CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-610

APPROVAL LETTER

NDA 20-610

Salix Pharmaceuticals, Inc.
Attention: Lorin Johnson, Ph.D.
Sr. Vice President Development and Chief Scientific Officer
9600 Bayshore Road, Suite 205
Palo Alto, CA 94303

JUL 18 2000

Dear Dr. Johnson:

Please refer to your new drug application (NDA) dated June 23, 1997, received June 23, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Colazal (balsalazide disodium) Capsules.

We acknowledge receipt of your submissions dated April 28, May 23, June 21, and July 10, 2000. Your submission of May 23, 2000 constituted a complete response to our March 24, 2000 action letter.

We also refer to the June 21, 2000 teleconference in which you were informed that your proposed tradename, Colazal, is acceptable.

This new drug application provides for the use of Colazal (balsalazide disodium) Capsules for the treatment of mildly to moderately active ulcerative colitis.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) with the following exception: Please modify Figure 1 in the package insert to include both the p values and sample sizes from the ITT-2 analysis (at eight weeks). This request was conveyed to you in our July 10, 2000 teleconference. In addition, the FPL must be identical to the immediate container and carton labels submitted July 10, 2000. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternately, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 20-610." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments, in response to our June 15, 1998 letter, specified in your submissions dated October 13, 1999 and February 28, 2000. These commitments, along with any completion dates agreed upon, are listed below.

1. You have agreed to conduct a food-effect study in healthy subjects to assess the effect of food on the absorption of balsalazide.

2. You have agreed to conduct a multiple dose PK study. The final study report will be submitted to [redacted] by the fourth quarter of 2000.

3. In the event that balsalazide plasma levels higher than 10 µg/ml are observed during the course of the multiple-dose PK study, you have committed to conducting an additional *in vitro* plasma binding study to cover the observed concentration range.

4. Regarding requested *in vitro* drug interaction studies, you have committed to conducting *in vitro* drug interaction studies to evaluate the potential for commonly co-administered drugs to interact with balsalazide.

5. With respect to requested *in vivo* drug interaction studies, based on the results of the *in vitro* drug interaction studies, you have agreed to conduct *in vivo* drug interaction studies in appropriate animal species and evaluate the PK (as deemed necessary). Based on the outcome of these studies, you will discuss with the Agency the need for any additional studies.

6. Regarding the requested renal impairment study, you have agreed to compare the PK data from the multiple-dose PK study to that obtained from literature on patients with varying degrees of renal impairment that are receiving mesalamine or related prodrugs. Based on the outcome of the analysis of the multiple-dose PK study, it will be decided whether an additional study is needed to assess PK of balsalazide in patients with varying degrees of renal impairment.

7. Regarding the hepatic impairment study, you have agreed to evaluate the PK of balsalazide in hepatically-impaired patients if clinically-relevant results are obtained in the renal impairment study.

8. You have agreed to conduct a study in the combined pediatric population of children and adolescents (2-18 years) to characterize PK of balsalazide in this age group. Please note that this will not fulfill the requirements of 21 CFR 314.55.

9. You have agreed to reanalyze the data from study GLY01/93 to examine the effect of gender on the disposition of balsalazide.

In addition, you have agreed to submit the study protocols prior to study initiation. Furthermore, the final protocols to for studies identified in items 1, 3, 4, and 8 will be submitted to the appropriate IND within one year of receiving the approval letter for NDA 20-610.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet any of your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632).

As noted above, you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until August 1, 2002. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR)

in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Gastrointestinal and Coagulation Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

mm 7/18/00

/S/

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

cc:
Archival NDA 20-610
HFD-180/Div. Files
HFD-180/M.McNeil
HFD-180/Gallo-Torres
HFD-180/Prizont
HFD-180/Talarico
HFD-180/Aurecchia
HFD-180/Zhou
HFD-180/Ysern
HFD-180/Choudary
HFD-715/Tsong
HFD-715/Permutt
HFD-870/Al-Fayoumi
HFD-870/Doddapaneni
HFD-440/Dempsey
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-103/ADRA (with labeling)
HFD-102/Post-Marketing PM
HFD-104/Peds/V.Kao (with labeling)
HFD-104/Peds/T.Crescenzi (with labeling)
HFD-42/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-095/DDMS-IMT (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE
Drafted by: mm/July 11, 2000
Initialed by: SAl-Fayoumi 7/11/00
SAurecchia 7/11/00
LTalarico 7/11/00
BCollier 7/13/00
FHoun 7/18/00
final: July 18, 2000
filename: c:\mydocuments\cso\n\20610007-ap.doc
APPROVAL (AP) (with Phase 4 Commitments)

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-610

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-610

Salix Pharmaceuticals, Inc.
Attention: Lorin Johnson
3600 West Bayshore Road
Suite 205
Palo Alto, CA 94303

MAR 24 2000

Dear Dr. Johnson:

Please refer to your new drug application (NDA) dated June 23, 1997, received June 23, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for balsalazide disodium capsules.

We acknowledge receipt of your submissions dated June 18, June 26, August 11, October 16, October 27, November 20, 1998, February 1, March 29, April 14, August 6, September 13, September 23, October 13, October 20, 1999, January 13, February 10, February 11, February 25, February 28, February 29, March 1, March 2, and March 17, 2000. Your submission of September 23, 1999 constituted a complete response to our June 15, 1998 action letter.

We also refer to your submission dated February 28, 2000, which contains your response to our letters dated June 15, 1998 and September 28, 1999, requesting a commitment for Phase 4 studies. This submission has not been reviewed in the current review cycle. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

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

Submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert, immediate container and carton labels).

Please submit 20 copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, the proposed tradename '——' has been found unacceptable. Please submit another proposed tradename for consideration. '——' was found unacceptable for the following reasons:

1. '——' is similar in sound alike and look alike to "Pentasa", another drug in the same therapeutic class. Both drugs are capsules.

2. '——' and "Pentasa" are of similar character length. Both end in "-asa" and each contain an upstroke letter in the middle of the name.

3. '——' and "Pentasa" 250 mg are similar when scripted.

The above similarities in names could lead to potential medication errors.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. 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.

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 Melodi McNeil, R.Ph., Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

/S/

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 20-610
HFD-180/Div. Files
HFD-180/A.Kacuba
HFD-180/M.McNeil
HFD-180/L.Talarico
HFD-180/S.Aurecchia
HFD-180/H.Gallo-Torres
HFD-180/R.Prizont
HFD-180/L.Zhou
HFD-180/M.Ysern
HFD-180/J.Choudary
HFD-180/K.Zhang
HFD-870/S.Doddapaneni
HFD-870/S.Al-Fayoumi
HFD-103/F.Houn
HFD-103/ADRA
HFD-002/ORM
HFD-40/DDMAC (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: A.Kacuba/March 5, 2000
Initialed by: H.Gallo-Torres/March 7, 2000
Initialed by: L.Talarico/March 8, 2000, March 20, 2000
Initialed by: B.Collier/March 13, 2000
Initialed by: F.Houn/March 17, 2000, March 22, 2000
Final: AK/March 22, 2000 AK 3-22-2000
Filename: c:\mydocumewnts\20610-2000-AE-letter.doc

APPROVABLE (AE)

**APPEARS THIS WAY
ON ORIGINAL**

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