CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-610

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

This firm has requested and been granted a categorical exclusion from the requirement for an EA.

/S/ 5/22/98
Melodi McNeil, Regulatory Health Project Manager

APPEARS THIS WAY
ON ORIGINAL

Number of Pages Redacted 98

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Confidential,
Commercial Information

NDA 20-610

Salix Pharmaceuticals, Inc.
Attention: Jim Shook, Ph.D.
9600 Bayshore Road, Suite 205
Palo Alto, CA 94303

JUN 15 1998

Dear Dr. Shook:

Please refer to your new drug application 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 20, August 1, 4, 6, 8, and 18; September 3, 5, and 8; October 10, and 23; November 7, 11, and 24; December 10 and 17, 1997; January 16, 23, and 29; February 9, 10, 18, and 20; March 4, 11, 18, and 30; and April 30, 1998. The User Fee goal date for this application is June 23, 1998.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to provide the following information:

1. Chemistry, Manufacturing, and Controls:

   A. Drug Substance:

      1. Please provide SOPs from the drug substance manufacturers that will ensure adequate equipment cleaning and preparation. This is particularly important for the final purification step(s).

      2. Tighter residual solvent specifications must be established, and we recommend that equivalent drying processes for the drug substance be established for each manufacturer in order to consistently meet the tightened specifications. Variations in the residual solvent content have been shown to affect the drug product manufacturing.

      3. A single drug substance reference standard must be established and used for release and acceptance testing of Balsalazide disodium dihydrate, and any secondary standards need to be qualified against the primary one.

      4. A particle size distribution specification must be established, in addition to the tapped bulk density specification. Also establish a validated sampling technique.

B. Drug Product:

1. The methods for roller compaction ———) and size reduction have to be carefully validated in order to assure reproducible results. Additional controls need to be established for the process, and ranges for the chilsonator operating parameters must be established instead of "approximate" values.

2. Update and submit the final methods validation volumes.

3. It is noted that some capsules have been reported as becoming brittle or faded after 6 months on stability at different temperatures (Lots N6272B01, N6272B02, N6289B01, P6272F02, P6272F01, see Vol. 1.4, pages 152 to 161). Provide an explanation for these observations and submit a proposed corrective action plan to eliminate these problems.

4. ——— ——— ——— . have been reviewed as authorized, and have been found deficient. Deficiencies have been communicated to the DMF holders.

2. Biopharmaceutics:

Insufficient data was provided to assess the systemic exposure of the parent drug and its metabolites for the to-be-marketed formulation as recommended for use in the proposed labeling. Please conduct a multiple-dose pharmacokinetic study in the target patient population using the to-be-marketed formulation from a representative production size batch of the drug. The drug should be administered as recommended in the proposed package insert. All moieties of the drug should be analyzed using a precise and accurate validated assay.

In addition, it will be necessary for you to submit final printed labeling (FPL) [package insert, carton, and immediate container labels] identical in content to the enclosed marked-up draft labeling. Please submit 20 copies of the final printed labeling, ten of which are individually mounted on heavy-weight paper or similar material.

Please refer to the October 3, 1997 letter in which you were informed that your original proposed trade name, Colazide, was unacceptable for use. In a March 11, 1998 response, you proposed (among others) the trade name — In a May 20, 1998 telephone conversation between Ms. Mary Ketchum, Regulatory Affairs, of your firm, and Ms. Melodi McNeil, Regulatory Health Project Manager, of this Agency, you were informed that the Agency considers ~

acceptable for use. The FPL described above should reflect [redacted] as the trade name. Alternatively, you may request that the Agency reconsider previously proposed trade names or submit other trade names for Agency review.

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

During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the inspector. A satisfactory inspection of the facility which encapsulates the drug product, Anabolic Laboratories, Inc., 17802 Gillette Avenue, Irvine, CA 92714, will be required before this application may be approved. Please notify us in writing when this facility is ready for reinspection.

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:

1. Retabulate 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 vs now will certainly facilitate review.

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

3. Provide details of any significant changes or findings, if any.

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

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

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. 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.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print.

Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

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 such action FDA may take action to withdraw the application.

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

Available stability data should be provided, including statistical analysis. To date, sufficient stability data has been provided to justify an 18-month expiry in both the 40cc and 600cc HDPE bottles with CRC caps.

If you have any questions, please contact Melodi McNeil, Regulatory Health Project Manager, at (301) 443-0483.

Sincerely yours,

/S/ MD

Paula Botstein, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Draft Labeling

cc:
Original NDA 20-610
HFD-180/Div. Files
HFD-002/ORM
HFD-95/DDM-DIAB
HFD-180/M.McNeil
HFD-180/Choudary
HFD-180/Duffy
HFD-180/Ysern
HFD-180/Gallo-Torres
HFD-180/Prizont
HFD-870/Chen
HFD-870/Hunt
HFD-870/Cronenberger
HFD-720/Sankoh
HFD-720/Tsong

HFD-103/Office Director
DISTRICT OFFICE
HFD-40/DDMAC (with draft labeling)

Drafted by: mm/May 22, 1998/c:\wpfiles\cso\n\20610805.ae
Initialed by: LTalarico 5/26/98
KJohnson 5/27/98
JChoudary 5/28/98
MYsern (for EDuffy) 5/28/98
SKoepke 6/1/98
BCollier 6/1/98
PBotstein 6/4/98

Final: June 11, 1998

APPROVABLE (AE)

Number of Pages Redacted 15

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Draft Labeling
(not releasable)

Pharmaceuticals, Ltd.

10/20/99
HC-T

ORIG
(POST APPROVAL COMMITMENT)
CC

CENTER FOR DRUG
RECD
OCT 14 1999
HFD-180
EVALUATION AND RESEARCH

ber 13, 1999

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
HFD-180, Room 6B-24
5600 Fishers Lane
Rockville, MD 20857

Subject: Response to FDA Letter dated September 28, 1999
Post Approval Commitment

Dear Dr. Talarico,

Please refer your letter dated September 28, 1999 in response to Salix Pharmaceuticals, Inc.'s meeting request dated September 13, 1999, concerning conducting the multiple dose pharmacokinetic study, requested in the June 15, 1999 Approvable Letter, as a post-approval commitment. Attached is the requested commitment.

ere are any questions concerning this submission, please do not hesitate to contact d Kashiwase at (650) 849-5908 or by facsimile to (650) 856-1555.

Sincerely,

Lorin Johnson, Ph.D.
Vice President Research and Development
Salix Pharmaceuticals, Inc

3600 W. Bayshore Rd., Suite 205, Palo Alto, CA 94303 USA T. 650.849.5900 F. 650.856.1555

S A L I X
Pharmaceuticals, Ltd.

Commitment Statement, NDA 20-610, For Multiple Dose Pharmacokinetic Study

Please refer to Salix Pharmaceuticals, Inc.'s request dated September 13, 1999 and the FDAs response date September 28, 1999 (attached) for NDA 20-610 [redacted] (balsalazide disodium).

Salix Pharmaceuticals, Inc. agrees to the following post-approval commitments with respect to the multiple dose pharmacokinetic study (Salix study number CP109801, refer to [redacted] Serials 093 and 096) requested by the FDA in the June 15, 1998 Approvable Letter, please refer specifically to Item 2 of the Approvable Letter, and the FDA letter dated September 28, 1999.

1. Patient enrollment will be initiated in November 1999.
2. A final study report will be submitted to the FDA, under [redacted] with a letter of cross-reference submitted to NDA 20-610, by the fourth quarter of 2000.

Lorin Johnson, Ph.D.
Vice President, Research and Development
Salix Pharmaceuticals, Inc

13 Oct 1999
Date

3600 W. Bayshore Rd., Suite 205, Palo Alto, CA 94303 USA T. 650.849.5900 F. 650.856.1555

SUMMARY OF PHASE IV COMMITMENTS

In an NDA amendment dated February 28, 2000 Salix Pharmaceuticals, Inc. responded to FDAs June 15, 1998 request for post-approval (Phase IV) studies. A copy of the Salix Pharmaceutical, Inc.'s response is attached. Salix Pharmaceuticals, Inc. is certifying that the attached copies are true copies of the February 28, 2000 submission.

In the June 15, 1998 Approvable Letter, FDA requested that Salix Pharmaceuticals, Inc. conduct a multiple dose pharmacokinetic study in the intended patient population. In a amendment dated September 13, 1999, Salix Pharmaceuticals, Inc. requested a meeting with the FDA to discuss our proposal to make this a post-approval study requirement. In response to this request, FDA in a letter dated September 28, 1999, stated that a meeting was not necessary. Additionally, the FDA had agreed to Salix Pharmaceuticals, Inc. proposal to identify the multiple dose pharmacokinetic study as a post-approval study requirement and requested that such a commitment be submitted by Salix Pharmaceuticals, Inc. In an amendment dated October 13, 1999, Salix Pharmaceuticals, Inc. submitted the commitment requested by the FDA. Attached are copies, certified by Salix Pharmaceuticals, Inc. as true copies, of the September 28, 1999 FDA request and the October 13, 1999 commitment letter from Salix Pharmaceuticals, Inc.

The current status, as of April 18, 2000, of the on-going multiple dose pharmacokinetic study in patients is summarized below:

Patient Status	Number of Patient
Planned enrollment:	25 patients (to obtain 20 evaluable patients)
Number of patients enrolled:	13
Number of screen failures:	1
Number of patients on-going:	1
Number of patients completed:	9
Number of patients discontinued:	2
Reasons for discontinuation:	1 patient: Worsening of ulcerative colitis
	1 patient: Use of prohibited concommitant medication

APPEARS THIS WAY
ON ORIGINAL

Commitment Statement, NDA 20-610, For Multiple Dose Pharmacokinetic Study

Please refer to Salix Pharmaceuticals, Inc.'s request dated September 13, 1999 and the FDAs response date September 28, 1999 (attached) for NDA 20-610 —— (balsalazide disodium).

Salix Pharmaceuticals, Inc. agrees to the following post-approval commitments with respect to the multiple dose pharmacokinetic study (Salix study number CP109801, refer to ——, Serials 093 and 096) requested by the FDA in the June 15, 1998 Approvable Letter, please refer specifically to Item 2 of the Approvable Letter, and the FDA letter dated September 28, 1999.

1. Patient enrollment will be initiated in November 1999.
2. A final study report will be submitted to the FDA, under —— with a letter of cross-reference submitted to NDA 20-610, by the fourth quarter of 2000.

13 Oct 1999

Lorin Johnson, Ph.D.
Vice President, Research and Development
Salix Pharmaceuticals, Inc

Date

008

S A L I X
Pharmaceuticals, Ltd.

October 13, 1999

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
HFD-180, Room 6B-24
5600 Fishers Lane
Rockville, MD 20857

Subject: Response to FDA Letter dated September 28, 1999
Post Approval Commitment

Dear Dr. Talarico,

Please refer your letter dated September 28, 1999 in response to Salix Pharmaceuticals, Inc.'s meeting request dated September 13, 1999, concerning conducting the multiple dose pharmacokinetic study, requested in the June 15, 1999 Approvable Letter, as a post-approval commitment. Attached is the requested commitment.

If there are any questions concerning this submission, please do not hesitate to contact David Kashiwase at (650) 849-5908 or by facsimile to (650) 856-1555.

Sincerely,

Lorin Johnson, Ph.D.
Vice President Research and Development
Salix Pharmaceuticals, Inc

APPEARS THIS WAY
ON ORIGINAL

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3600 W. Bayshore Rd., Suite 205, Palo Alto, CA 94303 USA T. 650.849.5900 F. 650.856.1555

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Salix Pharmaceutical, Inc.	13 October 1999
TELEPHONE NO. *(Include Area Code)* (650) 849-5900	FACSIMILE (FAX) Number *(Include Area Code)* (650)846-1555
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 3600 West Bayshore Road, Suite 205, Palo Alto, CA 94303	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE: Not applicable

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-610

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Balasazide disodium	Colazide, Balasa

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
E-5[[4-[[2-carboxyethyl]amino]carbonyl]phenyl]azo]-2-hydroxybenzoic acid	BX 661

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Capsule	750 mg/capsule	Oral

(PROPOSED) INDICATION(S) FOR USE:
Treatment of mild to moderate active ulcerative colitis

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION: Response to FDA inquiry

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

ce

tance

Annabolic, Irvine, CA, USA: Drug product

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

006

EF

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbioblogy (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.5 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) Response to FDA inquiry

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: a willful false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
[signature]	Lorin Johnson, Ph.D., Vice President of Research	13 Oct 1999

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
3600 West Bayshore Road, Suite 205 Palo Alto/California 94303	(650) 849-5900

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

007

Please DO NOT RETURN this form to this address.

FORM FDA 356h (5/97)

COPY OF SALIX PHARMACEUTICALS, INC. SUBMISSION DATED FEBRUARY 28, 2000

APPEARS THIS WAY
ON ORIGINAL

FDA PHASE IV COMMITMENTS FOR NDA 20-610 (Balsalazide disodium)
(Refer to FDA Letter dated June 15, 1998)

Please refer to the FDA letter dated June 15, 1998 containing post-approval (Phase IV) studies requested by the FDA for NDA 20-610. The following outlines Salix Pharmaceuticals, Inc. written commitments concerning each of the Phase IV requests made by the FDA. As recommended by the FDA, Salix Pharmaceuticals, Inc. will submit protocols for review prior to study initiation. Salix Pharmaceuticals, Inc. will submit final protocols to ——— for the studies identified in Items 1, 2, 3, and 8, within one year of receiving the approval letter for NDA 20-610. For the potential studies identified in Items 4, 6, and 7, whose necessity are dependant upon the prior completion and analysis of other studies, Salix Pharmaceuticals, Inc. commits to working with the FDA with due diligence to complete a final protocol following mutual agreement between Salix Pharmaceuticals, Inc. and the FDA as to the need for such a study.

1. *Please assess the effect of food on the absorption of balsalazide.*

Salix Pharmaceuticals, Inc. agrees to conduct a pharmacokinetic study in healthy volunteers to assess the effect of food on the absorption of balsalazide. As recommended by the Agency, the design of this study will be in accordance with the current FDA draft guidance on Food-Effect Bioavailability and Bioequivalence Studies, October 1997, BP X.

2. *Please provide in vitro plasma protein-binding information for balsalazide, covering the relevant concentration range.*

An *in vitro* plasma protein-binding study was previously conducted using human plasma (^{14}C-Balsalazide: Absorption, distribution metabolism and excretion following oral and intravenous administration to rats, refer to original NDA Volume 1.009, pages 081 and 149, see Attachment 1 for copies of referenced pages). Protein binding was evaluated for balsalazide over a wide concentration range of ——— . These studies demonstrated that protein binding of balsalazide in human plasma is greater than 99% over the concentration range studied and the binding was not concentration dependent.

Currently, a multi-dose pharmacokinetic study with oral balsalazide is ongoing (Study CP109801). If the plasma levels of balsalazide in this multi-dose pharmacokinetic study are above 10 μg/mL, Salix Pharmaceuticals, Inc. agrees to conduct a similar *in vitro* plasma protein binding study with human plasma to cover the therapeutic concentration range.

3. *In vitro metabolism/balsalazide drug interaction studies are recommended. Please consult the "Guidance for Industry; Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies in vitro" when designing these experiments.*

Salix Pharmaceuticals, Inc. agrees to conduct *in vitro* metabolism/balsalazide interaction studies. In vitro drug interaction studies will be evaluated using representative drugs that are typically coadministered and/or concomitantly administered with balsalazide in ulcerative colitis patients. As recommended by the Agency, the design of this study will be in accordance with the FDA guidance document on Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro, April 1997, Clin 3.

4. *Please conduct in vivo drug interaction studies with antibiotics and other drugs that are likely to be routinely coadministered with balsalazide.*

Based on the results of the *in vitro* drug metabolism/drug interaction studies proposed in response to Item 3, above, Salix Pharmaceuticals, Inc. agrees to conduct *in vivo* drug interaction studies in an appropriate animal species and evaluate plasma pharmacokinetic or other parameters as deemed necessary. Based on results from these studies, Salix Pharmaceuticals, Inc. will discuss with the FDA the need to conduct any additional studies.

5. *Since balsalazide is largely metabolized via the kidney, we recommend that once the multiple-dose PK study outlined in the June 15, 1998 Approvable letter has been completed and analyzed, you compare the systemic exposure/pharmacokinetic data obtained from this study to that available in the literature for subjects with varying degrees of renal impairment. Literature subjects administered mesalamine, as well as mesalamine prodrugs, such as sulfasalazine and olsalazine are acceptable. Pharmacokinetic comparative analyses and simulations, if appropriate, should be carried out to assess the metabolic fate of balsalazide in all degrees of renal impairment and the results submitted to the Agency for analysis.*

Upon completion of the ongoing multi-dose pharmacokinetic study with oral balsalazide (Study CP109801), Salix Pharmaceuticals, Inc. agrees to compare the pharmacokinetic data from this study with data available in the literature for patients receiving mesalamine or related prodrugs with varying degrees of renal impairment and submit the results to the FDA.

6. *If the data analysis described in point 5 (above) indicates that significant differences exist between the pharmacokinetics of mesalamine in normal and renally-impaired subjects, a well-designed and well-controlled study examining the disposition of balsalazide in patients with varying degrees of renal impairment would be recommended. You are encouraged to consult the "Guidance for Industry; PK in Patients with Impaired Renal Function," FDA, CDER, May 1998.*

Based on the outcome of the analysis proposed under the response to Item 5, Salix Pharmaceuticals, Inc. agrees to discuss, in good faith, with the FDA the necessity for an additional pharmacokinetic study to evaluate plasma levels of balsalazide in subjects with impaired renal function. If an additional study is the outcome following mutual discussion between the FDA and Salix Pharmaceuticals, Inc., the design of that study will be in accordance with the current FDA guidance document on the Pharmacokinetics in Patients with Impaired Renal Function, May 1998, BP 3.

7. *Please conduct a study examining balsalazide disposition in hepatically impaired subjects.*

As outlined by the FDA, balsalazide is largely metabolized via the kidney (refer to Item 5, above). Additionally, clinical pharmacokinetic data to date indicates that the systemic exposure to balsalazide is limited. Thus, Salix Pharmaceuticals, Inc. believes that evaluation of the disposition of balsalazide in hepatically impaired subject is secondary to completion of the evaluation of balsalazide in patients with varying degrees of renal impairment. Salix Pharmaceuticals, Inc. therefore proposes to evaluate the disposition of balsalazide in hepatically impaired subjects only if clinically significant results are obtained in Item 5 and Item 6, above.

8. *Please provide data to support use in various pediatric patients age groups (infants [ages 1 month to 2 years], children [ages 2-12 years], and adolescents [ages 12-16 years]) for this compound. Such data might include dosing information, including pharmacokinetic data, safety information, and/or effectiveness data.*

With reference to data to support the use of balsalazide in various pediatric patients age groups, Salix Pharmaceuticals, Inc. reviewed the FDA recommendations contained in the List of Approved Drugs for which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population (Docket Number 98N-0056), dated May 20, 1998. In this document FDA identified children (2 – 12 years) and adolescents (12 - 16 years) as benefiting from pediatric study with mesalamine and mesalamine prodrugs (sulfasalazine and olsalazine). It is important to note that the FDA did not identify neonates (birth – 1 month) or infants (1 month – 2 years) as meeting the pediatric priority inclusion criteria.

Infants (½ month – 2 years)

Salix Pharmaceuticals, Inc. believes that the study of balsalazide in the infant patient population is not appropriate. The diagnosis of ulcerative colitis in infants less than 2 years of age is usually rare and uncommon. It is estimated that there may be less than 1000 cases of the disease definitively diagnosed in this age group.

Children (2 – 12 years) and Adolescents (12 – 16 years)

Salix Pharmaceuticals, Inc. proposes to conduct a combined study in a pediatric age population of 2 – 18 years (children and adolescents). Salix Pharmaceuticals, Inc. has extended the adolescent age range to 18 years since the original Phase III studies had an ≥18 year age requirement as an inclusion criteria. Since children are in a period of rapidly changing body size, the protocol will include an evaluation of dose based on body weight or body surface area.

In the adolescent age category, the gastrointestinal tract has achieved adult development and the body is close to adult weight and height. The median weight of either a male and female 12 year old is approximately 40 kilograms which is comfortably within the range of body weight enrolled in our clinical trials (25.4 Kg-131.0 Kg). The average weight of a 15 year old subject is approximately 55 kg and approximately 16% of subjects in our database are at or below this weight (refer to Table 1, below). Analysis of adverse events and limited efficacy data suggest that there is no correlation between weight and either safety or efficacy. In adolescents, the body weight and height is reasonably close to adult weight and height. Thus, an adult dose of balsalazide is considered appropriate in patients whose body weight overlaps that of lower range of patients dosed in previous studies whereas dosing data by weight for children will be necessary. Salix Pharmaceuticals, Inc. will develop additional protocol details and work with FDA in preparation of the study protocol.

Table 1 : Weight Distribution of Patients[a]

Weight Range (Kg)	Number of Patients		% of Total Count	Cumulative %
	Number in Range	Cumulative Number		
25.4 – 36.0	1	1	0.6%	0.6%
36.0 – 46.5	3	4	1.7%	2.3%
46.5 – 57.1	24	28	14.0%	16.3%
57.1 – 67.6	28	56	16.3%	32.6%
67.6 – 78.2	48	104	27.9%	60.5%
78.2 – 88.8	29	133	16.9%	77.3%
88.8 – 993.	23	156	13.4%	90.7%
99.3 – 109.9	9	165.	5.2%	95.9%
109.9 – 120.4	3	168	1.7%	97.7%
120.4 – 131.0	4	172	2.3%	100.0%

[a] Data from Studies CP099301 (n = 52), 57-3001 (n = 49), and CP069101 (n = 71).

Pediatric Wavier and Pediatric Exclusivity

Please also note, that it is the intent of Salix Pharmaceuticals, Inc. to request a partial pediatric wavier for the neonate (birth – 1 month) and infant (1 month – 2 years) age groups. Salix Pharmaceuticals, Inc. will also be interacting with the FDA concerning a request for Pediatric Exclusivity.

9. *Lastly, please reanalyze the data from Study #GLY01/93, entitled "Pharmacokinetic Study of Balsalazide Disodium (Colazide) in Patients with Ulcerative Colitis Receiving Long-Term Maintenance Treatment" to examine the effect of gender on the disposition of balsalazide, taking into account the influence of body weight.*

Salix Pharmaceuticals, Inc. agrees to reanalyze the data from Study GLY01/93 to examine the effect of gender on the disposition of balsalazide taking into account the influence of body weight.

NDA 20-610

Salix Pharmaceuticals, Inc.
Attention: Lorin Johnson, Ph.D.
9600 Bayshore Road, Suite 205
Palo Alto, CA 94303

SEP 2 8 1999

Dear Dr. Johnson:

We acknowledge receipt on September 14, 1999 of your September 13, 1999 correspondence requesting a meeting. You indicated that the purpose of the meeting was to propose that the multiple dose pharmacokinetic study, previously requested in the June 15, 1998 approvable letter, become a post-approval (Phase IV) commitment.

After evaluating your September 13, 1999 correspondence, we agree that the study need not be conducted prior to approval. Please submit a commitment to initiate the study in November 1999 and to provide the final study report by the fourth quarter of 2000, as proposed in the September 13, 1999 correspondence. Since we have agreed to your proposal, we believe a meeting is not needed.

Please note that each of the application's remaining deficiencies must be satisfactorily addressed before the NDA will be approved.

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

Sincerely,

/S/ 9/28/99

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA
HFD-180/Division Files
HFD-180/M.McNeil
HFD-180/Gallo-Torres
HFD-870/Lee
HFD-180/Aurecchia

Drafted by: mm/September 28, 1999
Initialed by: LTalarico 9/28/99
final: September 28, 1999
filename: c:\mydocuments\cso\n\20610909-p4.doc

ADVICE

MEMORANDUM

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

DATE: 9-24-1999

FROM: Director Division of Gastrointestinal and Coagulation Drug Products

SUBJECT: Phase IV Pharmacokinetic study

TO: NDA 20-610

On June 23, 1997, Salix Pharmaceutical, Inc. submitted NDA 20-610 to market balsalazide, a prodrug of 5-aminosalicylic acid (mesalamine) for the treatment of mild to moderate active ulcerative colitis. On June 15, 1998, the application was approvable pending, among other things, a multiple-dose pharmacokinetic study using the to be marketed drug formulation in the target population. The study was considered necessary to assess the systemic exposure to the parent drug and its metabolites for the to-be-marketed formulation as recommended for use in the proposed labeling. The sponsor was asked to provide study protocols for review by the OCPB reviewer.

On July 28, 1998, the sponsor requested a teleconference to clarify objectives and study design for the parmacokinetic study. The study protocol was submitted on November 20, 1998. Comments on the study protocol were provided to the sponsor on June 23, 1999.

On September 13, 1999, the sponsor requested a meeting to propose that the pharmacokinetic study be allowed to be carried out as a post-approval Phase IV commitment. In the September 13, 1999 letter, the sponsor states that the tentative starting date at one of the study sites is November 1999. Allowing 8-10 months for conducting the study, analyzing the data and preparing a final report, the final report will be available by the fourth quarter of year 2000 or sooner.

On September 13, 1999, the sponsor submitted a summary of the Safety Update that includes 1186 patients from both acute and maintenance study. The sponsor states that the overall acute adverse event profile has not changed.

The sponsor can be allowed to conduct the pharmacokinetic study as Phase IV study with the commitment that the study is initiated in November 1999 and that the final report is available by the first quarter of lyear 2000 as anticipated in the September 13, 1999

correspondence. The sponsor should be advised that the approval of balsalazide for the treatment of mild to moderate active ulcerative colitis will still be determined by satisfactory resolution of all remaining outstanding issues.

/S/
Lilia Talarico, M.D.

cc:
NDA 20-610
HFD-180
HFD-181/MMcNeil
HFD-180/HGallo-Torres
HFD-180/SAurecchia
HFD-870/Lee
HFD-103/FHoun
HFD-103/VRaczkowski
f/t 9/24/99 jgw
N/20610909.0LT

-McNeil

NDA 20-610

Salix Pharmaceuticals, Inc.
Attention: Jim Shook, Ph.D.
9600 Bayshore Road, Suite 205
Palo Alto, CA 94303

JUN 15 1998

Dear Dr. Shook:

Please refer to your new drug application 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 20, August 1, 4, 6, 8, and 18; September 3, 5, and 8; October 10, and 23; November 7, 11, and 24; December 10 and 17, 1997; January 16, 23, and 29; February 9, 10, 18, and 20; March 4, 11, 18, and 30; and April 30, 1998.

We request that you commit, in writing, to conducting the following studies post-approval:

1. Please assess the effect of food on the absorption of balsalazide.

2. Please provide in vitro plasma protein-binding information for balsalazide, covering the relevant concentration range.

3. In vitro metabolism/balsalazide drug interaction studies are recommended. Please consult the "Guidance for Industry; Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies in vitro" when designing these experiments.

4. Please conduct in vivo drug interaction studies with antibiotics and other drugs that are likely to be routinely coadministered with balsalazide.

5. Since balsalazide is largely metabolized via the kidney, we recommend that once the multiple-dose PK study outlined in the June 15, 1998 Approvable letter has been completed and analyzed, you compare the systemic exposure/pharmacokinetic data obtained from this study to that available in the literature for subjects with varying degrees of renal impairment. Literature subjects administered mesalamine, as well as mesalamine prodrugs, such as sulfasalazine and olsalazine are acceptable. Pharmacokinetic comparative analyses and simulations, if appropriate, should be carried out to assess the metabolic fate of balsalazide in all degrees of renal impairment and the results submitted to the Agency for analysis.

6. If the data analysis described in point 5 (above) indicates that significant differences exist between the pharmacokinetics of mesalamine in normal and renally-impaired subjects, a

well-designed and well-controlled study examining the disposition of balsalazide in patients with varying degrees of renal impairment would be recommended. You are encouraged to consult the "Guidance for Industry; PK in Patients with Impaired Renal Function," FDA, CDER, May, 1998.

7. Please conduct a study examining balsalazide disposition in hepatically impaired subjects.

8. Please provide data to support use in various pediatric patients age groups (infants [ages 1 month to 2 years], children [ages 2-12 years], and adolescents [ages 12-16 years]) for this compound. Such data might include dosing information, including pharmacokinetic data, safety information, and/or effectiveness data.

9. Lastly, please reanalyze the data from Study #GLY01/93, entitled "Pharmacokinetic Study of Balsalazide Disodium (Colazide) in Patients with Ulcerative Colitis Receiving Long-Term Maintenance Treatment" to examine the effect of gender on the disposition of balsalazide, taking into account the influence of body weight.

We recommend that protocols for the studies described above be submitted to the Agency for review and comment before they are initiated. The final study protocols should be submitted to your IND within one year of receiving an NDA approval letter.

Please note that as an option, some of the assessments requested above can be incorporated into the multiple-dose pharmacokinetic study outlined in the June 15, 1998 Approvable letter as relevant, or obtained from the literature, if desired.

If you have any questions, please contact Melodi McNeil, Regulatory Health Project Manager, at (301) 443-0483.

Sincerely yours,

cc:

Original NDA 20-610
HFD-180/Division Files
HFD-180/McNeil
RD Init: LTalarico 5/26/98, 6/11/98 RIG for CT 6/15/98
BCollier 6/1/98
PBotstein 6/4/98, 6/12/98

Final: June 15, 1998

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

GENERAL CORRESPONDENCE (Request for Phase IV Commitments)

Number of Pages Redacted 4

❖❖❖

Draft Labeling
(not releasable)

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

3 pages

Number of Pages Redacted 37

❖❖❖

Draft Labeling
(not releasable,

9. DATE OF FIRST AUTHORIZATION

18th December 1997

10. DATE OF (PARTIAL) REVISION OF THE TEXT

14th July 1999

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 5/17/00	**DUE DATE:** 6/23/00	**OPDRA CONSULT #:** 00-0153

TO:
Lilia Talarico, M.D.
Director, Division of Gastro-Intestinal and Coagulation Drug Products
HFD-180

THROUGH:
Melodi McNeil
Project Manager
HFD-180

PRODUCT NAME:	**MANUFACTURER:** Salix Pharmaceuticals, Inc.
Colazal or ——— (balsalazide disodium) Capsules 750mg **NDA #:** 20-610	

SAFETY EVALUATOR: Peter Tam, RPh.

OPDRA RECOMMENDATION:
OPDRA has no objections to the use of the proprietary name, Colazal. We do not recommend use of the name, ———

FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

√ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

/S/ 6/15/2000

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/ 6/15/00

Peter Honig, M.D.
Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 6/13/00

NDA#: 20-610

NAME OF DRUG: Colazal or
(balsalazide disodium) Capsules, 750 mg

NDA HOLDER: Salix Pharmaceuticals, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Gastro-Intestinal and Coagulation Drug Products (HFD-180) for assessment of tradenames, Colazal . The sponsor had previously submitted the name , on 12/3/99. OPDRA concluded that the name was unacceptable for use since the existing approved product, Pentasa, sounds and looks like . Pentasa could be easily mistaken for . or vice versa. Both products are available in one strength and have striking similarity when written. The sponsor was notified of this decision.

The sponsor subsequently submitted two names for review on 5/17/00. They are Colazal and Colazal is proposed as the primary trade name and is considered as alternate trade name. The goal date is 7/25/00.

PRODUCT INFORMATION

Colazal (balsalazide disodium) is indicated for the treatment of mildly to moderately active ulcerative colitis.

In healthy individuals, the systemic absorption of intact balsalazide was very low and variable. Upon reaching the colon, bacterial azoreductases cleave the compound to release 5-aminosalicyclic acid the therapeutically active portion of the molecule, and 4-aminobenzoy-B-alanine. Colazal is mainly excreted through urine and feces. Usual dose for Colazal is 2.25 gm (3 x 750 mg) capsules 3 times a day, in divided doses, which provides 2.4 gm free mesalamine. According to the clinical Colazal studies, higher concentration of free mesalamine to treat ulcerative colitis is significantly better than lower free mesalamine level delivered to the colon.

Colazal will be supplied as 750 mg capsules in bottles of 18 and 280.

II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3] as well as several FDA databases[4] for existing drug names which sound alike or look alike to Colazal/ —— to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary names, Colazal and —— Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. Colazal

There were no proprietary names for currently marketed U.S. products identified by the Expert Panel that were believed to have significant look-alike and sound-alike properties. Clozaril and Cologel are two proprietary names that may have some potential sound-alike qualities. Clozaril is an antipsychotic and Cologel is an OTC (Over-The-Counter) laxative with methycellulose. Clozaril is available in 25 mg and 100 mg tablets while Cologel is a liquid suspension. The usual dose for Clozaril is 25-450 mg/day. Therefore, the potential for medication errors due to name confusion among these products appears to be minimal.

2. ——

Several product names were identified in the Expert Panel Discussion that were thought to have potential for confusion with —— These products are listed in the following table, along with the dosage forms available and usual FDA-approved dosage.

---

[1] MICROMEDEX Healthcare Intranet Series, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc).

[2] American Drug Index, online version, Facts and Comparisons, St. Louis, MO.

[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[4] Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

[5] WWW location http://www.uspto.gov/tmdb/index.html.

along with the dosage forms available and usual FDA-approved dosage.

[redacted]	[redacted]	[redacted]	[redacted]
Baycol	Tablets, 0.2,0.3,0.4 mg cerivastatin	0.4 mg once daily in evening	*SA/LA
Lescol	Capsules, 20mg, 40mg fluvastatin	20-40 mg once daily in evening	*SA
Pravachol	Tablets, 10,20 and 40 mg pravastatin	10-40 mg once daily in evening	*LA
Asacol	Tablets, 400mg mesalamine	3x 400mg tid	*SA

*SA = Sound-alike
*LA = Look-alike

Asacol is the product name that is identified to have the most potential for confusion with [redacted]. They belong to the same therapeutic class (mesalamine) in the treatment of active ulcerative colitis. They both are available in one strength and there is overlapping administering dosing interval at three times a day. Confusion of [redacted] with the following products seems unlikely, given differences in dosage forms, and dosing schedule: Baycol is dosed once daily, so is Lescol and Pravachol.

APPEARS THIS WAY
ON ORIGINAL

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Studies were conducted by OPDRA and involved 91/92 health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of Colazal/ —— with other drug names due to the similarity in handwriting and verbal pronunciation of the name. Inpatient and outpatient prescriptions were written, each consisting of (known/unknown) drug products and a prescription for Colazal or —— (see below). These prescriptions were scanned into a computer and were then delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

1. Colazal Rx

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Colazal #60 Sig: 3 p.o. tid	Take Colazal 3 capsules by mouth three times a day
Inpatient RX: Colazal 3 capsules p.o. tid	

2 ——

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient Rx: —— #60 Sig: 3 capsules p.o.tid	Take 3 capsules by month 3 times a day
Inpatient Rx: —— 3 caps p.o. tid	

APPEARS THIS WAY
ON ORIGINAL

2. Results:

The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Colazal Rx				
Written Outpatient	30	17(57%)	17	0
Verbal	31	13(42%)	11	2
Written Inpatient	30	18(60%)	17	1
Total	91	48(53%)	45(94%)	3(6%)
[redacted]				
Written Outpatient	31	13(42%)	13	0
Verbal	30	14(47%)	12	2
Written Inpatient	31	15(48%)	15	0
Total	92	42(46%)	40(95%)	2(5%)

a. Colazal

Ninety-four percent of the participants responded with the correct name, Colazal. The incorrect written and verbal responses are summarized in the Table II.

b. [redacted]

Ninety-five percent of the participants responded with the correct name, [redacted]. The incorrect written and verbal responses are summarized in the following table.

Table II

Colazal	Incorrectly Interpreted
Written Inpatient	
Verbal	
[redacted]	
[redacted]	
Verbal	

C. SAFETY EVALUATOR RISK ASSESSMENT

1. Colazal

Clozaril tablets were identified in the Expert Panel Discussion to have some potential for confusion with Colazal. They both share 5 characters in common in their name. They also have similar character lengths, Clozaril has 8 and Colazal has 7. In addition, they both are available as tablets. Despite these similarities, Colazal and Clozaril differ in dosing strength

and therapeutic class. One is for colitis and the other one is an antipsychotic agent. Considering all the circumstances under which Colazal will be used, it seems unlikely that Clozaril would be confused and result in potential medication errors.

The results of the verbal prescription study indicate that two (out of thirteen) participants interpreted the name, Colazal, incorrectly. In the inpatient written study, only one (out of eighteen) participant interpreted Colazal incorrectly. There was no incorrect interpretation (seventeen out of seventeen) noted in the outpatient written prescription study. Finally, in all three studies, the incorrect responses did not overlap with Clozaril or any existing drug names.

2. ~~

Several proprietary product names were identified in the Expert Panel Discussion that were thought to have potential for confusion with the proposed name, ~~. They are Baycol, Lescol and Asacol. They all share three suffix characters "col" and they all have the same exact 6 character lengths. Of the three, Asacol is considered to have the most potential for confusion with ~~. They belong to the same therapeutic class and there are overlapping administering dosing intervals. In addition, they both are available in one strength.

Results of the verbal prescription study indicate that two (out of fourteen) participants interpreted ~~ incorrectly. There was no incorrect interpretation by any participants for both outpatient and inpatient written prescription studies (twenty-eight out of twenty-eight). Our studies and searches conducted within FDA did not reveal any other existing drug names that would be confused with the proposed proprietary name, ~~. A negative finding, however, in a small sample size does not provide persuasive evidence that an error might not occur when exposed to the general population. Due to apparent similar dosing strength and identical dosing administering intervals between ~~ and Asacol, we do not recommend the use of ~~ as the proposed proprietary name.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

We have no comments.

IV. RECOMMENDATIONS:

OPDRA has no objections to the use of the proprietary name, Colazal.
We do not recommend use of the name, ~~

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Peter Tam at 301-827-3241.

/S/ 6/15/00

Peter Tam, RPh.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/ 6/15/2000

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

APPEARS THIS WAY
ON ORIGINAL

CC:

NDA – 20-610
Office Files
HFD-180; Melodi McNeil, Project Manager, DGCDP
HFD-180; Lilia Talarico, M.D., DGCDP
HFD-042; Patricia Staub, Regulatory Review Officer, DDMAC (Electronic Only)
HFD-440; Patrick Guinn, Project Manager, DDREII, OPDRA (Electronic Only)
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Sammie Beam, Project Manager, OPDRA
HFD-400; Peter Honig, Director, OPDRA (Electronic Only)
HFD-002; Murray Lumpkin, Deputy Center Director for Review Management (Electronic Only)

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 12/3/99	DUE DATE: February 7, 2000	OPDRA CONSULT #: 99-102

TO (Division):
Lilia Talarico, M.D.
Director, Division of Gastro-Intestinal and Coagulation Drug Products
HFD-180

Through: Melodi McNeil, Project Manager

PRODUCT NAME:	MANUFACTURER: Salix Pharmaceuticals, Inc.
(balsalazide disodium) NDA #: 20-610	
Safety Evaluator: Peter Tam	

OPDRA RECOMMENDATION:
OPDRA does not recommend the use of proprietary name

/S/ 2/7/2000
Jerry Phillips
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 480-8173

/S/ 2/8/00
Peter Honig, MD
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

Date of Review: 1/24/00

NDA#: 20-610

Name of Drug: — ᵊ
(balsalazide disodium)

NDA Holder: Salix Pharmaceuticals Inc.

I. INTRODUCTION

This consult was written in response to a request from the Division of Gastro-Intestinal and Coagulation Drug Products (HFD-180) on December 3, 1999, to review the proposed proprietary drug name — ᵊ in regard to potential name confusion with existing proprietary/generic drug names.

The Labeling and Nomenclature Committee (LNC) has previously reviewed this proprietary name and concluded that the proposed proprietary name — ᵊ was acceptable on 5/14/98.

PRODUCT INFORMATION

— (balsalazide disodium) is supplied as capsules for oral administration. Each capsule contains 750 mg balsalazide disodium.

System absorption of intact balsalazide was negligible and variable with healthy individuals, with mean C_{max} occurring at approximately 1-2 hours after single oral doses of 1.5 gm and 2.25 gm. It is delivered intact to the colon where it is cleaved by bacterial azoreduction to release equimolar quantities of mesalamine, which is the therapeutically active portion of the molecule. — is mainly excreted through urine and feces. Usual dose for — is 2.25 gm (3 x 750mg) capsules 3 times a day, in divided doses, which provides 2.4 gm free mesalamine. According to the clinical — studies, higher concentration of free mesalamine to treat ulcerative colitis is significantly better than lower free mesalamine level delivered to the colon.

— will be supplied as 750 mg capsules.

II. RISK ASSESSMENT

In order to determine the potential for medication errors and to find out the degree of confusion of the proposed proprietary name, [redacted], with other drug names, the medication error staff of OPDRA searched Micromedex online, PDR (1999 Edition), American Drug Index (43rd Edition), Drug Facts and Comparison (updated monthly), the Electronic Orange Book, and US Patent and Trademark Office online database. In addition, OPDRA also searched several FDA databases for potential sound-alike and look-alike names to approved/unapproved drug products through Drug Product Reference File (DPR), Medline online, Decision Support System (DSS), Establishment Evaluation System (ESS), and LNC database. A drug expert group discussion was conducted to review all the findings from the searches. OPDRA also conducted studies of written and verbal analysis of the proposed proprietary name employing health practitioners within FDA to evaluate potential errors in handwriting and verbal communication of the name. This exercise was conducted to simulate the prescription order process.

A. EXPERT PANEL DISCUSSION:

The group discussed some sound alike and look-alike drug names such as Pentasa® and Rowasa®. The group voiced concern on sound-alike names confusion among study drug [redacted] with existing proprietary names of Pentasa and Rowasa. The dosage form for Pentasa comes as delay-released 250 mg capsules and Rowasa is supplied as 500 mg suppository and rectal suspension in 4 gm/60 ml enema package.

B. STUDY CONDUCTED BY OPDRA

Methodology:

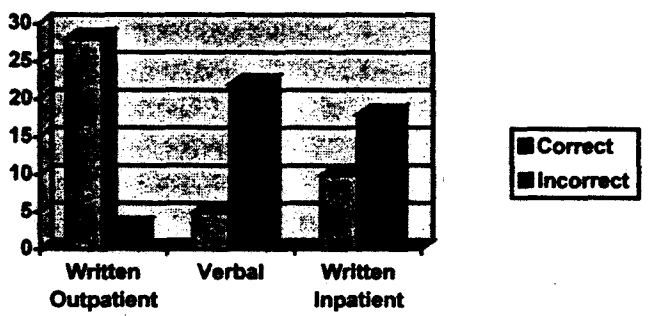
This study involved 137 health professionals consisting of physicians, nurses and pharmacists within FDA to determine the degree of confusion of [redacted] with other drug names due to the similarity in handwriting and verbal pronunciation of the name. An OPDRA staff member wrote two outpatient prescriptions and one inpatient order, each consisting of a known drug product and a prescription for [redacted]. These prescriptions were scanned into the computer and a random sample of the written orders were then delivered to the participating health professionals via e-mail. Outpatient prescriptions were sent to 47 participants and inpatient orders were sent to 45 participants for review and interpretation. In addition, one pharmacist with a foreign accent recorded the outpatient orders on voice mail. The voice mail messages were then sent to 45 participating health professionals for their review and interpretation. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the

medication error staff. We recognize that our sampling is small and the study is designed to increase the likelihood of detecting failures.

The results are summarized in Table I.

Table I

Study	# of Samples	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Outpatient	47	31 (66%)	28	3
Verbal	45	27 (60%)	5	22
Written Inpatient	45	28 (62%)	10	18



Fifty percent of the participants responded with the correct name [illegible]. The incorrect written and verbal responses are listed in Table II :

Table II

	Incorrectly Interpreted
Written	
Verbal	Phonetic Variable Responses

*Currently marketed product (from written outpatient)

C. CONTAINER LABEL.

a. The triangular logo with **C Z** beneath it is quite distracting and has no importance in the safe use of the product. We would recommend against the use and placement of this logo.

b. The net quantity (280 capsules) has been bolded and appears more prominently than the strength. The most prominent aspect of any Rx label should include the name and strength of the product.

c. We would recommend that the strength be more prominent and that the dosage form (capsules) be part of the established name. In addition, we would suggest that the strength not be placed in written brackets.

(balasalazide disodium capsules)
750 mg

(Note: it is not necessary and is distracting to place an asterisk after the Registered Trademarks symbol).

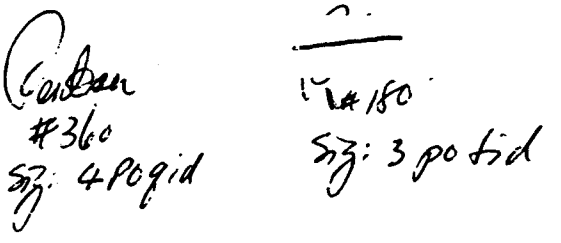
d. The proposed manufacturer/packer /distributor relationship is not allowed under 21 CFR 201.1 (g) (5). and requires revision. It appears that both Salix Pharmaceuticals, Inc. and [redacted] are both distributors.

e. We believe that " Rx only" would be more appropriate on the main panel and that storage recommendations are more appropriately placed on a side panel.

f. The listing of a U.S. Patent should be moved to a side panel.

D. CONCLUSIONS:

The results of the verbal and written analysis studies show forty-three participants interpreted the proprietary name [redacted] correctly. However, the inaccurate interpretations of the proposed name did overlap with an existing approved drug product, Pentasa®. That was what we predicted in the expert panel discussion, and is a significant finding in a study with a small sample size. Pentasa® [redacted] belong to the same therapeutic classification mainly used for chronic inflammatory bowel disease. These two names may sound-alike, but they come with different strengths. Pentasa® is available in one strength as 250 mg delayed released capsules and [redacted] is available as 750 mg capsules. Dosage for Pentasa® is 1 gm four times a day for up to 8 weeks while [redacted] is 2.25 gm three times a day for up to 8 weeks. Pentasa® and [redacted] have striking similarity when written (see sample below)



Both have similar character lengths (Pentasa has 7 and [redacted] has 6). Both end in "asa" and both have one similar upstroke (l and t) in the name. Also; the "P" and "B" have similarities and could easily be confused for each other.

An additional risk factors in considering the possibility of an error is the fact that both products are available as a single strength (although different) and both are capsules. As such, our experience with Pentasa® prescriptions is that physicians often omit the strength, since it is unnecessary, (as seen in the example above).

When examining the clinical consequences of an error between these products, several possibilities exist:

1. [redacted] misinterpreted for Pentasa®. A [redacted] prescription that is misinterpreted for Pentasa® will most likely result in an <u>underdosage</u> where the patient would be dosed with 3 capsules TID and might experience an exacerbation of the symptoms of colitis.

2. Pentasa® Rx misinterpreted for [redacted] could result in an <u>overdosage</u> of mesalamine when a patient would be instructed to take 4 [redacted] capsules 4 times a day. This might lead to electrolyte abnormalities.

3. A Rx for ——— could be written with the strength as:

——— 750mg
Sig: 3 po tid
1 month supply

If interpreted and filled with 250mg Pentasa®, a patient would be instructed to take three 250 mg capsules of Pentasa® three times a day.

III. RECOMMENDATIONS

A. OPDRA does not recommend the use of the proprietary name ———.

B. OPDRA has provided some labeling comments which might lead to safer use this product.

OPDRA would appreciate feedback of the final outcome of this consult. We will be willing to meet with the Division for further discussion.

Should you have any questions concerning this review, please contact Peter Tam at 301-827-3241

/S/

Peter Tam, RPh.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur

/S/ 2/7/2000

Jerry Phillips, RPh.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

C.C.

NDA- 20-610
Office Files
HFD-120; Melodi McNeil, Project Manager, DGCDP
HFD-180; Lilia Talarico, Division Director, DGCDP
HFD-440; Ann Corken, Safety Evaluator, DDREII
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Deputy Director, OPDRA
HFD-002; Murray Lumpkin, Acting Director, OPDRA

REQUEST FOR TRADEMARK REVIEW

998

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Gastrointestinal and Coagulation Drug Products	**HFD-180**
Attention: Melodi McNeil, Project Manager	**Phone:** (301) 443-0487
Date: March 18, 1998	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: C [redacted] r	**NDA/ANDA#** NDA 20-610
Established name, including dosage form: balsalazide disodium Capsules	
Other trademarks by the same firm for companion products: N/A	
Indications for Use (may be a summary if proposed statement is lengthy): Treatment of mild to moderate active ulcerative colitis	
Initial Comments from the submitter (concerns, observations, etc.): Please evaluate all four of the firm's proposed proprietary names. The firm previously proposed the proprietary name " [redacted] " but based on a 9/9/97 consult review from the LNC, the firm was informed that that name was unacceptable. Please provide a response before May 31, 1998.	

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original NDA 20-610; HFD-180/division file; HFD-180/M.McNeil; HFD-180/Ysern

Rev. December 95

Submission Date: 3/11/98

mm 3/18/98

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT # 998 HFD# 180 PROPOSED PROPRIETARY NAME: PROPOSED ESTABLISHED NAME:

ATTENTION: Melodi McNeil #1 balsalazide disodium capsules

#2

#3

#4

A. Look-alike/Sound-alike **Potential for confusion:**

COLAGYN	___	Low	XXX	Medium	___	High
CLOMID	___	Low	XXX	Medium	___	High
COLAZIDE	___	Low	XXX	Medium	___	High
COLOGEL	XXX	Low	___	Medium	___	High
COLCHICINE	XXX	Low	___	Medium	___	High

B. Misleading Aspects:

C. Other Concerns:

D. Established Name

___ Satisfactory

___ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

XXX ACCEPTABLE ___ UNACCEPTABLE AS TO:

F. Signature of Chair/Date /S/ 5/14/98

(851)

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Gastrointestinal and Coagulation Drug Products	**HFD-180**
Attention: Melodi McNeil, Project Manager	**Phone:** (301) 443-0483
Date: June 30, 1997	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: ——	**NDA/ANDA#** NDA 20-610
Established name, including dosage form: balsalazide disodium Capsules	
Other trademarks by the same firm for companion products: N/A	
Indications for Use (may be a summary if proposed statement is lengthy): Treatment of mildly to moderately active ulcerative colitis	
Initial Comments from the submitter (concerns, observations, etc.): For your covenience, the firm's proposed labeling is included.	

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original NDA 20-610; HFD-180/division file; HFD-180/M.McNeil; HFD-180/Ysern

Rev. December 95

APPEARS THIS WAY
ON ORIGINAL

mm 4/21/97

Consult #851 (HFD-180)

COLAZIDE balsalazide disodium capsules

The following look-alike/sound-aljke conflicts were noted: CORAZIDE, CAPOZIDE, and DYAZIDE. The Committee feels there is a high potential for mix-up between these products. Additionally, the Committee is concerned that "-azide" is widely associated with thiazide diuretics, adding another confusing element in the proprietary name.

Overall, the Committee finds the proposed proprietary name unacceptable.

9/9/97, Chair
CDER Labeling and Nomenclature Committee

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

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

DATE: July 12, 2000

FROM: Lilia Talarico, M.D., Director, Division of Gastrointestinal and Coagulation Drug Products (HFD-180) 7-12-00

SUBJECT: NDA 20-610; Colazal (mesalamine) Capsules-Approval Recommendation

TO: Florence Houn, M.D., M.P.H., Director, Office of Drug Evaluation III (HFD-103)

Balsalazide is a non-absorbable 5-ASA derivative. Following oral administration, balsalazide is cleaved in the colon by bacterial azoreductase to release the active compound (5-ASA) and the inactive carrier (4-ABA); the two compounds are further metabolized into NASA and NABA, respectively. Balsalazide, like mesalamine, has a topical anti-inflammatory effect on the colonic mucosa.

Balsalazide has been developed by Salix Pharmaceutical Inc. for the treatment of mild to moderate Ulcerative Colitis (UC).

On June 24, 1997, Salix Pharmaceutical Inc. submitted NDA #20-610 for the approval of Colazide (balsalazide) Capsules for the indication as a single oral agent for the treatment of mildly to moderately active ulcerative colitis.

Five clinical trials were included in the NDA. Two clinical trials were defined as pivotal: CP099301 and 57-3001. Three additional studies were also included as supportive.

The efficacy of balsalazide was demonstrated in study CP099301 where two dose regimens were compared. The higher dose regimen of 6.75 g/d was significantly more effective for reducing rectal bleeding, stool frequency and sigmoidoscopy scores than the lower dose regimen of 2.25 g/d.

A second study, conducted in Europe with a locally marketed formulation of mesalamine, confirmed the results of symptomatic improvement of mild to moderate UC.

Treatment with balsalazide for periods of 8 to 12 weeks did not induce complete remission of mild or moderate ulcerative colitis.

Treatment with balsalazide for the duration of 8 to 12 weeks showed an acceptable pattern of safety.

Based on the results of efficacy and safety, the NDA was approvable on June 15, 1998 pending the resolution of chemistry, labeling, and biopharmaceutics deficiencies. The firm was also informed that the tradename "Colazide" was unacceptable, and asked to provide revised final printed labeling and a Safety Update (SU).

On September 23, 1999, the sponsor submitted a revised labeling and an SU which encompassed the period from May 1998 to April 1999. The SU included safety information from the clinical trials and from maintenance trials with administration of Balsalazide for up to 1 year conducted in Germany and in the United Kingdom where the drug was approved in 1997. No serious adverse events were reported. In the 9-23-99 submission, the sponsor submitted information on the mesalamine formulation used as comparative active control. Although some difference in solubility were noted by the Biopharmaceutical reviewer, the formulation of mesalamine was accepted as clinically equivalent. Balsalazide was made approvable, for a second time, on March 24, 2000. In the approvable letter, the sponsor was informed that the proposed tradename Balasa was found unacceptable and was requested to provide the labeling as revised by the Agency and to provide a safety update.

On May 2, 2000, the sponsor submitted an amended proposed labeling in response to the Agency's Approvable Letter and a SU covering the period from April 1999 to April 2000. The sponsor's proposed labeling is unacceptable and it has been revised as shown in the labeling included in tab A3.

The SU included data from a total of 513 patients in acute studies and 962 patients in maintenance studies. No significant changes were noted in the incidence of overall adverse events or serious adverse events. The data are presented in detail in the Medical Officer's review dated June 27, 2000.

The foreign marketing safety update indicates that a total of 6.3 million capsules corresponding to 0.7 million treatment days have bee distributed in Europe (UK) since July 1997.

Two cases of congenital anomaly/birth defects were initially reported in two babies born from mothers who had received balsalazide during early pregnancy. The cases were reviewed by _____ who concluded that the teratogenicity of balsalazide was low, and the drug is similar to mesalamine which is widely used and found to be non teratogenic in animals. The medical literature fails to show any increases mesalamine teratogenicity in humans. On subsequent review of the cases, the sponsor notified the Agency that the two cases of congenital anomaly were actually duplicate reports of the same case.

A report of a SAE from Sweden consisted of young female who experienced worsening of UC and elevation of LFTs and bilirubin after two weeks of balsalazide therapy. The patient was on oral contraceptive and had negative serology for viral hepatitis. The LFTs improved after discontinuation of balsalazide and OC.

A teleconference with the sponsor was held on 7-10-2000 to discuss labeling issues, including the initial request by the Agency to include in the labeling information regarding the cases of congenital anomaly. This requirement was dropped after clarification of duplication of reports. The sponsor was, however, requested to report promptly any other case of congenital malformation from post-marketing surveillance and to highlight this information in the Periodic Safety Reports.

The sponsor agreed to carry out the other labeling changes as requested by the Agency.

Recommendation: Approval of Balsalazide for the treatment of mildly to moderately active UC is recommended. The sponsor is required to submit final printed labeling identical to the enclosed labeling.

cc:
Original NDA
HFD-180/Division Files
HFD-180/McNeil

Memorandum

Date: 22 March 2000

From: David E. Morse, Ph.D. /S/
Asc. Director (Pharm./Tox.), Office of Drug Evaluation III

To: Florence Houn, M.D.
Director, Office of Drug Evaluation III

Cc: Lillia Talarico, M.D., Dir., DGCDP (HFD-180)
Jasti Choudary, Ph.D., TL Pharm./Tox., DGCDP (HFD-180)
Melodi McNeil, Project Manager, DGCDP (HFD-180)
Alice Kacuba, Project Manager, DGCDP (HFD-180)

Subject: NDA 20-610
——— (balsalazide disodium) Capsules[1], 750 mg
Review of Pharm./Tox. Information and Sections of Proposed Product Label

Chemical: (E)-5-[[-4-[[(2carboxyethyl) amino]carbonyl] phenyl]azo]-2-hydroxybenzoic acid, disodium salt, dihydrate

I. Materials Included in Review

1. Pharm./Tox. Reviews of NDA 20-610, dated 4 Nov. 1997, written by Ke Zhang, Ph.D.
2. Pharm./Tox. Team Leader Label Review of NDA 20-610, written by Jasti Choudary, B.V.Sc., Ph.D., dated 10 June 1998.
3. NDA 20-610 Approval Package, with Draft Product Labeling, dated 7 March 2000.

II. Comments and Conclusions

1. A review of the action package for NDA 20-610, ———, suggests that the product has been adequately evaluated in multiple repeat-dose non-clinical safety studies (including completed or ongoing carcinogenicity studies conducted in the rat and P53 transgenic mouse) for approval of the requested indication (treatment of active ulcerative colitis). In general, the proposed product labeling adequately reflects the toxicological findings for balsalazide disodium as regards carcinogenesis, mutagenesis, fertility, pregnancy and overdosage.

2. The non-clinical safety studies do not suggest a risk of congenital malformations or other alterations to fetal growth or viability for female patients administered ——— (balsalazide disodium) during or immediately preceding pregnancy. There were no adverse effects on the fertility of male or female rats (F_0 or F_1 generations), or the peri-natal development of male or female offspring (F_1 generation) following balsalazide disodium treatment of the F_0 generation. However, because animal data are not always predictive of the human response, some residual level of risk can not be excluded based on the available animal data.

---

[1] Due to multiple similarities between the proposed tradename for this product and that of a previously approved product, the sponsor of this application has been asked to consider the use of an alternative product name. Therefore, at the time of product approval, the tradename for the marketed product may not correspond to that specified in this memorandum.

3. Specific comments related to the product label follow:

- W

- time
  der
  f

Summary

A review of the action package for NDA 20-610 ——— (balsalazide disodium) Capsule, suggests that the product has been adequately evaluated in multiple repeat-dose non-clinical safety studies (including carcinogenicity studies), along with reproductive and genotoxicity studies, for approval of the requested indication (treatment of active ulcerative colitis). The proposed product label, with possible revision as suggested in the preceding section, accurately reflects the non-clinical safety data for this product.

---

2 If it is the opinion of the reviewing Division that there is insufficient non-clinical and/or clinical pharmacokinetic data included in the NDA to allow for interspecies exposure comparisons to be based on kinetic parameters, then it is recommended that the sponsor be requested to develop such information as part of their continued product safety assessment and development

Number of Pages Redacted 1

❖❖❖

Draft Labeling
(not releasable,

MEMORANDUM

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

DATE: March 24, 2000 /S/

FROM: Florence Houn MD

SUBJECT: Office Director Memo

TO: NDA File 20-610 balsalazide disodium

This memo supports the recommendation of the division of gastrointestinal and coagulation drug products to issue an approvable letter to the sponsors of balsalazide, Salix Pharmaceuticals, Inc. The manufacturer must address outstanding deficiencies in manufacturing, labeling, and select a tradename that will minimize prescription error. However, during this review cycle, the firm provided information that does not adequately justify use of an non-FDA-approved comparator, European Asacol, used in their clinical trials to support effectiveness for the treatment of mildly to moderately active ulcerative colitis (UC). Because the pivotal trials were designed as superiority trials, this would not be an issue had superiority been demonstrated in two adequate and well-controlled trials. However, only one of two trials showed superiority of the drug over European Asacol (#57-3001) in patients with UC in remission (not the intended use population). The other trial (CP99301) showed that higher dose balsalazide was superior to lower dose drug, but the higher dose was no different in symptomatic improvement of patients with mildly and moderately active UC than European Asacol. The Office of Clinical Pharmacology and Biopharmaceutics does not find the European Asacol used in the pivotal clinical trials bioequivalent to the US approved Asacol, given the submitted data. Furthermore, there is no pharmacokinetic data on the to-be-marketed-product in the intended-use population. Information was not submitted to show that the European preparation and the US approved product are comparable.

The review division supports comparability of the European Asacol with the US approved product, stating:

1) that the active moiety 5-amino-salicylic acid is the same as US approved compounds,
2) the US approved Asacol's clinical trial results can be used to compare results from CP99301,
3) the dissolution comparison showing differences at 30-60 minutes are not meaningful because the experimental system is not directly relevant to small intestine milieu,
4) the dissolution results showing comparability at 90 and 120 minutes are the relevant results,
5) "similar PK of the [European] UK Asacol [to the US approved Asacol] would allow demonstration of relevant comparability," and,
6) the dose-response finding in CP99301 supports activity of the drug,

However, some of these statements do not supply the rationale needed because:

1) balsalazide may not be metabolized (cleaved by colonic bacterial azoreduction to mesalamine) in the same timeframe as the approved drug, and this timing could affect exposure-response. Furthermore, clinical results are needed to support effectiveness given that this is a new compound with a new carrier that could potentially interfere with the cleaved active moiety's activity.
2) US trials for Asacol cannot be directly compared with trial results from balsalazide except through a head to head trial.
3) Either the system for dissolution is meaningful or not (above 3 and 4).

I agree that similar PK results would provide demonstration of an important aspect of comparability. However, these data are absent.

I also agree that the dose-response finding in CP99301 is important in supporting activity of the drug product. It is the fact of this study, together with the results of patients in remission, (despite this study population being different from the intended use population, but nevertheless, a clinically significant population for ulcerative colitis) supports activity of the drug. The drug's superiority over European Asacol (if, in the worst case, this formulation was no better than placebo) for keeping patients in remission by having less bloody stool is clinically meaningful and supports activity of balsalazide.

However, I would recommend that all comparisons be deleted from the labeling because there should be no implied equivalence or superiority to European Asacol, which has never been reviewed for efficacy in the division.

Specifically, I would recommend:

1) Editing the clinical trials section highlighting dose response and replacing '

2) Trial 57-3001 showing superiority can be rewritten to: "In a second study, conducted in Europe, confirmed findings of symptomatic improvement."

3)

4) Communicating these changes to the company.

APPEARS THIS WAY
ON ORIGINAL