DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-610

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

Dear Dr. Johnson:

Reference is made to your Proposed Pediatric Study Request submitted on November 8, 2000 for Colazal (balsalazide disodium) Capsules to NDA 20-610.

To obtain needed pediatric information on balsalazide disodium, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies:

- *Type of studies*:

  Study 1: Pharmacokinetics and Safety Study: This will be a randomized, repeated-dose pharmacokinetic study of at least three dose levels of balsalazide disodium in pediatric patients with mildly- to moderately-active ulcerative colitis (UC). Patients will have ulcerative colitis that is either newly diagnosed or that has recently relapsed. Patients will be treated with balsalazide disodium for at least 4 weeks after randomization, and will visit the clinic for a clinical evaluation at baseline, at the end of the study, and at least every other week in between (e.g., visits at 0, 2, and 4 weeks). Study 1 will precede Study 2 (see below) and the pharmacokinetic and clinical endpoints results of Study 1 will be used to select doses of balsalazide disodium to be used in Study 2. The results of Study 1 should be reported to the Agency before initiating treatment of patients in Study 2.

  Study 2: Exposure/Response and Safety Study: This will be a randomized, double-blind study of at least two dose levels of balsalazide disodium in which responses to balsalazide disodium will be compared to a relevant historical control of pediatric patients receiving either placebo or no treatment. Patients will have ulcerative colitis that is either newly diagnosed or that has recently relapsed, with a baseline Disease Activity Index (DAI) [see RI Breuer et al., *Gut* 1997; **40**: 485-491] score between 4 and 11. Patients will be treated with balsalazide disodium for at least 8 weeks after randomization, and will visit the clinic for a clinical evaluation for safety and compliance at baseline, at the end of study, and at least every other week in between (e.g., visits at 0, 2, 4, and 8 weeks). At each dose level, at least 40 patients will undergo flexible sigmoidoscopy at baseline and after eight weeks of treatment with balsalazide disodium. DAI scores and endoscopic findings will be recorded at these time points. Note that, although desirable, this study need not be formally powered for efficacy.

- *Indication(s) to be studied (i.e., objective of each study):*

  Studies 1 and 2: Treatment of mildly- to moderately-active UC

- *Age group in which studies will be performed*:

  Study 1: At each dose level, at least 12 patients aged 5 years to 17 years will complete four weeks of treatment with balsalazide disodium. At each dose level, at least six patients will be age 5 years to 8 years and at least six will be age 9 years to 17 years. To the extent possible, patients should be approximately uniformly distributed through the requested age ranges.

  Study 2: At each dose level, at least 40 patients aged 5 to 17 years will complete at least eight weeks of treatment with balsalazide disodium. At each dose level, at least 20 patients will be age 5 years to 8 years and at least 20 will be age 9 years to 17 years. To the extent possible, patients should be approximately uniformly distributed through the requested age ranges.

- *Study endpoints:*

  Pharmacokinetic endpoints (Study 1 only): Peak (approximately 1-2 hours after dosing) and trough (just prior to next dose) blood levels of balsalazide, 5-aminosalicylic acid (5-ASA), N-acetyl-5-ASA, 4-aminobenzoyl-β-alanine (4-ABA), and N-acetyl-4-ABA. Blood samples should be obtained after repeated dosing and at approximately two and four weeks after the start of treatment with balsalazide disodium.

  Efficacy endpoints (Study 2 only): The primary efficacy endpoint will be the proportion of patients with clinical improvement, defined as a reduction from baseline to week 8 of the DAI score by at least 3 points. Endoscopic findings (e.g., visualization of the mucosa) should be recorded.

  Safety and compliance endpoints (Studies 1 and 2): Adverse events, tolerability, vital signs, clinical laboratory parameters (including complete blood count, liver function studies, serum creatinine, BUN, urinalysis), compliance, weight, height.

- *Drug information:*

  The studies described above should use an age-appropriate formulation of balsalazide disodium. The relative bioavailability of this formulation should be determined and compared with the marketed formulation of balsalazide disodium. Full study reports of any relative bioavailability studies should be submitted to the Agency. If an age-appropriate formulation cannot be developed, complete documentation of your attempts and a detailed explanation of why the attempts were unsuccessful should be submitted. Under these circumstances other formulations can be use, if they are standardized, palatable, and shown in adults to be of acceptable relative bioavailability (compared with the marketed product).

- *dosage form:*

  Studies 1 and 2: age-appropriate formulations

- *route of administration:*

  Studies 1 and 2: Oral

- *regimen:*

  Study 1: Dose levels and the frequency at which balsalazide disodium is administered should be justified.

  Study 2: Appropriate dose levels should be selected based on the pharmacokinetic and clinical endpoints results of Study 1 and other data on the use of balsalazide disodium in pediatric and adult patients with mildly- to moderately-active ulcerative colitis. Justify the dosage regimens used.

- *Drug specific safety concerns*: Renal toxicity, hepatic toxicity, pericarditis, myocarditis, pancreatitis, gastritis, and cholecystitis.

- *Statistical information, including power of study and statistical assessments:*

  Pharmacokinetics (Study 1 only): Provide descriptive statistics for the concentration-time data. Compare blood levels (of balsalazide disodium and its metabolites) with those obtained historically from adults.

  Safety and Compliance endpoints (Studies 1 and 2): Provide descriptive statistics for each variable overall and by dose level. Compare safety, compliance, and endoscopic results across dose levels and with those obtained from a relevant pediatric historical control.

  Efficacy endpoints (Study 2): Provide descriptive statistics for each variable overall and by dose level. Compare efficacy endpoints across dose levels and with those obtained from a relevant pediatric historical control.

  Literature review: Perform a thorough search of the world literature on the use of balsalazide disodium and mesalamine in this pediatric population, summarize the data, and provide a critical summary.

- *Labeling that may result from the studies*: Appropriate sections of the label may be changed to incorporate the findings of the studies.

- *Format of reports to be submitted*: Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation.

- *Timeframe for submitting reports of the studies:* Reports of the above studies must be submitted to the Agency on or before December 31, 2005. Please keep in mind that pediatric exclusivity only

attaches to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as **a new drug application or as a supplement to an approved NDA** with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

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

Sincerely,

{See appended electronic signature page}

Victor F.C. Raczkowski, M.D., M.S.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Victor Raczkowski

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