E L E C T R O N I C M A I L M E S S A G E

Date: 10-Mar-2000 10:18am EST
From: John Gibbs
GIBBS
Dept: HFD-820 PKLN 14B31
Tel No: 301-827-6420 FAX 301-827-0878

'O: Bronwyn Collier (COLLIERB)
'O: Alice Kacuba (KACUBAA)

'C: Liang Zhou (ZHOUL)
C: Maria Ysern (YSERNM)

ubject: Tertiary Chemistry Review of NDA 20-610

DA #20-610 Clinical Division: HFD-180

rug: ——— (Balzalazide disodium) Dosage Form: Capsules

ype of Letter: Approvable Drug Classification: 1S

hemistry Tertiary Review:

A: Categorical exclusion granted 5/22/98

ER: Previously Not Acceptable. Scheduled for reinspection of Anabolic 3/13/00.

O: Not Applicable. Drug Product is capsule for oral administration.

RADENAME: Tradename ——— NOT ACCEPTABLE per OPDRA review dated 2/7/00.

ABELING: FDA's revised labeling is being sent to applicant with action letter.

MC: This NDA is APPROVABLE in chemistry pending a satisfactory GMP inspection eport per Chemistry Review #5 dated 2/29/00.

ohn J. Gibbs, Ph.D.

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

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

DATE: March 2, 2000

FROM: Dr. Lilia Talarico, Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180
and
Dr. Hugo Gallo-Torres, Medical Team Leader /S/ HGT

SUBJECT: NDA 20-610
— (balsalazide disodium)

TO: Dr. Florence Houn, Director
Office of Drug Evaluation III

On June 24, 1997, Salix Pharmaceutical Inc. submitted NDA 20-610 for the approval of (balsalazide disodium) for the indication "as a single oral agent for the treatment of mildly to moderately active ulcerative colitis". As indicated in Division's memorandum of 26 May 1998 to the Office, approvability was recommended on the basis of the results of two pivotal clinical trials: CP099301 (3 arms: dose response and active comparator balsalazide 6.75 g vs. balsalazide 2.25 g vs mesalamine 2.4 g), and 57-3001 (2 arms: balsalazide 6.75 g vs mesalamine 2.4 g).

In study CP99301, balsalazide at the oral dose of 6.75 g per day was significantly more efficacious than the lower dose of the drug (2.25 g per day) for important clinical endpoints. These included rectal bleeding, stool frequency and sigmoidoscopy score. The efficacy of Balsalazide 6.7 g/day was comparable to that of mesalamine 2.5 g/day, the active comparator.

In study 57-3001, the proportion of patients experiencing symptomatic response at weeks 4, 8, and 12 was significantly higher among patients receiving balsalazide than in those receiving mesalamine with clinically meaningful therapeutic gains of 26%, (p=0.005), 32% (p=0.0018), and 25% (p=0.015), at week 4, 8 and 12 respectively.

Prior to approval, the Agency learned that the mesalamine used in both pivotal trials, and addressed by the sponsor as Asacol®, was a mesalamine formulation approved in the U.K. but not in the U.S. Because this called into question the validity of the results in the pivotal trials, the sponsor was required to provide data to adequately demonstrate comparability between the unapproved and approved mesalamine formulations (letter to sponsor, 16 March 1999).

In the submission of September 23, 1999, the sponsor provided data to show that the mesalamine formulations employed in the pivotal studies (UK-93 formulation) and that approved in the U.S. (US-93 formulation) are both chemically and clinically equivalent. The firm's response to Agency comments was reviewed by the Office of Clinical Pharmacology and Pharmaceutical (OCPB/Division of Pharmaceutical Evaluation II) (refer to the review by Dr. Al-Fayoumi dated 02/25/00). Although the dissolution rates for the US-93 and the UK-93 formulations were different at 30 and 60 minutes, they were very similar by 90 minutes and nearly identical by 120 minutes. Since the later two points are more meaningful clinically than the earlier ones, these formulations can be declared to be clinically comparable to each other. Consequently, the result of the clinical trials can be considered valid as evidence of the effectiveness of balsalazide and accepted for recommendation of approval of balsalazide. The sponsor should be requested to revise the clinical trial section of the labeling to include the results of trials CP99301 and 57-3001 as follows:

Clinical Trials: Two randomized, double-blind studies have demonstrated the safety and efficacy of balsalazide tablets in patients with mildly to moderately active ulcerative colitis. In both studies, balsalazide was compared to a mesalamine formulation approved in Europe.

In the first trial, 154 patients with mild to moderate ulcerative colitis with sigmoidoscopy findings of friable or spontaneously bleeding mucosa were randomized and treated with balsalazide 6.75 g/day, balsalazide 2.25 g/day or mesalamine 2.4 g/day. The primary efficacy measure was improvement of symptoms, physician global assessment of disease activity (PGA), sigmoidoscopy score, and overall symptoms assessment. Primary efficacy endpoint was a statistically significant difference between high and low dose of balsalazide and between high dose balsalazide and mesalamine in favor of balsalazide for rectal bleeding and at least one of the other assessed symptoms. Outcome assessment for rectal bleeding at each interim period (week 2, 4, and 8) encompassed a 4 day period (96 hours). Balsalazide 6.75 g/day was shown to be significantly superior to mesalamine 2.25 g/day in improving stool blood, stool frequency and/or sigmoidoscopy score, and PGA. The efficacy of balsalazide 6.75 g/day was not different from that of mesalamine 2.25 g/day. Balsalazide 6.75 g/day was well tolerated; the safety profile did not differ from the mesalamine 2.25 g/day.

In the second study, conducted in Europe, 101 patients were randomized to receive daily doses of balsalazide 6.75 g or mesalamine 2.4 g for up to 12 weeks. Patients were assessed at 4, 8 and 12 weeks. Balsalazide was shown to be comparable to mesalamine in achieving symptomatic improvement of acute ulcerative colitis.

Based on the results of the above studies, we recommend that balsalazide 6.75 g per day be approved for the treatment of mildly to moderately active ulcerative colitis, pending satisfactory resolution of any outstanding issues, i.e., facility site inspections, labeling revision, selection of trade name.

cc:
NDA 20-610
HFD-180
HFD-180/HEGallo-Torres
HFD-180/LTalarico
HFD-180/JChoudary
HFD-180/LZhou
HFD-181/CSO
R/d typed deg: 3/2/3/3
F/t deg: 3/3/00
206102-memo

APPEARS THIS WAY
ON ORIGINAL

M E M O R A N D U M

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

DATE: May 26, 1998

FROM: Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: NDA 20-610

TO: Acting Director, Office of Drug Evaluation III

Ulcerative Colitis (UC) is a chronic inflammatory bowel disease of unknown etiology. The disease is characterized by episodes of acute flare ups and periods of remission. The traditional therapy of mild/moderate episodes of recurrence of UC is represented by the combination of sulfasalazine (SAS) and steroid enemas. This regimen is effective in reverting the exacerbation episodes of UC and in prolonging remission between flare ups. The active moiety in SAS is the amino-salicylate (5-ASA).

Other preparations of 5-ASA (mesalamine, olsalazine) have been approved for oral or rectal administration for the treatment of mild/moderate active UC. Most 5-ASA are formulated to prevent gastric digestion or small bowel absorption of 5-ASA in order to preserve its topical anti-inflammatory effect on the colonic mucosa.

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. The systemic absorption of balsalazide in normal subjects is <0.3%. Higher absorption of balsalazide occurs in patients with UC. Balsalazide, like mesalamine, has a topical anti-inflammatory effect on the colonic mucosa.

Balsalazide has been developed by Salix Pharmaceutical Inc.. Five clinical trials were performed in the USA and Europe for the clinical development of this compound for the treatment of mild to moderate UC.

On June 24, 1997, Salix Pharmaceutical Inc. submitted NDA #20-610 for the approval of balsalazide ———) 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.

Pivotal Trial CP099301: "A Phase III randomized, double-blind, dose-response comparison of Colazide® (balsalazide disodium) 6.75 g daily versus Colazide® 2,25 g daily, and Asacol® (mesalamine) 2.4 g daily in patients with active mild or moderate ulcerative colitis." This study was conducted at 13 US and one Puerto. Rico centers. A total of 154 newly diagnosed or recently relapsed patients with active mild to moderate UC with sigmoidoscopy findings of friable (moderate) or spontaneously bleeding (severe) mucosa were enrolled in the study. Study treatment was of 8 weeks duration.

The primary efficacy measure was improvement of symptoms, physician global assessment of disease activity (PGA), sigmoidoscopy score, and overall symptoms assessment. Primary efficacy endpoint was a statistically significant difference between high and low dose of balsalazide and between high dose balsalazide and Asacol in favor of balsalazide for rectal bleeding and at least one of the other assessed symptoms.

Outcome assessment for rectal bleeding at each interim period (week 2, 4, and 8) encompassed a 4 day period (96 hours). This was a change from the 24 hour period stated in the protocol. The protocol was amended after study completion but before unblinding of the data. The change was made because the longer period provided more stable data and less intra-patient variability.

All 154 patients enrolled were started on treatment. No significant demographic differences were noted among the three groups. Assessment was performed at week 2, 4 and 8 of treatment. At week 2, 150 patients were evaluable, at week 4, 125 patients were evaluable, at week 8, 109 of the initial 154 patients were evaluable. The number of patients withdrawn was similar in the three treatment groups, however, withdrawal for inadequate therapeutic effect involved 13 patients in the low dose balsalazide, 6 patients in the high dose balsalazide and 10 patients in the Asacol group.

Imbalance in disease activity scores at entry was observed among the group. The high dose balsalazide group had higher number of patients with severe grade sigmoidoscopy score but a lower number of patients with severe grade scores by biopsy; more patients in the high dose balsalazide group had mild scores by PGA.

A total of 147 patients from the 154 enrolled and treated (92.9%) were evaluable for efficacy.

A statistically significant difference for improvement in rectal bleeding was observed at the final assessment at week 8 between high dose and low dose balsalazide (65% vs 32% respectively; p=0.006), no difference was observed between high dose balsalazide and Asacol. The results were similar in the ITT analysis. In terms of absence of bleeding at week 8, this was achieved by 35% in the low dose group, 65% in the high dose group, and 47% in the Asacol group.

Stool frequency was significantly improved in the high dose compared to the low dose balsalazide group (58% vs 28% respectively; p=0.008). This difference was statistically significant even after multiple comparisons adjustment. No difference between high dose and Asacol groups was noted (58% vs 53%).

No differences among groups were noted for Patient Functional Assessment (PFA) and abdominal pain at any of the assessment periods. A trend in favor of the high dose balsalazide group was observed for sigmoidoscopy scores at week 8, no difference between balsalazide and Asacol was noted.

The Physician Global Assessment showed a significantly higher percentage of patients improved at week 8 in the high dose versus the low dose balsalazide group in the evaluable patient population analysis (106/154 or 68%), the difference was not statistically significant in the ITT analysis.

An overall assessment of the effects of treatment was made by assessing the proportion of patients improved by PGA plus 1 other symptom without worsening of any symptom: the high dose balsalazide was numerically superior to the low dose, but not different from Asacol.

When efficacy was assessed in terms of "remission" both symptomatic and by sigmoidoscopy, no difference among the three groups was observed. At week 8, 20% in the low dose, 22% in the high dose balsalazide and 18% in the Asacol groups had achieved remission.

In conclusion, the efficacy of balsalazide at the higher dose of 6.75 g/d was demonstrated for rectal bleeding, stool frequency and sigmoidoscopy scores.

No superiority of the higher dose balsalazide versus Asacol was demonstrated. Although no placebo group was included in the study, the statistically significant difference between balsalazide dose groups validates the efficacy results of balsalazide.

Pivotal Trial 57-3001: "A balsalazide/5-ASA comparison in Ulcerative Colitis." This clinical trial was a double blind, randomized, multi center study of patients with sigmoidoscopy verified grade 2-4 symptomatic (moderate/severe) UC treated with either balsalazide 2.25 g/tid (6.75 g/d) or mesalamine 0.8 g/tid (2.4 g/d). The symptomatic assessment was provided by patients' diary of stool frequency and rectal bleeding.

Primary efficacy variable was the number of patients achieving complete remission after 12 weeks of treatment. Efficacy assessment was made at 4, 8, and 12 weeks. Complete remission was defined as symptomatic remission (none or mild symptoms), no requirement for rescue medications during the past 92 hours prior to visit, and grade 0 or 1 UC on sigmoidoscopy.

The study enrolled and randomized 101 patients: 52 on balsalazide and 49 on Asacol®. Approximately 70% of the patients had moderate disease and 30% had severe disease. A total of 15 patients in the balsalazide group and 23 in the Asacol® group withdrew from the study; of these patients, 6 in the balsalazide group and 16 in the Asacol® group withdrew for treatment failure.

The percentage of patients in remission at week 4,8 and 12 was significantly higher in the balsalazide group compared to the Asacol® group (38%, 54% and 62% compared to 12%, 22% and 37%; p-values= 0.0050, 0.0018 and 0.0159 respectively).

The percentage of patients in symptomatic remission at week 2,4,8 and 12 was also significantly higher in the balsalazide group at each evaluation time. Patients in complete remission at week 4

or 8 left the acute phase of the study, but they were included as remissions for the 12 week assessment.

The results of this study showing superiority of balsalazide over Asacol® are weakened by some deficiencies in study design and data assessment. The overall symptomatic improvement was more frequent with balsalazide, however, relevant individual symptoms were assessed only in a reduced patient population.

Approximately 40% of patients in both groups did not have sigmoidoscopy proven UC. Approximately 40% of patients who were considered to have achieved sigmoidoscopic remission after treatment (31 for balsalazide and 18 for Asacol®) did not have histology at entry and after completion of treatment; furthermore, only 56% of the histology in the balsalazide patients and 40% of the Asacol® patients considered in remission were read as inactive or normal.

Supportive Clinical Trial 0028/011 and 0028/017: Two small clinical trials were conducted in the UK to compare balsalazide 6.75 g/d to sulfasalazine (SAS) 3.0 g/d. Most of the patients in these two studies had proctosigmoiditis or left-side UC and most were entered at the time of their first acute episode of UC.

A total of 50 patients were entered in **study 0028/011**, 26 to balsalazide and 24 to SAS. The number of patients in the two groups who completed the 8 week study in remission was not significantly different: 13 or 50% in the balsalazide group compared to 9 or 38% in the SAS group ($p > 0.2$).

A statistically significant difference was observed for the number of patients who withdrew because of adverse events: 1 patient in the balsalazide group compared to 9 in the SAS group ($p=0.004$). More patients completed the study not in remission in the balsalazide group than in the SAS group.

Notably a statistically significant difference was observed in both treatment groups when the effects of treatment on rectal bleeding and stool frequency at study completion were compared to study entry.

A total of 67 patients were enrolled in **study 0028\017**, 28 to balsalazide and 29 to 30 in each group. No difference in remission rates were observed between the two treatment. However

both treatments showed significant improvement over time. Notably, steroid therapy could be used in this trials if needed. Steroids requirements decreased over time in terms of frequency and dosage.

Placebo-Controlled Trial: This was a US multi center study of 180 patients treated with balsalazide or placebo. The study compared two doses of balsalazide, 4.5 g/d or 6.75 g/d to placebo in patients with active mild or moderate UC. The study duration was of 4 weeks. A total of 72 patients were entered in the balsalazide 6.75 g/d group, of these, 68 were evaluable at week 2 and 57 at week 4. Of the 35 patients entered in the placebo group, 34 were evaluable at week 2 and 31 at week 4. Of the 73 patients entered in the balsalaside 4.5 g/d group, 72 were evaluable at week 2 and 57 at week 4.

Balsalazide treatment at either dose regimen did not result in significant difference in symptom improvement, patient functional assessment, sigmoidoscopy scores, physician global assessment, overall assessment, or remission rates compared to placebo. As the study duration was limited to 4 weeks, it is not possible to draw definite conclusion of lack efficacy, particularly in view of the fact that the response rates in the other studies increased over time on treatment.

The safety of balsalazide was assessed in 1034 patients exposed to the drug. The most common adverse events were headache, abdominal pain and fatigue. Approximately 8% of patients discontinued treatment due to adverse events. Most of patients discontinued because of lack of efficacy. Serious adverse events were reported for 10 patients, of these patients, 5 experienced worsening of UC, 1 patient experienced an allergic reaction.

In conclusion, the results of 4 clinical trials indicate that balsalazide is effective for the symptomatic treatment of mild or moderate acute ulcerative colitis. The treatment with balsalazide at the dose of 6.75 g/d administered in three divided doses appears to be comparable to the recommended regimens of sulfasalazine or Asacol®. 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 8-12 weeks showed an acceptable pattern of safety.

Recommendation: I concur with Dr Prizont's recommendation that balsalazide be approvable for the "treatment of mildly to moderate ulcerative colitis", and not for remission of UC. Balsalazide should not be indicated only as a single oral agent.

The recommended oral dose of balsalazide is three 750 mg capsules administered three times daily for a total daily dose of 6.75 g. Treatment should be continued for a period of 8 weeks and up to 12 weeks for some patients.

The package insert of balsalazide has been reviewed and revised as indicated in the draft labeling.

The sponsor will be required to provide the CMC and the Biopharmaceutics information for final approval of balsalazide.

/S/

Lilia Talarico, M.D.

cc:
NDA 20,610
HFD-180
HFD-180/LTalarico
HFD-180/RPrizont
HFD-180/CSO
HFD-180/JChoudary
HFD-180/EDuffy
f/t deg: 5/26/98
wpfiles\colazide.wp5

APPEARS THIS WAY
ON ORIGINAL

PATENT INFORMATION AND CERTIFICATION STATEMENT

Product	Patent Coverage	Country	Patent Owner	Expiration Date	Patent No.
balsalazide and related salts	composition of matter/ method of manufacture /use	United States	Biorex, Ltd.	July 8, 2001	4,412,992

The undersigned declares that Patent No. 4,412,992 covers the composition. method of manufacture and method of use of balsalazide disodium. This product is the subject of this application for which approval is being sought:

Margie Nemcik-Cruz January 9, 1997

Margie Nemcik-Cruz
Director, Regulatory Affairs

Date

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINSTRATION	**OPDRA POSTMARKETING SAFETY REVIEW**	
.ilia Talarico, Director on of Gastrointestinal and Coagulation Drug Products HFD-180 PM-Melodi McNeil	FROM: DDRE II (HFD- 440)	OPDRA PID # D000492
DATE REQUESTED: Reply before July 10, 2000	REQUESTOR/Phone #:	
DATE RECEIVED: Result of PSC held June 21. 2000		
DRUG (Est): balsalazide	NDA/IND # 20-610	SPONSOR:
DRUG NAME (Trade): Colazal	THERAPEUTIC CLASSIFICATION:	
EVENT: Congenital anomalies—issue reviewed by SGE Angela Scheuerle, MD		

Executive Summary: CONCLUSIONS

Balsalazide meets three of the five criteria for establishment of a pregnancy registry and, as such, could be monitored in that fashion. However, balsalazide has close similarity to other widely used and apparently non-teratogenic medications. The active medication is only minimally absorbed and the carrier molecule is a common amino acid. If balsalazide is considered to meet other requirements for Food and Drug Administration approval, it would be reasonable to encourage provider reports of adverse pregnancy outcomes rather than pursuing formal pregnancy registration.

Of note, there are two conditions that have raised concerns in the literature regarding 5-ASA use: neonatal hyperbilirubinemia and congenital renal problems. No direct correlation has been demonstrated, and both of these clinical conditions are common, heterogeneous and usually sporadic. There may be only a coincidental association. The CDER may want to consider having some wording on physician and patient product information regarding these observations.

Reason for Request/Review:

Relevant Product Labeling:

Usage Information:

Search Date:	Search Type(s): X AERS X Literature Other

Search Criteria: Drug Names:

MEDDRA Terms:

Search Results:

Discussion / Conclusions:

See SGE review attached.

7/10/00

Reviewer's Signature / Date /S/	Team Leader's Signature / Date:
ion Director Signature / Date:	Office Director Signature / Date:

hments:
GE review attached [8 page review]

Cc: NDA #
HFD-XXX (Division File)/Requestor/
HFD-430/440 DD/TL/SE/Chron/Drug
HFD-400
HFD-2 (Medwatch)
:onic File Name:

APPEARS THIS WAY
ON ORIGINAL

Drug Indication - Treatment of Mild-Moderate Active Ulcerative Colitis
SGE Evaluator - Angela Scheuerle, M.D.

1) **Do these 2 cases of congenital anomalies appear to be related to the use of balsalazide, or is there insufficient information to determine that?**

The provided information relates 18 pregnancies to women taking balsalazide:

9 Healthy outcomes
3 Spontaneous abortions
2 Elective abortions with periconceptional medication exposure, but without specific malformation diagnosis
4 Pregnancies with malformations

The total number of exposed pregnancies is unknown.

Of the 4 pregnancies with malformation, two are reported as part of a controlled study: one is a case of Down syndrome in a previous pregnancy (no pregnancy exposure to the medication), and the other is a case of "bifid kidney" that is likely unrelated to medication exposure because the medication started at 12 weeks gestation. The other two cases are reported spontaneously from Europe. Both report periconceptional balsalazide use through significant portion of embryogenesis. These are the two cases of most interest in answering the above question.

Case 1 (Mfr Ctr #57-83): 25 year old mother, treated with 3000 mg/day of balsalazide 2 months prior to pregnancy until 4 weeks of pregnancy. The mother also took phentermine and folic acid. Amniocentesis was reported as normal, but the test done is not indicated. Presumably it was a chromosome report, but that cannot be assured. The baby was affected with atrial and ventricular septal defects, renal dysgenesis, low set ears and hand malformation. The latter two may be secondary complications of the renal dysgenesis. There is a suggested link between 5-ASA use and renal problems in adult patients and there is one case in the literature of renal insufficiency in a newborn conjectured to have been caused by in utero exposure to 5-ASA. Lacking more detailed information of dates or syndrome diagnosis, temporal association between balsalazide use and multiple congenital anomalies in case 1 cannot be ruled out. The phentermine exposure is problematic. Exposure dates are provided, but it is not clear how/whether they overlap with pregnancy. Phentermine is a pregnancy category C drug.

Case 2 (Mfr Ctr #57-94): Mother treated with 1500mg/day of balsalazide "for a few months" prior to pregnancy and through the first month of gestation. She also received mesalamine during pregnancy. The infant was live born and was reported with "multiple congenital anomalies". There is insufficient information on this case to determine temporal association with medication exposure. Specific information about the anomalies and exposure time would help. However, concomitant exposure to the related drug mesalamine complicates the picture. It would be very difficult to specify a problem with the balsalazide as separate from the dosage of mesalamine since mesalamine is the active ingredient of balsalazide.

Please remember that the gestational dates are estimates since 4 weeks pregnancy from LMP is only 2 weeks post conception - when discussing embryogenesis, that 2 week difference is important. Also lacking is the total number of pregnancies. We know that for the one controlled trial, but the two European spontaneous reports do not indicate incidence/prevalence of defects in exposed pregnancies.

So, temporal association with balsalazide exposure cannot be ruled out for case one, and there are complicating factors. There is insufficient information in case 2 to determine temporal association.

2) What is your opinion as to balsalazideís teratogenicity, based on the information provided?
What further information would be desirable to understand more definitely this drug's potential to have an adverse affect on fetal outcome?

The information available about teratogenicity is about the related drugs - sulfasalazine, mesalamine and olsalazine. The current Catalog of Teratogenic Agents indicates that sulfasalazine does not have increase malformation rate; however, the related compound sulfonamide does show a significant increase in renal agenesis and cleft palate in mice. The included literature by Vener and Spiro indicates that some studies have shown cleft palate and bony abnormalities in sulfonamide-exposed pregnancies. The active ingredient in sulfasalazine is 5-aminosalicylate, just as in all the other medications.

Ota et al, demonstrated in 1994 that mesalamine has no teratogenic effects in mice. The literature fails to show any increased teratogenicity in either humans or experimental animals and does not show cluster of any particular malformation syndrome; however, for mesalamine the available information for many MedWatch cases is simply "congenital malformation NOS". The sulfasalazine and mesalamine have been in use for many years and it seems reasonable to assume that measurable teratogenicity would have been demonstrated by now. Olsalazine comprises two molecules of mesalamine so presumably has the same teratogenicity.

Balsalazide is formed from a molecule of mesalamine and a molecule of alanine. Alanine is a common amino acid which should be inert or at least innocuous. Pharmacokinetics show that balsalazide is minimally absorbed, does not accumulate in tissue, and is largely excreted in the feces as its metabolites. Thus, there should be minimal chance of fetal exposure to either the drug or its metabolites. There are only two reported cases of fetal malformation, neither of which can be confirmed as related to the medication.

My opinion, based upon the available information, is that balsalazide's teratogenicity is probably low; however, that opinion is not based upon demonstrated safety, only upon inference from the related relevant information.

The drug's potential teratogenic affects could best be measured by a prospective study of all exposed pregnancies. This would provide the two most helpful pieces of information: 1) what percentage of all exposed pregnancies have adverse outcomes and; 2) within the set of adverse outcomes, is there a particular pattern of structural malformation or physiologic dysfunction. These questions could also be answered by a case-control study or pregnancy registry.

3) Does balsalazide look any different than the other drugs used to treat Ulcerative Colitis, based on the AERS reports?

Please see above answer to question #2 for the comparison of teratogenicity based upon the literature.

Included in the evaluation packet are many adverse event reports for mesalamine, sulfasalazine and olsalazine. The spectrum of malformations is comparable among the three drugs. Balsalazide simply has not been used enough to generate many AER and, as such, a spectrum of malformation is not present. Generally speaking, the medications are similar because of the lack of specific teratogenicity, which may or may not be significant.

Somewhat more information is available in the published literature, but again the studies are not congruent. The review article by Venter and Spiro is very helpful in that it lists all the publications to date; however, primary reports sometimes exclude infants with malformations from their statistical analyses, so it is difficult to interpret summaries in which no congenital anomalies are reported.

Biochemically, balsalazide seems to be similar to the other medications. It contains the same active moiety. The difference is the inactive transporter. If the mesalamine is truly non-teratogenic, as the other studies seem to report, then it is likely that balsalazide is equally non-teratogenic.

4) **What is the background rate for adverse fetal outcome in women with ulcerative colitis: is it higher than that for the general population? Is it possible that there could be confounding by indication (i.e., the underlying condition increases the risk for congenital anomalies, not the drugs)?**

The available studies show no increased risk for adverse fetal outcome in women with Ulcerative Colitis. In fact, there appears to be no significant adverse effect on fertility or ease of conception. There is an increased percentage of "voluntary infertility" in women with Ulcerative Colitis, but that is not a medical issue.

It is possible that the presence of Ulcerative Colitis in the mother could contribute to apparent medication teratogenicity. Though unlikely for Ulcerative Colitis itself, there are cases in which chronic maternal disease itself can cause a problem in the baby. For example, in maternal myasthenia gravis antibodies from the mother's autoimmune disease cross the placenta and cause transient neuromuscular problems in the baby. The baby recovers when the mother's antibodies are cleared from the system. More likely for Ulcerative Colitis, secondary problems from the disease could be teratogenic. The complications of malnutrition and other medication exposure are most likely to cause problems in the baby. (The increasingly obvious importance of folic acid in normal embryologic development suggests that malnutrition may be a particular problem.)

5) Referring to the Pregnancy Registry Guidance to Industry, do you think the sponsor should consider conducting a prospective registry of exposed women?

According to the Pregnancy Registry Guidance to Industry, there are five criteria for a pregnancy registry. I will evaluate each of these criteria for balsalazide:

1) Live, attenuated vaccines or other products with the potential to cause subclinical infection in the mother.

Not applicable to balsalazide.

2) Any product expected to be used commonly by women of reproductive potential.

Balsalazide is intended for treatment of acute and chronic Ulcerative Colitis. Ulcerative Colitis most frequently affects people ages 15 to 40 and half of the affected patients are women, thus it may be expected that roughly half of the potential balsalazide recipients are women of reproductive age. Ulcerative Colitis has not been shown to diminish the biologic fertility of affected women, though there is an increased rate of voluntary infertility and one study showed that about 40% of women with Ulcerative Colitis have completed their families by the time of disease onset. There is a baseline population infertility rate of about 10%. So, it must be assumed that 90% of reproductive age women with Ulcerative Colitis have a reproductive potential. This translates to approximately 40% of potential balsalazide patients. Thus, within the target patient population, balsalazide may be used commonly by women of reproductive potential.

3) Products continued during pregnancy because they are necessary for conditions associated with high morbidity or mortality.

Ulcerative Colitis has a significant morbidity, though the disease course and severity vary among patients. Because of its chronicity, medications are used long-term. If symptoms are severe around or during pregnancy, medications, including balsalazide are likely to be used because of danger to the mother's health.

4) **Products suspected of adverse effects in human pregnancy based on structure, pharmacologic activity, pharmaceutical class, findings from laboratory animal studies or spontaneous human case reports.**

Balsalazide shares a biochemical structure with other Ulcerative Colitis drugs currently on the market. The active compound in all is 5-aminosalicylate (5-ASA). The drugs differ in their transporter molecules. Balsalazide employs the amino acid alanine as a covalently bound transport compound. (Sulfasalazine breaks down into sulfapyridine and 5-ASA, mesalamine is 5-ASA alone and olsalazine is two molecules of 5-ASA).

5-Aminosalicylate is poorly absorbed in the intestines, the primary site of action in Ulcerative Colitis, so there is little systemic exposure. Additionally, the other 5-ASA medications have not been shown to increase birth defect rates. Spontaneous reports of serious isolated or syndromic malformations are few.

Ulcerative Colitis is a fairly common condition, and since a significant number of affected patients are women of child bearing age, it must be assumed that many pregnancies have been exposed to one or more of the available medications; however, without knowing the actual exposure rate, it is impossible to determine the relative risk for adversely affected pregnancy.

5) **Products known to be harmful if used during human pregnancy, but for which the magnitude or other risk characterization is unknown.**

At the current time, this criterion can not be said to apply to balsalazide.

Conclusion:

Balsalazide meets three of the five criteria for establishment of a pregnancy registry and, as such, could be monitored in that fashion. However, balsalazide has close similarity to other widely used and apparently non-teratogenic medications. The active medication is only minimally absorbed and the carrier molecule is a common amino acid. If balsalazide is considered to meet other requirements for Food and Drug Administration approval, it would be reasonable to encourage provider reports of adverse pregnancy outcomes rather than pursuing formal pregnancy registration.

Of note, there are two conditions that have raised concerns in the literature regarding 5-ASA use: neonatal hyperbilirubinemia and congenital renal problems. No direct correlation has been demonstrated, and both of these clinical conditions are common, heterogeneous and usually sporadic. There may be only a coincidental association. The CDER may want to consider having some wording on physician and patient product information regarding these observations.

EXCLUSIVITY SUMMARY for NDA # 20-610 SUPPL # N/A

Trade Name Colazal Generic Name balsalazide disodium
Applicant Name Salix Pharmaceuticals, Inc. HFD- 180

Approval Date 7/18/00

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X__/- NO /___/

   b) Is it an effectiveness supplement? YES /___/_ NO /_X__/

      If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

   d) Did the applicant request exclusivity?

YES /___/ NO /__X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product. **NOT APPLICABLE**

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ - NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
	_____
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

/S/ 6/19/00
Signature of Preparer Date
Title: Project Manager

/S/ 7-12-00
Signature of Office of Division Director Date

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

CLAIMED EXCLUSIVITY

Salix Pharmaceuticals, Inc. hereby claims exclusivity for Colazide® (balsalazide disodium) Capsules under 21 CFR 314.108(b)(2). Colazide® is a new drug product which is the subject of this application, NDA 20-610.

No drug product containing balsalazide disodium, the active moiety in Colazide® Capsules for which Salix Pharmaceuticals, Inc, seeks approval, has previously been approved under section 505(b) of the Food, Drug and Cosmetic Act.

Margie Nemcik-Cruz 4/4/97

Margie Nemcik-Cruz
Director Regulatory Affairs

Date

APPEARS THIS WAY
ON ORIGINAL

SALIX
Pharmaceuticals, Inc.

DEBARMENT CERTIFICATION

NDA 20-610

——— (balsalazide disodium)

Salix Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any persons debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application (NDA20-610).

3/17/00

Lorin Johnson, Ph.D.
Sr. Vice President Development and Chief Scientific Officer
Salix Pharmaceuticals, Inc.

Date

APPEARS THIS WAY
ON ORIGINAL

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

DEBARMENT CERTIFICATION STATEMENT

The undersigned certifies that Salix Pharmaceuticals, Inc, did not and will not knowingly use in any capacity the services of any person debarred under subsection (a) or (b) [section 306 (a) or (b)] of the Generic Drug Enforcement Act of 1992 in connection with NDA 20-610 for Colazide® (balsalazide disodium) Capsules.

Margie Nemcik-Cruz 4/4/97

Margie Nemcik-Cruz
Director, Regulatory Affairs

Date

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: July 10, 2000

APPLICATION NUMBER: NDA 20-610; Colazal (balsalazide disodium) Capsules

BETWEEN:

Name: Mr. David Kashiwase, Regulatory Affairs
Dr. Lorin Johnson, Sr. VP Development & Chief Scientific Officer

Representing: Salix Pharmaceuticals, Inc.

AND

Name: Ms. Melodi McNeil, Project Manager
Dr. Lilia Talarico, Division Director
Dr. Steven Aurecchia, Deputy Division Director
Dr. Hugo Gallo-Torres, GI Team Leader
Dr. Robert Prizont, Reviewing Medical Officer
Dr. Jasti Choudary, Supervisory Pharmacologist
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Dr. Yi Tsong, Statistical Reviewer
Division of Biometrics, HFD-715
Dr. Suliman Al-Fayoumi, Biopharmaceutics Reviewer
Division of Biopharmaceutics, HFD-870

SUBJECT: Colazal Labeling Revisions

BACKGROUND: NDA 20-610 provides for Colazal (balsalazide disodium) Capsules in the treatment of mildly to moderately active ulcerative colitis. The application is due for sign-off (at the Office level) on July 25, 2000.

On July 6, 2000, the Division faxed the firm marked up draft labeling. (See July 6, 2000 t-con memo.) In response, the firm provided a July 6, 2000 fax (attached). The fax contained the firm's counterproposal, along with supporting justification, for four areas in the labeling. Today's teleconference was arranged to discuss these four areas.

TODAY'S PHONE CALL:

Note: The first four discussion points below correspond with the numbering of items in the firm's proposed agenda, contained in their July 6, 2000 fax.

1. FDA agreed that the fourth sentence of the CLINICAL PHARMACOLOGY section, Absorption subsection could read, "In a study of ulcerative colitis patients receiving balsalazide, 1.5 grams twice daily, for over one year, systemic drug exposure, based on mean AUC values, was up to 60 times greater (8 ng*hr/mL to 480 ng*hr/mL) after equivalent multiple doses of 1.5 grams twice daily when compared to healthy subjects who received the same dose."

2. —

   —

   —

3. The FDA reiterated that the last sentence, second paragraph of the PRECAUTIONS section, Carcinogenesis, Mutagenesis, Impairment of Fertility subsection is to read, "However, it was genotoxic in the *in vitro* Chinese hamster lung cell...forward mutation test," and the firm agreed.

   The Division agreed that the firm could revise the first sentence of this paragraph to read, "Balsalazide disodium was not genotoxic in the following *in vitro* or *in vivo* tests:..."

4. Based on the information provided in the firm's July 6, 2000 fax, and the July 10, 2000 consult review by an SGE geneticist, the Division agreed that the package insert need not describe the single case of congenital abnormality that occurred in the newborn child of a woman treated early in pregnancy with balsalazide. At the Division's request, the firm agreed to report and analyze every case of congenital abnormalities the newborns of in pregnant women treated with Colazal, and to prominently display this information in the Periodic safety reports.

5. Note: Division representatives clarified that in the July 6, 2000 fax to Salix, Figures 1 and 2 were inadvertently transposed.

The call was then concluded. Note: The labeling which resulted from today's teleconference is attached. The background text is the labeling that was faxed to Salix on July 6, 2000. Added text conveyed in today's teleconference is indicated by a double underline; deleted text that was agreed to in today's teleconference is indicated by a strikethrough.

/S/ 7/12/00

Melodi McNeil
Regulatory Health Project Manager

cc: Original NDA 20-610
HFD-180/Div. File
HFD-180/McNeil
RD Init: JChoudary 7/11/00
SAl-Fayoumi 7/11/00
SAurecchia 7/11/00
LTalarico 7/11/00

TELECON

Number of Pages Redacted 4

❖❖❖

Draft Labeling
(not releasable,

MEMORANDUM OF TELECON

DATE: July 6, 2000

APPLICATION NUMBER: NDA 20-610; Colazal (balsalazide disodium) Capsules

BETWEEN:

Name: David Kashiwase, Regulatory Affairs
Phone: (650) 849-5908
Representing: Salix Pharmaceuticals, Inc.

AND

Name: Melodi McNeil, Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: FDA Requests for Labeling Revision

BACKGROUND: NDA 20-610 provides for Colazal (balsalazide disodium) Capsules in the treatment of mildly to moderately active ulcerative colitis. The application is due for sign-off (at the Office level) on July 25, 2000.

The firm's most recently submitted labeling (submitted June 21, 2000) was revised by the Division, based on the various discipline review recommendations and faxed to the applicant. Note: The labeling that was faxed to the applicant is provided as an attachment. The background text is the firm's June 21, 2000 labeling; FDA deletions are represented by a strikethrough, and FDA additions are represented by a double underline.

TODAY'S PHONE CALL: I informed Mr. Kashiwase that FDA revised labeling had just been faxed. I asked him to provide a response as quickly as possible, given the rapidly approaching user fee goal date. I also reminded him that the requested labeling revisions reflected division-level review only. Specifically, I said that once the review package is sent to the Office, additional requests for labeling (or other) revisions may be forthcoming. The call was then concluded.

/S/ 7/10/00

Melodi McNeil
Regulatory Health Project Manager

cc: Original NDA 20-610
HFD-180/Div. File
HFD-180/McNeil

TELECON

Number of Pages Redacted 6

❖❖❖

Draft Labeling
(not releasable

McNeil

NDA 20-610

Salix Pharmaceuticals, Inc.
Attention: Lorin Johnson, Ph.D.
Sr. Vice President Development and Chief Scientific Officer
3600 West Bayshore Road, Suite 205
Palo Alto, CA 94303

JUN - 5 2000

Dear Dr. Johnson:

We acknowledge receipt on May 25, 2000 of your May 23, 2000 resubmission to your new drug application (NDA) for balsalazide disodium capsules.

This resubmission, along with your April 28, 2000 amendment, contains additional labeling, a new proposed tradename, and a safety update submitted in response to our March 24, 2000 action letter.

We consider this a complete class 1 response to our action letter. Therefore, the primary user fee goal date is July 25, 2000 and the secondary user fee goal date is September 25, 2000.

If you have any questions, call me at (301) 827-7310.

Sincerely,

/S/ 6/5/00

Melodi McNeil
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 20-610
HFD-180/Div. Files
HFD-180/M.McNeil
HFD-180/Talarico
HFD-180/Aurecchia
HFD-180/Gallo-Torres
HFD-180/Prizont
HFD-180/Choudary
HFD-180/Zhou
HFD-180/Ysern
HFD-715/Permutt
HFD-715/Tsong
HFD-870/Doddapaneni
HFD-870/Al-Fayoumi

DISTRICT OFFICE
Drafted by: mm/June 5, 2000
final: June 5, 2000
filename: c;\mydocuments\cso\n\20610006-ack.doc

CLASS 1 RESUBMISSION ACKNOWLEDGEMENT (AC)
(DDR: Update the user fee goal date based on the class of resubmission.)

MemEL

MEMORANDUM OF TELECON

DATE: March 24, 2000

APPLICATION NUMBER: NDA 20-610; balsalazide disodium capsules

BETWEEN:

Name: Lorin Johnson, Sr. VP and Chief Scientific Officer
Bob Ruscher, President & CEO
Randy Hamilton, Chairman of the Board
David Kashiwase, Regulatory Affairs Consultant
Debra Hathaway, VP Regulatory Affairs
Phone: 650-849-5908
Representing: Salix Pharmaceuticals

AND

Name: Bronwyn Collier, Associate Director for Regulatory Affairs, ODE III (HFD-103)
Alice Kacuba, Regulatory Project Manager, Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

SUBJECT: Labeling and approvable action

Prior to issuing the March 24, 2000 approvable letter for balsalazide disodium capsules, I called the applicant to explain the following conclusions we had reached regarding the data submitted:

The review was very difficult due to issues concerning the active comparator, mesalamine, used in the clinical trials. Specifically, the comparator was not valid as the drug used was not approved in the U.S. –It was very disturbing to us that the information relating to the comparator drug used came so late in the review of this application. This put us in a difficult position and has been the subject of intense discussions within the review division and with this office. We concluded that the mesalamine products approved here in the U.S. and in Europe are not bioequivalent. In addition, the studies submitted to support efficacy were conducted in different populations (the populations were related but not the same).

There was strong feeling that a second trial would be necessary to approve the drug. Nevertheless, we concluded that, although none of the data support that the mesalamine used as a comparator and the mesalamine approved in the U.S. are bioequivalent, the studies do support activity of balsalazide.

In addition, I explained that while an approvable letter would be issued, the labeling that is subject to the action would be very different from labeling associated with the June 15, 1998 approvable letter. Because the data from the active comparator were not valid and the drug used was not bioequivalent to the U.S. product, no comparisons or comparative claims to mesalamine

will be allowed in the labeling. In order to retain information regarding mesalamine in the labeling, another study will have to be conducted using the U.S. approved mesalamine product. In response to the firm's questions, Ms. Kacuba and I informed them that their response to the approvable letter will need to address labeling and the proposed trade name, — , as it was found unacceptable (too similar to other trade names already in use—e.g. Pentasa). The resubmission would be a class 1 resubmission. Finalization of phase 4 commitment agreements will be handled in the next review cycle with the resubmission. And finally, copies of the reviews can not be release until after an application is approved. The call was then concluded.

/S/ 3/27/2000
Bronwyn Collier
Associate Director for Regulatory Affairs, ODE III

cc: Original NDA 20-610
HFD-180/Div. File
HFD-103/F.Houn, V.Raczkowski, Bronwyn Collier
HFD-180/A.Kacuba, M.McNeil, L.Talarico, S.Aurecchia

TELECON

APPEARS THIS WAY
ON ORIGINAL

FDA

TO:

Name: Lorin Johnson
David Kashiwasi
Fax No: 650-856-1555

Phone No: 650-849-5908

Location: Salix Pharmaceuticals, Inc.

FROM:

Name: Alice Kacuba

Fax No: 301-443-9285

Phone No: 301-827-7450

Location: FDA/HFD-180

Attached is the action letter and FDA revised labeling for NDA 20-610, balsalazide disodium capsules. This fax is 15 pages long, which includes a 3 page action letter and 12 pages of labeling.

Please confirm receipt of fax by phone. Thank you.

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES		S.COD
03/24 15:13	05'12"	9165085615555	016/016	OK			0000

NO.	MODE	BOX	GROUP
462	TX		

MESSAGE CONFIRMATION

03/24/00 15:18
ID=FDA/ODE-111

McNeil

NDA 20-610

Salix Pharmaceuticals, Inc.
Attention: Lorin Johnson, Ph.D.
Vice President Research and Development
3600 W. Bayshore Road, Suite 205
Palo Alto, CA 94303

OCT 28

Dear Dr. Johnson:

We acknowledge receipt on September 24, 1999 of your September 23, 1999 resubmission to your new drug application (NDA) for —— (balsalazide disodium) Capsules.

This resubmission contains additional chemistry, manufacturing, and controls, labeling, clinical, and biopharmaceutics information submitted in response to our June 15, 1998 action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is March 24, 2000.

If you have any questions, contact me at (301) 827-7310.

Sincerely,

/S/ 10/28/99

Melodi McNeil
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 20-610
HFD-180/Div. Files
HFD-180/M.McNeil
HFD-180/Talarico
HFD-180/Aurecchia
HFD-180/Gallo-Torres
HFD-180/Prizont
HFD-180/Zhou
HFD-180/Ysern
HFD-715/Flyer
HFD-715/Tsong
HFD-870/Lee
HFD-870/Al-Fayoumi
HFD-103/Houn
HFD-103/Raczkowski
DISTRICT OFFICE

Drafted by: mm/October 28, 1999
final: October 28, 1999
filename: c:\mydocuments\cso\n\20610910-ack.doc

CLASS 2 RESUBMISSION ACKNOWLEDGEMENT (AC)
(DDR: Update the user fee goal date based on the class of resubmission.)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-610

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

SEP 28 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/

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

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

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, ——— (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 ———————) 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.

L. Johnson

13 Oct 1999

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

Date

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

NDA 20 610

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

JUN 23 1999

Dear Dr. Johnson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for balsalazide disodium Capsules.

Please also refer to your pending June 23, 1997 new drug application for [redacted] balsalazide disodium) Capsules and to the June 15, 1998 approvable letter in which you were requested (among other things) to conduct a pharmacokinetic study.

We also refer to your November 20, 1998 IND amendment, submitted at our request, which contained Protocol **CP 109801** entitled "A Multiple-Dose Pharmacokinetic Study of Balsalazide Disodium in Patients with Active, Mild to Moderate Ulcerative Colitis."

We have completed our review of your submission and have the following comments and information requests:

1. Please indicate whether the pharmacokinetic study will be conducted with the balsalazide disodium formulation proposed for marketing, as requested in the approvable letter.

2. Please ensure that a complete assay description and validation, i.e., specificity, linearity, sensitivity, stability of the samples, accuracy and precision for the drug and metabolites is included in the study report.

3. Since balsalazide will be administered as three daily divided doses, please comment on whether AUC_{0-t}, where t is the time within each divided dosing interval (e.g., AUC 5 to 10 hours after the morning dose, i.e., AUC_{0-5}), may be a more relevant pharmacokinetic parameter compared to AUC_{0-24}. Also, regarding t_{max} and C_{max}, on days 14 and 56, there will be three t_{max} and C_{max} values. Please further elaborate or define what is meant by t_{max} and C_{max} (section 11.2 of the protocol). Likewise, there will be three C_{min} assessments/measurements. Please further elaborate on the proposed "C_{min}" value as stated in the protocol. Specifically, please indicate which of the three C_{min} values will be reported.

4. Please provide information regarding the composition of the meals to be administered in the pharmacokinetic study. In addition, the manner in which balsalazide will be administered in relation to meals (i.e., fasting, before, after, or with meals) should be specified.

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

Sincerely yours,

/S/ 6/22/99

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

cc:
Archival
Archival NDA 20-610
HFD-180/division file
HFD-180/McNeil
HFD-870/Lee
HFD-870/Al-Fayoumi

Drafted by: mm/June 21, 1999
Initialed by: DLee 6/10/99
LTalarico 6/21/99
Final: June 22, 1999
filename: c:\mydocuments\cso\

INFORMATION REQUEST (IR)

APPEARS THIS WAY
ON ORIGINAL

C50/McNeil

MEMORANDUM OF TELECON

DATE: March 25, 1999

APPLICATION NUMBER: NDA 20-610: balsalazide disodium capsules

BETWEEN:

Name: David Kashiwase, Regulatory Affairs
Phone: (650) 849-5908
Representing: Salix Pharmaceuticals, Inc.

AND

Name: Melodi McNeil, Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Revised Dissolution Specification

BACKGROUND: NDA 20-610, sponsored by Salix Pharmaceuticals Inc., provides for balsalazide disodium capsules in the treatment of mildly to moderately active ulcerative colitis. The NDA was Approvable on June 15, 1998, pending labeling, biopharmaceutics, and chemistry, manufacturing, and controls deficiencies. In a February 1, 1999 correspondence, the sponsor proposed to correct a discrepancy associated with a transcription error in the dissolution specifications limits.

TODAY'S PHONE CALL: Based on the March 16, 1999 memo by Ms. Maria Ysern, chemistry reviewer, and Dr. Eric Duffy, chemistry team leader, I called Mr. Kashiwase and notified him that the revised dissolution specification of [redacted] at 30 minutes is acceptable. The call was then concluded.

/S/ 4/9/99
Melodi McNeil
Regulatory Health Project Manager

cc: Original NDA 20-610
HFD-180/Div. File
HFD-180/McNeil
HFD-180/Duffy
HFD-180/Ysern

TELECON

CSO/Mail Unit

MEMORANDUM OF TELECON

DATE: March 24, 1999

APPLICATION NUMBER: NDA 20-610; balsalazide disodium capsules

BETWEEN:

Name: David Kashiwase, Regulatory Affairs
Phone: (650) 849-5908
Representing: Salix Pharmaceuticals, Inc.

AND

Name: Melodi McNeil, Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Multipoint Dissolution Study

BACKGROUND: NDA 20-610, sponsored by Salix Pharmaceuticals, Inc., provides for balsalazide disodium capsules in the treatment of mildly to moderately active ulcerative colitis. The NDA was Approvable on June 15, 1998, pending labeling, biopharmaceutics, and chemistry, manufacturing, and controls deficiencies. In a February 1, 1999 correspondence, the sponsor submitted the outline for a multipoint dissolution study to support capsule composition and manufacturing changes. The firm requested review and comment of the outline by the Division's chemistry reviewers.

TODAY'S PHONE CALL: Based on the March 16, 1999 memo by Ms. Maria Ysern, Chemistry Reviewer, and Dr. Eric Duffy, Chemistry Team Leader, I called Mr. Kashiwase and notified him (via voice mail) that the proposed dissolution testing to support capsule composition and manufacturing changes is acceptable.

3/24/99

Melodi McNeil
Regulatory Health Project Manager

cc: Original NDA 20-610
HFD-180/Div. File
HFD-180/McNeil
HFD-180/Duffy
HFD-180/Ysern

TELECON

NDA 20-610

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

MAR 16 1999

Dear Dr. Johnson:

Please refer to your pending new drug application (NDA) for balsalazide disodium capsules.

We also refer to the June 15, 1998 approvable letter in which you were notified of biopharmaceutics, chemistry, manufacturing, and controls, and labeling deficiencies. (See the June 15, 1998 letter for complete details.)

The following studies, described in the NDA as pivotal, were provided by you in support of balsalazide disodium for the treatment of mildly to moderately active ulcerative colitis:

1. **CP099301** was a double-blind, double-dummy, parallel group study which randomized 154 patients with ulcerative colitis to one of three treatment groups (balsalazide 2.25 gm/day, balsalazide 6.75 gm/day, or Asacol 2.4 gm/day).

2. **57-3001** was a double-blind, double-dummy, parallel group study which randomized 101 patients with ulcerative colitis to one of two treatment groups (balsalazide 6.75 gm/day or Asacol 2.4 gm/day).

According to 21 CFR 314.126(b)(2)(iv), active treatment concurrent control occurs when the test drug is compared with known effective therapy. We have recently learned that the formulation of "Asacol" employed in both pivotal studies as an active comparator may not be currently approved for marketing in the United States. This development calls into question the validity of the clinical database upon which the June 15, 1998 approvable action was based, since the safety and/or effectiveness of the "Asacol" formulation used in the pivotal studies may never have been evaluated by this Agency.

For each pivotal study, please specify whether the formulation of the active comparator was the formulation of Asacol currently approved for marketing in the United States. If, for either study, an unapproved formulation of "Asacol" was used as the active comparator, it will be necessary for you to address the following deficiency (in addition to the deficiencies previously identified in the June 15, 1998 approvable letter) before this application can be approved:

Information regarding the specific comparability between the "Asacol" formulation used in each pivotal clinical trial and the one approved for marketing in the United States could not be located in the original NDA or subsequent submissions. Please submit this information, or provide a reference (by submission date and page number) where these data can be found. Your response

should include, at a minimum, a side-by-side comparison of the formulations for each product, a discussion of the clinical comparability between the unapproved and approved formulations, comparative dissolution data, and other clinical and physical characteristics, as well as the manufacturing source, of the unapproved "Asacol" formulation. The data showing comparability between the unapproved and approved formulations must be sufficient to demonstrate that the results of Studies **CP099301** and **57-3001** remain valid. If these data are sufficient to demonstrate such validity, please submit revised draft labeling which accurately characterizes the active comparator used in each pivotal study.

If the formulation of "Asacol" used in the pivotal studies was not identical to the one approved for use in the United States, the labeling which accompanied the approvable letter may be both false and misleading, thus rendering any product associated with it as misbranded under sec. 502(a) of the Food, Drug, and Cosmetic Act. Specifically, the CLINICAL STUDIES section suggests that the "[redacted]

Your resubmission to this application will not be considered complete and the review clock will not be activated unless the resubmission addresses all deficiencies listed in this letter and in the June 15, 1998 letter.

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

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

Sincerely,

mm 3/12/99

/S/ 3/15/99

Victor Raczkowski, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 20-610
HFD-180/Div. Files
HFD-180/M.McNeil
DISTRICT OFFICE

Drafted by: mm/December 15, 1998
Initialed by: RPrizont 12/22/98, 12/28/98
LTalarico 12/28/98, 3/11/99
DKatz 1/26/99
VRaczkowski 2/19/99, 3/5/99
final: March 12, 1999
filename: c:\mydocuments\cso\n\20610812-AE2.DOC

INFORMATION REQUEST (IR [Addendum to June 15, 1998 Approvable Letter])

CSO/McNeil

NDA 20-610

Salix Pharmaceuticals, Inc.
Attention: David Kashiwase
3600 W. Bayshore Road, Suite 205
Palo Alto, CA 94303

SEP 23 1998

Dear Mr. Kashiwase:

Please refer to your new drug application (NDA) for balsalazide disodium Capsules.

We also refer to the September 11, 1998 facsimile in which you requested copies of the biopharmaceutics and chemistry, manufacturing, and controls reviews of the application referenced above.

The reviews are enclosed for your convenience.

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

Sincerely,

/S/ /S/

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

Enclosures:
May 19, 1998 biopharmaceutics review
May 22, 1998 chemistry, manufacturing, and controls reviews

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 20-610
HFD-180/Div. Files
HFD-180/M.McNeil
HFD-870/Cronenberger
HFD-870/Lee
HFD-870/Chen
HFD-180/Duffy
HFD-180/Ysern
DISTRICT OFFICE
Drafted by: mm/September 22, 1998
final: 09/22/98
filename: c:\mydocuments\cso\n\20610809-gc.DOC
GENERAL CORRESPONDENCE

CSO/MMcNeil

NDA 20-610

Salix Pharmaceuticals, Inc.
Attention: David Kashiwase
3600 W. Bayshore Road, Suite 205
Palo Alto, CA 94303

SEP 15 1998

Dear Mr. Kashiwase:

Please refer to the teleconference between representatives of your firm and FDA on July 28, 1998. The purpose of the teleconference was to discuss the pharmacokinetics study that was requested in the June 15, 1998 Approvable letter.

As requested, a copy of our minutes of that teleconferencee is enclosed. Please notify us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, contact me at (301) 443-0483.

Sincerely,

/s/

Melodi McNeil
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Minutes of July 28, 1998 teleconference

cc:
HFD-180/Division Files
HFD-180/M.McNeil

Drafted by: mm/September 8, 1998
final: September 8, 1998
filename: 20610809.DOC

GENERAL CORRESPONDENCE (MINUTES SENT)

CSO/Mailed

NDA 20-610

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

SEP - 1 1998

Dear Mr. Kashiwase:

Please refer to your pending new drug application for balsalazide disodium Capsules.

We also refer to the June 15, 1998 letter in which you were informed that your application was Approvable, pending (among other things) final printed labeling revised as indicated in the draft labeling which accompanied the letter.

The Agency has received more than 30 spontaneous safety reports describing patients who have developed serious liver toxicity after exposure to products which contain or are metabolized to mesalamine. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Currently, there are no data which suggest that one brand name product is more or less hepatotoxic than another. In addition, although the labeling for most of these products mentions specific liver toxicity events such as hepatitis and changes in liver function tests, there are no apparent differences in the frequency of reports or the nature of these events. Therefore, the Agency is asking all manufacturers of products which contain or are metabolized to mesalamine to revise their package inserts to provide further information for the safe and effective use of these drugs, as well as consistent and inclusive labeling..

In addition to the revisions requested in the Approvable letter, please revise the package insert for balsalazide disodium Capsules as follows:

1. Create a subsection in the ADVERSE REACTIONS section entitled, "Postmarketing Reports."

2. The Postmarketing Reports subsection should read,

> "The following events have been identified during post-approval use of products which contain (or are metabolized to) mesalamine in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of seriousness, frequency of reporting, or potential causal connection to mesalamine:

Gastrointestinal:-Reports of hepatotoxicity, including elevated liver function tests (SGOT/AST, SGPT/ALT, GGT, LDH, alkaline phosphatase, bilirubin), jaundice, cholestatic jaundice, cirrhosis, and possible hepatocellular damage including liver necrosis and liver failure. Some of these cases were fatal. One case of Kawasaki-like syndrome which included hepatic function changes was also reported."

When you resubmit labeling in response to the Approvable letter, please ensure that it contains the revisions described above to be consistent with other mesalamine products.

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

Sincerely yours,

/S/ 8/31/98

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

cc:
Original NDA 20-610
HFD-180/Div. Files
HFD-180/CSO/M.McNeil
HFD-180/Gallo-Torres
HFD-180/Prizont
HFD-180/Choudary
HFD-180/Duffy
HFD-870/Chen
HFD-870/Cronenberger
HFD-870/Hunt
HFD-720/Tsong
HFD-720/Sankoh
HFD-735/Pamer
HFD-730/O'Neill

Drafted by: mm/August 31, 1998/c:\wpfiles\cso\n\19715808-mes.doc
Initialed by: LTalarico 8/31/98
final: 08/31/98

SUPPLEMENT REQUEST (SR)

APPEARS THIS WAY
ON ORIGINAL

McNeil

MEMORANDUM

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

DATE: August 31, 1998

FROM: Melodi McNeil, Regulatory Health Project Manager, Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

mm 8/31/98

AUG 3 1 1998

SUBJECT: December 4, 1997 Memo from Ms. C. Pamer, Postmarketing Safety Evaluator (HFD-735) to Dr. L. Talarico, Division Director (HFD-180)

TO: NDA 7-073
NDA 19-618
NDA 19-651
NDA 19-715
NDA 19-919
~~NDA 20-049~~
NDA 20-610

Reference is made to the December 4, 1997 memo from Ms. Carol Pamer, Postmarketing Safety Evaluator (HFD-735) to Dr. Lilia Talarico, Division Director (HFD-180) [attached], which provides a summary and analysis of cases of hepatotoxicity associated with the use of products which contain (or are metabolized to) mesalamine. According to the memo, there should be more consistent and inclusive labeling regarding hepatotoxicity for all mesalamine products. Therefore, sponsors of the applications listed above will be requested to revise the products' labeling as suggested in the memo.

Attachment: 12/4/97 memo
cc:
HFD-180/Division Files
HFD-180/McNeil (7 copies)
HFD-180/Talarico
HFD-180/Gallo-Torres

Number of Pages Redacted 11 pages

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Confidential,
Commercial Information