CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-610

MEDICAL REVIEW(S)

Medical

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Medical Officer Review

JUL 6 2000

NDA: 20-610/AL

Sponsor: Salix Pharmaceuticals, Inc

Drug: Balsalazide Disodium Capsules

Indication: Treatment of Mildly to Moderately Active Ulcerative Colitis.

Documents Submitted: (1) Proposed Amended Label, (2) Updated Safety (4 Volumes).

Date Received by the DGICDP (HFD-180): May 2, 2000

Date Received by the Medical Officer: June 3, 2000 (PM E-mail)

Date of Draft: June 27, 2000

Medical Officer: Dr. Robert Prizont, MD

I Introduction. In this document, Salix has included the following: (a) An amended proposed label, in response and compliance to the March 24, 2000 Approvable Letter from the ODE III Director, and (b) A Safety Update covering the period from April 1999 to April 2000.

II. Salix Response to the FDA Proposed Amended Label.

- *This reviewer will only present and discuss **relevant** parts the clinical section, indications, dose, and ADRs from the proposed label.*

i. Label Proposed by FDA. In the approvable March 24, 2000 letter, the Agency proposed a label which included the following relevant clinical section *(scanned)*:

CLINICAL TRIALS:
Two randomized, double-blind studies were conducted.

In the first trial, 103 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 or balsalazide 2.25 g/day. The primary efficacy endpoint was reduction of rectal bleeding and improvement of at

least one of the other assessed symptoms (stool frequency, patient functional assessment, abdominal pain, sigmoidoscopic grade, and physician's global assessment). Outcome assessment for rectal bleeding at each interim period (week 2, 4, and 8) encompassed a 4 day period (96 hours). Results demonstrated a statistically significant difference between high and low doses of balsalazide.

A second study, conducted in Europe, confirmed findings of symptomatic improvement.

INDICATIONS AND USAGE: TRADENAME is indicated for the treatment of mildly to moderately active ulcerative colitis.

PRECAUTIONS: Of the 229 patients treated with TRADENAME 6.75 g/day in controlled clinical trials of active disease, exacerbation of the symptoms of colitis, possibly related to drug use, has been reported by 3 patients.

Renal: There have been no reported incidents of renal impairmer in patients taking TRADENAME. At doses up to 2000 mg/kg (approximately 21 times the recommended 6.75 g/day dose on a mg/kg basis for a 70 kg person), TRADENAME had no nephrotoxic effects in rats or dogs. Renal toxicity has been observed in animals and patients given other mesalamine produc Therefore, caution should be exercised when administering TRADENAME to patients with known renal dysfunction or a history of renal disease.

ADVERSE REACTIONS: Over 1000 patients received treatment with TRADENAME in domestic and foreign clinical trials. In controlled clinical trials patients receiving a TRADENAME dose of 6.75 g/day most frequently reported the following events (reporting frequency , headache), abdominal pain (6%), diarrhea (5%), arthralgia , nausea (3%), respiratory infection), vomiting , and

Withdrawal from therapy due to adverse events was comparable among patients on TRADENAME and placebo.

DOSAGE AND ADMINISTRATION: For Treatment of Active Ulcerative Colitis the usual dose in adults is three 750 mg capsules to be taken three times a day for a total daily dose of 6.75 grams for a duration of 8 weeks. Some patients in the clinical trials required treatment for up to 12 weeks.

ii. Amended Label Submitted by Salix. The sponsor submitted the following amended clinical sections *(scanned)*:

CLINICAL TRIALS: Two randomized, double blind studies were conducted.

In the first trial, 103 patients with active mild to moderate ulcerative colitis with sigmoidoscopy findings of friable or spontaneously bleeding mucosa were randomized and treated with balsalazide 6.75 grams/day or balsalazide 2.25 grams/day. The primary efficacy endpoint was reduction of rectal bleeding and improvement of at least one of the other assessed symptoms (stool frequency, patient functional assessment, abdominal pain, sigmoidoscopic grade, and physician's global assessment (PGA)). Outcome assessment for rectal bleeding at each interim period (week 2, 4, and 8) encompassed a 4 day period (96 hours). Results demonstrated a statistically significant difference between high and low doses of Colazal™ (Figure 1).

Figure 1 :Percentage of Patients Improved at 8 Weeks

The following Figures 2 and 3 were taken (*scanned*) from the Package Insert Draft, Vol 1/1. Figure 2 of the submitted Package Insert differs from Figure 2 in the Unannotated Package Insert, Vol. 1/7.

Figure 2 : Percentage of Patients with Sigmoidoscopic Improvement

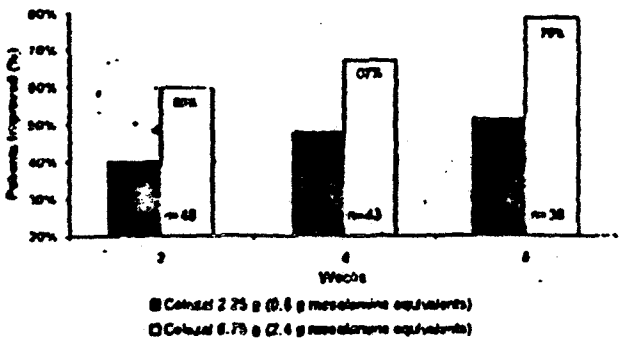
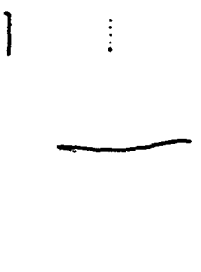


Figure 3 : Median Time to Complete Relief of Symptoms



INDICATIONS AND USAGE: Colazal™ is indicated for the treatment of mildly to moderately active ulcerative colitis.

- The remaining parts of the clinical sections, i.e., adverse reactions, dosage, duration of treatment of the Salix's Package Insert, are identical to the proposed amended FDA label.

iii. Reviewer Comments.

1. The relevant and obvious discrepancy between the proposed FDA label and the amended Salix label is in the **CLINICAL TRIALS** section. In addition, there are inconsistencies between the total number of patients randomized, i.e., 103, and the numbers included in Figures 1 and 2. My observations are the following:

(a). The **proposed FDA label** for the *first trial* included the total number of patients randomized to the trial, i.e., 103, but, it did **not** include results with numerical comparisons between the high and low balsalazide doses, of the five primary efficacy endpoint components. It merely stated that the *primary efficacy outcome was reduction of rectal bleeding and improvement of at least one of the other assessed symptoms (stool frequency, patient functional assessment, abdominal pain, sigmoidoscopic grade, and physician's global assessment).* The FDA proposed label added that *outcome assessment for rectal bleeding...demonstrated a statistically significant difference between high and low doses of balsalazide.*

In its **amendment** *(first trial)*, **Salix** included two figures with numerical and statistical comparisons between the high and low balsalazide doses. Figure 1 represents differences in primary efficacy between the two balsalazide doses in four of the five primary efficacy endpoints, i.e., stool blood , stool frequency, sigmoidoscopy and PGA. The group of patients included in this figure, encompass the evaluable patient population, and are **not** representative of the total group of 103 patients randomized to balsalazide treatment , i.e., 50 randomized to the low dose, and, 53 randomized to the high dose. For instance, this figure shows the 8 week primary efficacy in stool blood improvement of only 34/50 (68%) of patients randomized to the low dose, and 34/53 (64%) of patients randomized to the high dose. Hence, this comparison of primary efficacy of stool blood, the cardinal symptom to assess degree of ulcerative colitis (UC), excludes between 32-36% of UC patients randomized to each of the balsalazide doses.

In Pages 27-29 of my first review of this NDA (May 15, 1998), I noted exclusion of a considerable proportion of patients in the Salix Intention-to-Treat (ITT) analysis; I stated that ***"In order to fully assess the impact of exclusions upon the robustness of the primary efficacy results, this reviewer requested from the sponsor two additional ITT efficacy analysis. In ITT-1, the sponsor was required to include All-Randomized-Patients, a rigorous test for robustness in efficacy. In the ITT-2, the sponsor was required to include All-Randomized-And-Treated Patients, which is perhaps clinically, a more relevant assessment of efficacy, as long as the excluded patients represent <10% of the overall randomized population"***. In the ITT-2, as well as in the sponsor's own ITT, comparison of the PGA endpoint did not reveal statistically significant superiority of the high balsalazide over the low balsalazide dose. The comparison of the other three remaining primary efficacy endpoints included in Figure 1 by the ITT-2 analysis revealed significant superiority of the high dose. The 8-Week primary efficacy ITT-2 results of improved patients was the following *[taken from Salix Tables 20, 21, 22 (Intent-to-Treat 2), Pages 28-29, MO review, May 18, 1998]*:

Stool Blood = Low Dose 17/49 (35%) vs. High Dose 27/49 (55%); *p-value of 0.045**

Stool Frequency = Low Dose 12/49 (25%) vs. High Dose 24/49 (49%); *p-value of 0.013*

Sigmoidoscopy = Low Dose 26/50 (52%) vs. High Dose 39/53 (74%); *p-value of 0.031*

** Two Sided by Cochran-Mantel-Haenszel Test.*

In the view of this reviewer, the proportion of patients included in the proposed Salix Figure 1, i.e., 62-66%, is unacceptable. The sponsor should be given the choice of either include wording without numerical results, *as included in the proposed FDA label*, or alternatively, include a schematic or tabular comparison of primary efficacy results between the low and high balsalazide doses, using the Intention-to-Treat 2 data, included in Salix Table 20, 21, and 22.

(b) Figure 2 is repetitious, inappropriate, and, somehow misleading. The difference between the balsalazide doses in sigmoidoscopic improvement, was already represented in Figure 1, and hence, its representation in Figure 2 is repetitious. It is similarly inappropriate to select an efficacy endpoint prospectively included as part of a composite multiple primary efficacy endpoint with the purpose to highlight its relevance. The sigmoidoscopic improvement illustrated in Figure 2 does not specify whether there was some degree of improvement or a total resolution of rectosigmoid inflammation as view by endoscopy. In this sense, it is somehow, also misleading. Due to all these reasons, it would be highly advisable to omit Figure 2 from the CLINICAL TRIAL section label.

(c) Figure 3 does not add anything to the preceding text, for it has no comparison control.

III. Updated Safety.

- *This Safety Update encompasses Adverse Events (AE) associated with balsalazide treatment reported during the last 12 month period, between April 30 1999, and April 30 2000. This MO reviewed the last Safety Update (Safety Update 1), which encompassed the period from May 1998 to April 30, 1999. My review of the last Safety Update + Biopharmacology of Control Drug was completed on February 25, 2000. In this Safety Update 2, I will include only those ADR not included in my previous Safety Update. If needed, the reader will be referred to specific pages or sections of my February 2000 review.*

1. Overall Incidence of AE. The next Table 1 (*scanned*) compares the incidence of AE (≥3%) between Safety Update 1 and Safety Update 2 in acute and maintenance clinical studies with balsalazide. In Safety Update 2, there is the addition of 84 patients in the acute phase and 118 patients in the maintenance phase. As noticeable, the addition of these patients had little effect on the incidence of AE.

Table 1: Incidence of Common (≥3%) Adverse Events in Acute and Maintenance Clinical Studies of Balsalazide

Adverse Event	Acute Studies		Maintenance Studies	
	Safety Update 2 N = 513	Safety Update 1[a] N = 429	Safety Update 2 N = 962	Safety Update 1 N = 844
Headache	89 (17%)	80 (19%)	127 (13%)	120 (14%)
Abdominal Pain	76 (15%)	71 (17%)	119 (12%)	104 (12%)
Nausea	48 (9%)	40 (9%)	90 (9%)	86 (10%)
Fatigue	43 (8%)	40 (9%)	72 (8%)	70 (8%)

Scanning of Table 1 continues.

Table 1: Incidence of Common (≥3%) Adverse Events in Acute and Maintenance Clinical Studies of Balsalazide

Adverse Event	Acute Studies		Maintenance Studies	
	Safety Update 2 N = 513	Safety Update 1[a] N = 429	Safety Update 2 N = 962	Safety Update 1 N = 844
Diarrhea	38 (7%)	32 (8%	80 (8%)	71 (8%)
Dyspepsia	38 (7%)	36 (8%)	48 (5%)	46 (6%)
Flatulence	28 (6%)	23 (5%)	78 (8%)	76 (9%)
Dizziness	22 (4%)	21 (5%)	38 (4%)	37 (4%)
Vomiting	21 (4%)	16 (4%)	14 (2%)	14 (2%)
Pain	19 (4%)	17 (4%)	59 (6%)	56 (7%)
Respiratory Infection	19 (4%)	16 (4%)	71 (7%)	67 (8%)
Back Pain	16 (3%)	14 (3%)	46 (5%)	45 (5%)
Arthralgia	13 (3%)	9 (2%)	29 (3%)	29 (3%)
Rash	10 (2%)	9 (2%)	39 (4%)	36 (4%)
Infection Viral	6 (1%)	5 (1%)	35 (4%)	32 (4%)
Malaise	6 (1%)	5 (1%)	30 (3%)	30 (4%)

Note: A complete list of adverse events is presented in Table U6e-2 for acute studies and in Table U6e-5 for maintenance studies. The following adverse events from Safety Update 1 (Aug. 27, 1999) fell below 3% and, therefore, are not included in this table : cramps, flu-like disorder, constipation and pharyngitis.

2. ***Overall Incidence of AE in Well-Controlled Trials.*** The following Table 2 (*scanned*) is an update of AE (≥1%) of patients treated with balsalazide 6.75 g/d in four adequate and well-controlled acute studies of UC (CP069101, CP099301, 57-3001, and CP079701). Again, there is little or no difference in incidence of AE between Safety Update 1 and Safety Update 2. The sponsor makes reference in the text of AE in the mesalamine preparation used as comparator. The reviewer will not comment on the AE with this mesalamine preparation, since the pharmacological and clinical properties of this preparation have not been fully submitted and reviewed by this Agency.

Table 2: Incidence of Common (≥ 1%) Adverse Events in Four Adequate and Well-Controlled Studies of Balsalazide (Volunteered Complaints Excluded)

Adverse Event	Safety Update 2			Safety Update 1	
	Balsalazide 6.75 g/d N = 259	Mesalamine 2.4 g/d N = 189	Placebo[a] N = 35	Balsalazide 6.75 g/d N = 175	Mesalamine 2.4 g/d N = 100
Urinary tract infection	3 (1%)	0	0	1 (1%)	0
Constipation	3 (1%)	1 (.5%)	0	2 (1%)	1 (1%)
Cramps	3 (1%)	2 (1%)	0	3 (2%)	1 (1%)
Sinusitis	3 (1%)	3 (2%)	1 (3%)	1 (1%)	0
Myalgia	3 (1%)	4 (2%)	0	2 (1%)	2 (2%)
Flu-like disorder	3 (1%)	5 (3%)	0	3 (2%)	5 (5%)
Dizziness	3 (1%)	6 (3%)	2 (6%)	2 (1%)	2 (2%)

[a] There is no change in the placebo group.

Note: This table includes events with incidence rates ≥ 1% in patients treated with Balsalazide 6.75 g/d. A complete list of adverse events is presented in Table U6e-4. The following adverse events from Safety Update 1 fell below 1% and, therefore, are not included in this update: accident and/or injury, bowel irregularity, colitis ulcerative aggravated, dyspnea, ear infection, melena, and pruritus.

Scanning continuation of Table 2.

Table 2: Incidence of Common (≥ 1%) Adverse Events in Four Adequate and Well-Controlled Studies of Balsalazide (Volunteered Complaints Excluded)

Adverse Event	Safety Update 2			Safety Update 1	
	Balsalazide 6.75 g/d N = 259	Mesalamine 2.4 g/d N = 189	Placebo[a] N = 35	Balsalazide 6.75 g/d N = 175	Mesalamine 2.4 g/d N = 100
Headache	22 (8%)	34 (18%)	3 (9%)	13 (7%)	20 (20%)
Abdominal pain	16 (6%)	17 (9%)	1 (3%)	11 (6%)	4 (4%)
Diarrhea	14 (5%)	11 (6%)	1 (3%)	8 (5%)	3 (3%)
Nausea	14 (5%)	20 (11%)	2 (6%)	6 (3%)	7 (7%)
Vomiting	11 (4%)	5 (3%)	2 (6%)	5 (3%)	4 (4%)
Respiratory infection	9 (4%)	5 (3%)	5 (14%)	6 (3%)	5 (5%)
Arthralgia	9 (4%)	11 (6%)	0	5 (3%)	3 (3%)
Insomnia	6 (2%)	4 (2%)	0	2 (1%)	1 (1%)
Rhinitis	6 (2%)	6 (3%)	0	2 (1%)	3 (3%)
Fatigue	6 (2%)	8 (4%)	0	3 (2%)	2 (2%)
Dyspepsia	5 (2%)	7 (4%)	0	3 (2%)	5 (5%)
Flatulence	5 (2%)	8 (4%)	0	0	3 (3%)
Hemorrhage rectum	5 (2%)	4 (2%)	1 (3%)	3 (2%)	3 (3%)
Fever	5 (2%)	12(6%)	0	2 (1%)	3 (3%)
Anorexia	4 (2%)	1(.5%)	0	2 (1%)	0
Coughing	4 (2%)	2 (1%)	0	0	1 (1%)
Back pain	4 (2%)	6 (3%)	1 (3%)	2 (1%)	5 (5%)
Pain	4 (2%)	7 (4%)	1 (3%)	2 (1%)	5 (5%)
Pharyngitis	4 (2%)	11 (6%)	0	1 (1%)	5 (5%)
Dry mouth	3 (1%)	0	0	2 (1%)	0
Stools frequent	3 (1%)	0	1 (3%)	3 (2%)	0

3. Incidence of AE (≥1%) By Organ-System in Adequate and Well-Controlled Studies. Salix submitted a comparison of incidence of AE (≥1%) by organ-system between Safety Update-1 and Safety Update-2. As in the previous comparisons, there was little or no difference between the past and present safety update. Salix Tables 8, 9 and 10 illustrate this point.

Salix Tables 8,9, and 10, Pages 38, 39, 41-42, 44-46, Vol. 2, is included as Appendix 1 of this review.

4. Incidence of Serious AE. In this Update-2, there are no serious AE reported **in completed or ongoing clinical trials.** The reader is referred to Page 10, and Appendix 4 of my first review (February 25, 2000) on Safety Update-1, for specific serious AE reported by Salix. As stated in that review, most of the serious AE in patients treated with balsalazide were associated with worsening of ulcerative colitis.

5. Safety Update from Sources Other than Clinical Trials. Foreign Marketing Experience:

- Balsalazide was approved for marketing in the United Kingdom in July 14, 1997, and in 1998 was approved in Austria, Denmark, Sweden, Luxembourg, Italy and Belgium (see MO Review on Safety-1, February 2000). According to Salix, the **European Safety Update Report of July 1999, stated that approximately [redacted] corresponding to about [redacted] treatment days have been sold since the product was first launched in the UK** (July 1997).

In this latest European Safety Update Report two ***"serious unexpected"*** events of congenital abnormalities from the UK following balsalazide treatment. The report narratives of these two postmarketing AE, are the following:

1. [redacted]. Reported initially on July 14, 1999, and a follow-up COMIS on January 19, 2000. This is a 25 year old female (UK), who received treatment with balsalazide (Colazide) capsules, 3000 mg/day for two months prior to her pregnancy (*Manufacturer: AstraZeneca R&D Lund, LUND, Sweden. Mfr Ctrl No 57-83*). On confirmation of pregnancy. balsalazide treatment was discontinued. At 28 weeks gestation, a scan revealed a possible heart defect, abnormal fingers and pleural effusion. At 34 weeks amniocentesis was done because of polyhydramnious. The results were normal. The baby was born 15 days before the date of expected delivery. Low set ears and facial features were observed. The baby was diagnosed with atrial and ventricular septal defect, The report considered the event serious; a congenital anomaly/birth defect.

In the follow-up report of January 19, 2000, Salix letter to the Division Director stated that *"A causal relationship to the drug cannot be confirmed. However, Salix is taken a conservative position by reporting this event as a Safety Report".*

2. [redacted] Female patient (UK, initials and age unknown), received treatment with balsalazide (1500 mg/day) for a few months prior to pregnancy and during the first month of pregnancy. She also received mesalazine (US mesalamine) during this period. The baby was born with multiple congenital abnormalities (not specified in the report).

IND Reports of these two reproductive SAE are included as Appendix 2 of this review.

ii. A third postmarketing SAE came from Sweden, and reports abnormal liver function tests (LFT). The Swedish authorities reported that a 30 y old female who received 2 weeks of balsalazide (6750 mg/d) for ulcerative colitis, was hospitalized because of deterioration of UC and LFT, i.e. elevation of bilirubin (30 μmol/L), ASAT (13.45 μmol/L), ALT (40.63 μmol/L), prothombrin time decreased (78% to 62%). Concomitant medications were prednisolone and

contraceptives. She was hospitalized for 13 days and discontinued from balsalazide and oral contraceptives. Serology for viral hepatitis was negative. Her condition resolved app. 1 month later. The LFT AE were considered probably related to balsalazide administration.

The CIOMS report of this Swedish AE. Appendix D, Vol 6 of this submission, is included as Appendix 3 of this review.

i. Reviewer Comments.

1. With the exception of the postmarketing SAE, the AE reported in this Safety Update-2 had already been examined in the last February 2000, MO review. Overall, balsalazide is a safe drug with the exception of the renal abnormalities seen in association of mesalamine therapy, and, rare worsening of ulcerative colitis, i.e., 3 cases included in the PRECAUTIONS section of the label.

2. The two postmarketing reports of congenital malformations associated with balsalazide therapy of ulcerative colitis in pregnant women, should be considered SAE. However, in considering an actual relationship to the use of balsalazide, we should take into consideration the UK prevalence of congenital anomalies, and the adverse impact of ulcerative colitis on pregnancy and the fetus. My observations are the following:

(a) The 2 congenital malformations were reported 3 years after the release of balsalazide into the UK market. As in other parts of the world, there is an UK annual prevalence of congenital anomalies, documented well before the marketing of balsalazide, in 1997. The prevalence rate of congenital anomalies in Glasgow from 1990-1996 was 241 per 10,000 live births (***see Appendix 4 of this review***). This prevalence was similar in Dublin, i.e., 243/10,000 live births. As seen in the table, the UK prevalence rate of congenital anomalies are rather high, as compared to the prevalence rate reported in 4 cities or regions from Spain, and 3 regions from Italy.

(b) The controlled and uncontrolled studies included 1910 total UC patients treated with balsalazide. Approximately, between 40-50% were women, i.e., 764-955 women treated with balsalazide. Eleven women become pregnant during these clinical trials, including women who had more than 1 pregnancy. None of the women delivered babies with congenital abnormalities while or immediately after treatment with balsalazide. One woman delivered a baby diagnosed with Down syndrome, but had not used balsalazide during pregnancy. She delivered a healthy boy while on treatment with balsalazide up to week 10 of gestation. ***This information is illustrated in Salix Table 20, Page 83, Vol. 2 and is included as Appendix 5 of this review.***

(c) Investigations conducted in Europe (Italy, France), and the US (Lenox Hill Hospital, NY) on the possible adverse effect of mesalamine, or of other drugs used in the treatment of pregnant women with ulcerative colitis, has failed to show fetal abnormalities associated with the use of these drug therapies[1,2,3,4].

(d) Pregnancy may affect ulcerative colitis. Quiescent ulcerative colitis may be re-activated into a recurrence, in some cases serious recurrences leading to fulminant ulcerative colitis and colectomy. Women with active ulcerative colitis or steroid-dependent ulcerative colitis are generally advised not to become pregnant[5,6,7,8]. Drug treatment of ulcerative colitis during pregnancy is the same as in non-pregnant women. A small and rather controversial number of publications, have reported spontaneous improvement of ulcerative colitis during pregnancy. Overall, ulcerative colitis appears not to impact upon the course of pregnancy, as long as women are closely followed and therapies are appropriate. Miscarriages are not uncommonly observed in women with active inflammation of the colon, sometimes despite good treatment.

Literature Cited by the Reviewer

1, Trallori G et al. 5-Aminosalicylic acid in pregnancy: clinical report. Ital J Gastroenterol, 26:75-78, 1994.

2. Jonville-Bera AP et al. Pentasa (mesalazine) and pregnancy. Therapie, 49:443-445, 1994.

3. Modigliani R. Drug therapy for ulcerative colitis during pregnancy. Eur J Gastroenterol Hepatol, 9:854-957, 1997.

4. Korelitz BI. Inflammatory bowel disease and pregnancy. Gastroenterol Clin North Am, 27:213-224, 1998.

5. Vender JR and Spiro HM. Inflammatory bowel disease and pregnancy. J Clin Gastroenterol, 4:231-249, 1982.

6. Boulton R et al. Fulminant ulcerative colitis in pregnancy. Am J Gastroenterol, 89:931-933, 1994.

7. Benavides E et al. Ulcerative colitis and pregnancy. Rev Med Chil, 126:363-366, 1998.

8. Fedorkow DM et al. Inflammatory bowel disease: a controlled study of late pregnancy outcome. Am J Obstet Gynecol, 160:998-1001, 1989.

IV. Recommendations for Regulatory Actions.

The following are my recommendations on the Salix amended CLINICAL TRIALS section of the label:

[redacted]

[redacted]

The following are my recommendations of the Updated Safety-2:

[redacted]

[redacted]

/S/

Robert Prizont, M.D.

cc:
NDA 20-610
HFD-180
HFD-180/LTalarico
HFD-180/SAurecchia
HFD-180/HGallo-Torres
HFD-180/RPrizont
HFD-181/MMcNeil
HFD-180/JChoudary
HFD-180/LZhou
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APPENDIX 1

Table 8: Incidence of Common (≥1%) Adverse Events in Acute Studies of Balsalazide

Adverse Event	Safety Update -2				Safety Update -1	
	Balsalazide N = 513	Mesalamine N = 189	Sulfasalazine N = 53	Placebo N = 35	Balsalazide N = 429	Mesalamine N = 100
BODY AS A WHOLE	**103 (20%)**	**48 (25%)**	**18 (34%)**	**5 (14%)**	**88 (21%)**	**27 (27%)**
Asthenia	5 (1%)	5 (3%)	3 (6%)	0	5 (1%)	3 (3%)
Back Pain	16 (3%)	6 (3%)	5 (9%)	1 (3%)	14 (3%)	5 (5%)
Fatigue	43 (8%)	13 (7%)	8 (15%)	2 (6%)	40 (9%)	7 (7%)
Fever	10 (2%)	13 (7%)	1 (2%)	0	7 (2%)	4 (4%)
Flu-like disorder	11 (2%)	5 (3%)	1 (2%)	0	11 (3%)	5 (5%)
Malaise	6 (1%)	0	1 (2%)	0	5 (1%)	0
Pain	19 (4%)	7 (4%)	2 (4%)	1 (3%)	17 (4%)	5 (5%)
Rigors (Chills)	5 (1%)	3 (2%)	2 (4%)	1 (3%)	4 (1%)	0
NERVOUS SYSTEM	**103 (20%)**	**44 (23%)**	**32 (60%)**	**8 (23%)**	**94 (22%)**	**26 (26%)**
Dizziness	22 (4%)	7 (4%)	6 (11%)	2 (6%)	21 (5%)	3 (3%)
Headache	89 (17%)	39 (21%)	30 (57%)	7 (20%)	80 (19%)	25 (25%)
GASTROINTESTINAL	**205 (40%)**	**71 (38%)**	**39 (74%)**	**9 (26%)**	**178 (42%)**	**39 (39%)**
Abdominal pain	76 (15%)	24 (13%)	16 (30%)	4 (11%)	71(17%)	12 (12%)
Colitis ulcerative aggravated	9 (2%)	5 (3%)	0	0	9 (2%)	5 (5%)
Constipation	7 (1%)	3 (2%)	1 (2%)	0	6 (1%)	3 (3%)
Diarrhea	38 (7%)	17 (9%)	2 (4%)	2 (6%)	32 (8%)	9 (9%)
Dyspepsia	38 (7%)	8 (4%)	16 (30%)	1 (3%)	36 (8%)	6 (6%)
Feces discolored	5 (1%)	0	0	0	5 (1%)	0
Flatulence	28 (6%)	12 (6%)	4 (8%)	3 (9%)	23 (5%)	7 (7%)
Hemorrhage rectum	7 (1%)	4 (2%)	0	3 (9%)	5 (1%)	3 (3%)
Melena	8 (2%)	1 (.5%)	1 (2%)	0	8 (2%)	1 (1%)
Mouth dry	7 (1%)	0	1 (2%)	0	6 (1%)	0
Nausea	48 (9%)	24 (13%)	22 (42%)	4 (11%)	40 (9%)	11(11%)

Table 8: Incidence of Common (≥1%) Adverse Events in Acute Studies of Balsalazide

Adverse Event	Safety Update -2				Safety Update -1	
	Balsalazide N = 513	Mesalamine N = 189	Sulfasalazine N = 53	Placebo N = 35	Balsalazide N = 429	Mesalamine N = 100
Stools frequent	7 (1%)	0	0	2 (6%)	7 (2%)	0
Tenesmus	10 (2%)	4 (2%)	0	1 (3%)	9 (2%)	3 (3%)
Vomiting	22 (4%)	5 (3%)	6 (11%)	2 (6%)	16 (4%)	4 (4%)
MUSCULOSKELETAL SYSTEM	**32 (6%)**	**18 (10%)**	**2 (4%)**	**1 (3%)**	**25 (6%)**	**7 (7%)**
Arthralgia	13 (3%)	11 (6%)	0	0	9 (2%)	3 (3%)
Cramps	11 (2%)	2 (1%)	1 (2%)	0	11 (3%)	1 (1%)
Myalgia	5 (1%)	4 (2%)	0	1 (3%)	4 (1%)	2 (2%)
PSYCHIATRIC	**27 (5%)**	**11 (6%)**	**12 (23%)**	**1 (3%)**	**21 (5%)**	**5 (5%)**
Anorexia	12 (2%)	1 (.5%)	3 (6%)	0	9 (2%)	0
Insomnia	9 (2%)	4 (2%)	2 (4%)	0	5 (1%)	1 (1%)
RESPIRATORY SYSTEM	**41 (8%)**	**24 (13%)**	**5 (9%)**	**6 (17%)**	**31 (7%)**	**15 (15%)**
Coughing	7 (1%)	3 (2%)	1 (2%)	0	3 (1%)	2 (2%)
Pharyngitis	7 (1%)	11 (6%)	2 (4%)	0	4 (1%)	5 (51%)
Respiratory infection	19 (4%)	5 (3%)	3 (6%)	5 (14%)	16 (4%)	5 (5%)
Rhinitis	9 (2%)	7 (4%)	0	0	5 (1%)	4 (4%)
Sinusitis	6 (1%)	3 (2%)	0	1 (3%)	4 (1%)	0
OTHER						
Eosinophilia	6 (1%)	0	0	0	6 (1%)	0
Infection viral	6 (1%)	4 (2%)	4 (8%)	0	5 (1%)	2 (2%)
Rash	10 (2%)	2 (1%)	4 (8%)	0	9 (2%)	2 (2%)

Note: This table includes events with incidence rates ≥1% in patients treated with Balsalazide.
A complete list of adverse events is presented in Table U6e-2.

Table 9: Incidence of Common (≥1%) Adverse Events in Four Adequate and Well-Controlled Acute Studies of Balsalazide

Adverse Event	Safety Update 2			Safety Update 1	
	Balsalazide 6.75 g/d N = 259	Mesalamine 2.4 g/d N = 189	Placebo[a] N = 35	Balsalazide 6.75 g/d N = 175	Mesalamine 2.4 g/d N = 100
BODY AS A WHOLE	**45 (17%)**	**48 (25%)**	**5 (14%)**	**30 (17%)**	**27 (27%)**
Back pain	8 (3%)	6 (3%)	1 (3%)	6 (3%)	5 (5%)
Fatigue	17 (7%)	13 (7%)	2 (6%)	14 (8%)	7 (7%)
Fever	5 (2%)	13 (7%)	0	2 (1%)	4 (4%)
Flu-like disorder	3 (1%)	5 (3%)	0	3 (2%)	5 (5%)
Pain	5 (2%)	7 (4%)	1 (3%)	3 (2%)	5 (5%)
NERVOUS SYSTEM	**36 (14%)**	**44 (23%)**	**8 (23%)**	**27 (15%)**	**26 (26%)**
Dizziness	6 (2%)	7 (4%)	2 (6%)	5 (3%)	3 (3%)
Headache	34 (13%)	39 (21%)	7 (20%)	25 (14%)	25 (25%)
GASTROINTESTINAL	**89 (34%)**	**71 (38%)**	**9 (26%)**	**61 (35%)**	**39 (39%)**
Abdominal pain	23 (9%)	24 (13%)	4 (11%)	18 (10%)	12 (12%)
Constipation	4 (2%)	3 (2%)	0	3 (2%)	3 (3%)
Diarrhea	23 (9%)	17 (9%)	2 (6%)	17 (10%)	9 (9%)
Dyspepsia	11 (4%)	8 (4%)	1 (3%)	9 (5%)	6 (6%)
Flatulence	14 (5%)	12 (6%)	3 (9%)	9 (5%)	7 (7%)
Hemorrhage rectum	6 (2%)	4 (2%)	3 (9%)	4 (2%)	3 (3%)
Melena	4 (2%)	1 (0.5%)	0	4 (2%)	1 (1%)
Mouth dry	3 (1%)	0	0	2 (1%)	0
Nausea	21 (8%)	24 (13%)	4 (11%)	13 (7%)	11 (11%)
Stools frequent	5 (2%)	0	2 (6%)	5 (3%)	0
Tenesmus	3 (1%)	4 (2%)	1 (3%)	2 (1%)	3 (3%)
Vomiting	11 (4%)	5 (3%)	2 (6%)	5 (3%)	4 (4%)
MUSCULOSKELETAL SYS	**19 (7%)**	**18 (10%)**	**1 (3%)**	**12 (7%)**	**7 (7%)**
Arthralgia	10 (4%)	11 (6%)	0	6 (3%)	3 (3%)

Table 9: Incidence of Common (≥1%) Adverse Events in Four Adequate and Well-Controlled Acute Studies of Balsalazide

Adverse Event	Safety Update 2			Safety Update 1	
	Balsalazide 6.75 g/d N = 259	Mesalamine 2.4 g/d N = 189	Placebo[a] N = 35	Balsalazide 6.75 g/d N = 175	Mesalamine 2.4 g/d N = 100
Cramps	4 (2%)	2 (1%)	0	4 (2%)	1 (1%)
Myalgia	3 (1%)	4 (2%)	1 (3%)	2 (1%	2 (2%)
PSYCHIATRIC	**11 (4%)**	**11 (6%)**	**1 (3%)**	**5 (3%)**	**5 (5%)**
Anorexia	5 (2%)	1 (0.5%)	0	3 (2%)	0
Insomnia	6 (2%)	4 (2%)	0	2 (1%)	1 (1%)
RESPIRATORY SYSTEM	**22 (8%)**	**24 (13%)**	**6 (17%)**	**12 (7%)**	**15 (15%)**
Coughing	4 (2%)	3 (2%)	0	0	0
Pharyngitis	4 (2%)	11 (6%)	0	0	0
Respiratory infection	9 (4%)	5 (3%)	5 (14%)	6 (3%)	5 (5%)
Rhinitis	6 (2%)	7 (4%)	0	2 (1%)	4 (4%)
Sinusitis	3 (1%)	3 (2%)	1 (3%)	0	0
URINARY SYSTEM	**7 (3%)**	**5 (3%)**	**1 (3%)**	**3 (2%)**	**1 (1%)**
UTI	3 (1%)	0	0	1 (1%)	0

[a] There is no change in the placebo group from Safety Update 1.

Note: This table includes events with incidence rates ≥1% in patients treated with Balsalazide 6.75 g/d.
A complete list of adverse events is presented in Table U6e-3.
The following adverse events from Safety Update 1 fell below 1% and, therefore, are not included in this update: accident and/or injury, bowel irregularity, colitis ulcerative aggravated, dyspnea, ear ache, ear infection NOS, feces discolored, and pruritus

Table 10: Incidence of Common (≥1%) Adverse Events in Maintenance Studies of Balsalazide

Adverse Event	Safety Update 2				Safety Update 1
	Balsalazide N = 962	Mesalamine[a] N = 94	Sulfasalazine[a] N = 38	Placebo[a] N = 15	Balsalazide N = 844
BODY AS A WHOLE	**210 (22%)**	**21 (22%)**	**4 (11%)**	**2 (13%)**	**195 (23%)**
Abdomen enlarged	10 (1%)	0	0	0	0
Accident or Injury	19 (2%)	1 (1%)	0	0	18 (2%)
Asthenia	13 (1%)	0	0	0	11 (1%)
Back Pain	46 (5%)	4 (4%)	0	0	45 (5%)
Fatigue	72 (8%)	4 (4%)	3 (8%)	1 (7%)	70 (8%)
Flu-like Disorder	17 (2%)	2 (2%)	0	0	15 (2%)
Malaise	30 (3%)	0	0	1 (7%)	30 (4%)
Pain	59 (6%)	5 (5%)	0	0	56 (7%)
GASTROINTESTINAL	**325 (34%)**	**20 (21%)**	**11 (29%)**	**5 (33%)**	**297 (35%)**
Abdominal Pain	119 (12%)	4 (4%)	2 (5%)	0	104 (12%)
Colitis Ulcerative aggravated	16 (2%)	0	0	0	16 (2%)
Constipation	25 (3%)	0	0	0	24 (3%)
Diarrhea	80 (8%)	5 (5%)	2 (5%)	0	71 (8%)
Dyspepsia	48 (5%)	2 (2%)	2 (5%)	3 (20%)	46 (6%)
Flatulence	78 (8%)	3 (3%)	2 (5%)	1 (7%)	76 (9%)
Hemorrhoids	11 (1%)	0	0	1 (7%)	11 (1%)
Hemorrhage rectum	14 (2%)	0	0	0	
Melena	19 (2%)	0	1 (3%)	0	13 (2%)
Nausea	90 (9%)	3 (3%)	1 (3%)	1 (7%)	86 (10%)
Stools Frequent	10 (1%)	0	0	0	10 (1%)
Tenesmus	14 (2%)	1 (1%)	0	0	11 (1%)

Table 10: Incidence of Common (≥1%) Adverse Events in Maintenance Studies of Balsalazide

Adverse Event	Safety Update 2				Safety Update 1
	Balsalazide N = 962	Mesalamine[a] N = 94	Sulfasalazine[a] N = 38	Placebo[a] N = 15	Balsalazide N = 844
Tooth Disorder	10 (1%)	0	1 (3%)	0	10 (1%)
Vomiting	14 (1%)	0	0	0	14 (2%)
MUSCULOSKELETAL	**71 (7%)**	**4 (4%)**	**5 (13%)**	**1 (7%)**	**66 (8%)**
Arthralgia	29 (3%)	2 (2%)	4 (10%)	0	29 (3%)
Arthritis	11 (1%)	0		0	11 (1%)
Arthropathy	12 (1%)	0	1 (3%)	1 (7%)	12 (1%)
Myalgia	17 (2%)	0	0	0	17 (2%)
NERVOUS SYSTEM	**149 (15%)**	**8 (9%)**	**1 (3%)**	**3 (20%)**	**142 (17%)**
Dizziness	38 (4%)	0	0	2 (13%)	37 (4%)
Headache	127 (13%)	8 (8%)	1 (3%)	2 (13%)	122 (15%)
PSYCHIATRIC	**53 (6%)**	**2 (2%)**	**3 (8%)**	**1 (7%)**	**46 (6%)**
Anorexia	11 (1%)	1 (1%)	0	0	11 (1%)
Depression	15 (2%)	0	0	0	15 (2%)
Insomnia	10 (1%)	0	0	0	0
Somnolence	11 (1%)	0	2 (5%)	0	11 (1%)
RESISTANCE MECHANISM	**64 (7%)**	**4 (4%)**	**0**	**0**	**58 (7%)**
Infection	15 (2%)	1 (1%)	0	0	14 (2%)
Infection Viral	35 (4%)	3 (3%)	0	0	32 (4%)
RESPIRATORY	**120 (12%)**	**16 (17%)**	**2 (5%)**	**0**	**99 (12%)**
Bronchitis	12 (1%)	2 (2%)	0	0	10 (1%)
Coughing	16 (2%)	1 (1%)	0	0	14 (2%)

Table 10: Incidence of Common (≥1%) Adverse Events in Maintenance Studies of Balsalazide

Adverse Event	Safety Update 2				Safety Update 1
	Balsalazide N = 962	Mesalamine[a] N = 94	Sulfasalazine[a] N = 38	Placebo[a] N = 15	Balsalazide N = 844
Pharyngitis	27 (3%)	5 (5%)	0	0	25 (3%)
Respiratory Infection	71 (7%)	11 (12%)	2 (5%)	0	67 (8%)
Sinusitis	17 (2%)	1 (1%)	0	0	10 (1%)
SKIN AND APPENDAGES	**99 (10%)**	**5 (5%)**	**6 (16%)**	**4 (27%)**	**95 (11%)**
Pruritus	19 (2%)	1 (1%)	0	1 (7%)	19 (2%)
Rash	39 (4%)	0	1 (3%)	1 (7%)	36 (4%)
OTHER					
Anemia	10 (1%)	3 (3%)	0	0	10 (1%)
Urinary tract infection	10 (1%)	1 (1%)	0	0	0

[a]There is no change in the treatment groups of Mesalamine, Sulfasalazind and Placebo.

Note: This table includes events with incidence rates ≥1% in patients treated with Balsalazide.
A complete list of adverse events is presented in Table U6e-5.
The following adverse events from Safety Update 1 fell below 1% and, therefore, are not included in this update: hemorrhage rectum, hypertension, migraine, skin disorder, stomatitis ulcerative, and weight increase.

APPENDIX 2

January 19, 2000

Lilia Talarico, MD
Director
Division of Gastrointestinal and Coagulation Drug Products
HFD-180, Room 6B-24
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: [redacted]
balsalazide disodium

IND Safety Report – Follow-up

Dear Dr. Talarico,

Please find enclosed follow-up information for Safety Reports that were previously filed to this IND. These adverse events were reported for ulcerative colitis patients who were treated with balsalazide in the United Kingdom. Balsalazide disodium was approved for marketing in the UK in July 1997. As indicated in the initial Safety Reports, none of these events meets the criteria of an IND Safety Report either because the event is not unexpected or there was too little information to assess causality. According to our agreement with the Division (Serial No. 089), only foreign post-marketing reports that meet the criteria under 21 CFR 312.32 will be submitted as Safety Reports to the IND. However, we will continue to submit follow-up reports for foreign post-marketing events that have already been submitted to the IND. CIOMS forms for these follow-up reports are attached.

Control No. 57-83
The initial report for this patient was submitted on July 14, 1999 in Serial No. #095. This female patient received treatment with balsalazide for two months prior and during the first 4 weeks of pregnancy. At 28 weeks gestation a scan revealed fetal abnormalities. The follow-up CIOMS confirms that the baby was born with a congenital defect. The baby was diagnosed with atrial septal defect and ventricular septal defect. A causal relationship to the drug cannot be confirmed. However, Salix has taken a conservative position by reporting this event as a Safety Report.

APPEARS THIS WAY
ON ORIGINAL

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1b. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6. REACTION ONSET Day	Month	Year	8-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION
Unknown	UK	-	-	-	25	F	-	-	-	☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING

7 + 13. DESCRIBE REACTION(S) (including relevant tests/lab data)

	Serious	Unexpected
MALFORMATION HAND	Yes	Yes
PLEURAL EFFUSION	Yes	Yes
HEART MALFORMATION	Yes	Yes
RENAL DYSGENESIS	Yes	Yes

Female patient who received treatment with Colazide (balsalazide) capsules for two months prior to her pregnancy. On positive pregnancy the treatment was discontinued. At 27 weeks gestation foetal abnormalities were observed with the fingers, kidney and heart as well as pleural effusion. The event was serious according to the definition; A congenital anomaly/birth defect.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)	20. DID REACTION ABATE AFTER STOPPING DRUG?
COLAZIDE (balsalazide).	☐ YES ☐ NO ☒ NA
15. DAILY DOSE(S) 3000 mg	**16. ROUTE(S) OF ADMINISTRATION** ORAL, CAPSULE
17. INDICATION(S) FOR USE Unknown	**21. DID REACTION REAPPEAR AFTER REINTRODUCTION?** ☐ YES ☐ NO ☒ NA
18. THERAPY DATES (from/to) Startdate unknown Stopdate unknown	**19. THERAPY DURATION** Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

-

23. OTHER RELEVANT HISTORY (e.g. diagnoses, allergies, pregnancy with last menstrual period, etc.)

-

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER	COMMENTS
AstraZeneca R&D Lund S-221 87 LUND Sweden	More information requested.
REFERENCE Local No.200010	**24b. MFR CONTROL NO.** 57-83
24c. DATE RECEIVED BY ASTRA 29-JUN-1999	**24d. REPORT SOURCE** ☐ STUDY ☐ LITERATURE ☒ HEALTH PROFESSIONAL
DATE OF THIS REPORT 02-JUL-1999	**25a. REPORT TYPE** ☒ INITIAL ☐ FOLLOW-UP

* = Approximated date

07/21/99
HG-T

July 14, 1999

Lilia Talarico, MD
Director
Division of Gastrointestinal and Coagulation Drug Products
HFD-180, Room 6B-24
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: ——
balsalazide disodium

IND Safety Report Initial

Dear Dr. Talarico,

Please find enclosed information regarding a serious adverse event report for an ulcerative colitis patient who was treated with balsalazide in the United Kingdom. Balsalazide disodium was approved for marketing in the UK in July 1997. This is a post-marketing safety report for a 25-year-old female patient who was being treated with balsalazide capsules for two months prior to becoming pregnant. When pregnancy was confirmed, balsalazide treatment was discontinued. At 27 weeks gestation, fetal abnormalities were observed. This event is serious and unexpected, however, a relationship to drug cannot be established at this time due to lack of information. We have chosen a conservative course of action by reporting this serious adverse event as an IND Safety Report at this time. We will submit a follow-up report when additional information becomes available. The control number for this report is 57-83.

If you have any questions concerning the enclosed material, please do not hesitate to call me.

Sincerely,

Donna Kato for LJ

Lorin Johnson, Ph.D
Vice President, Research and Development
(650) 849-5900

APPEARS THIS WAY
ON ORIGINAL

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6. REACTION ONSET Day	Month	Year	8-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION
Unknown	UK	-	-	-	foetal	U	-	-	-	☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING

7 + 13. DESCRIBE REACTION(S) (including relevant tests/lab data)

	Serious	Unexpected
ATRIAL SEPTAL DEFECT	Yes	Yes
PLEURAL EFFUSION	Yes	Yes
VENTRICULAR SEPTAL DEFECT	Yes	Yes
MALFORMATION NAND	Yes	Yes
CONGENITAL ANOMALY NOS	Yes	Yes

A female patient received treatment with Colazide (balsalazide) capsules for two months prior and 8-4 weeks of pregnancy. On positive pregnancy the treatment was discontinued. At 28 weeks a scan revealed a possible heart defect, abnormal fingers and pleural effusion. At 34 weeks amniocentesis was done because of polyhydramnious. Results were normal. The baby was born 15 days before date of expected delivery. Low set ears and facial features were observed. The baby was diagnosed with atrial septal defect and ventricular septal defect. He/she is at home awaiting surgery. The event was serious according to the definition; A congenital anomaly/birth defect.

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
COLAZIDE (balsalazide).

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)
3000 mg

16. ROUTE(S) OF ADMINISTRATION
VIA PLACENTA, CAPSULE

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

17. INDICATION(S) FOR USE
ULCERATIVE COLITIS

18. THERAPY DATES (from/to)
Startdate unknown Stopdate unknown

19. THERAPY DURATION
Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

PHENTERMINE	(phentermine)	01-JAN-1999* - 01-MAR-1999
FOLIC ACID	(folic acid)	Startdate unknown Stopdate unknown

23. OTHER RELEVANT HISTORY (e.g. diagnoses, allergies, pregnancy with last menstrual period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
AstraZeneca R&D Lund
S-221 87 LUND
Sweden

COMMENTS

REFERENCE
Local No.200010

24b. MFR CONTROL NO
57-83

24c. DATE RECEIVED BY ASTRA
13-OCT-1999

24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☒ HEALTH PROFESSIONAL

DATE OF THIS REPORT
15-OCT-1999

25a. REPORT TYPE ☐ INITIAL ☒ FOLLOW-UP

* = Approximated date

N-100
S2

December 1, 1999

Lilia Talarico, MD
Director
Division of Gastrointestinal and Coagulation Drug Products
HFD-180, Room 6B-24
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: ←
balsalazide disodium

IND Safety Report Initial

Dear Dr. Talarico,

Please find enclosed information regarding a serious adverse event report for an ulcerative colitis patient who was treated with balsalazide in the United Kingdom. Balsalazide disodium was approved for marketing in the UK in July 1997. This is a post-marketing safety report for a female patient who received treatment with balsalazide capsules (1500 mg/day) a few months prior to pregnancy and during about the first month of pregnancy. The CIOMS form also indicates that the patient received treatment with mesalazine commencing on January 21, 1999 with an unknown stop date. On positive pregnancy test treatment with balsalazide was discontinued. A child with multiple congenital abnormalities was born. The event is considered serious and unexpected. The causality of the adverse event was listed as "possible" by the source. However, the sponsor of the drug in the UK, AstraZeneca, lists causality as "can not be classified" due to a lack of information. We have chosen a conservative course of action by reporting this serious adverse event as an IND Safety Report. We will submit a follow-up report when additional information becomes available. The control number for this report is 57-94. A completed CIOMS form is attached.

If you have any questions concerning the enclosed material, please do not hesitate to call me.

Sincerely,

Joanne Kato for LJ

Lorin Johnson, Ph.D
Vice President, Research and Development
(650) 849-5900

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	3a. AGE Years	3. SEX	4&. REACTION ONSET Day	Month	Year	5-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION
Unknown	UK	-	-	-	[illegible]	U	02	[illegible]	1999	

7 + 13. DESCRIBE REACTION(S) (including relevant tests/lab data) — Serious: Yes — Unexpected: Yes

MALFORMATIONS MULTIPLE

A female patient received treatment with Colazide (balsalazide) capsules a few months prior and about one month of pregnancy. On positive pregnancy the treatment was discontinued. A child with multiple congenital abnormalities was born. The event was serious according to the definition; A congenital anomaly/birth defect.

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20. DID REACTION ABATE AFTER STOPPING DRUG?
COLAZIDE (balsalazide).		☐ YES ☐ NO ☒ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
1500 mg	VIA PLACEBTA, CAPSULE	☐ YES ☐ NO ☒ NA
17. INDICATION(S) FOR USE		
ULCERATIVE COLITIS		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	
Startdate unknown Stopdate 01-JAN-1999*	Unknown	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

MESALAZINE (mesalazine) 21-JAN-1999 Stopdate unknown

23. OTHER RELEVANT HISTORY (e.g. diagnoses, allergies, pregnancy with last menstrual period, etc.)

-

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		COMMENTS
AstraZeneca R&D Lund S-221 87 LUND Sweden		Report from the authorities in Uk.
REFERENCE	24b. MFR CONTROL NO.	
-	57-94	
24c. DATE RECEIVED BY ASTRA 15-NOV-1999	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL	
DATE OF THIS REPORT 17-NOV-1999	25a. REPORT TYPE ☒ INITIAL ☐ FOLLOW-UP	

* = Approximated date

APPENDIX 3

APPEARS THIS WAY
ON ORIGINAL

UKMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6. REACTION ONSET Day	Month	Year	8-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION
Unknown	SWEDEN	-	-	-	30	F	22	JUL	1999	☐ PATIENT DIED ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING

7 + 13. DESCRIBE REACTION(S) (including relevant tests/lab data)

	Serious	Unexpected
BILIRUBIN INCREASED	Yes	Yes
LIVER FUNCTION TESTS ABNORMAL NOS	Yes	Yes
ASAT INCREASED	Yes	Yes
ALAT INCREASED	Yes	Yes
PROTHROMBIN TIME SHORTENED	Yes	Yes
COLITIS ULCERATIVE AGGRAVATED	Yes	Yes

Female patient who was admitted to hospital due to deterioration of ulcerative colitis and increased liver values while treated with Colazide (balsalazide). Symptoms of 10-20 stools/day were present and injections of Solu-Cortef (hydrocortisone) introduced. During the hospitalisation bilirubin increased from <20 to 30 µmol/L (normal values:<20 µmol/L), ASAT 5.53 to 13.45-8.05 µmol/L (normal values:<0.7µmol/L, ALT 11.66 to 40.63 µmol/L (normal values:<0.7 µmol/L), GGT 1.1 to 3.6 µmol/L (normal values:<1.20 µmol/L), ALP 3.1 to 2.9 µmol/L (normal values:0.8-4.6 µmol/L) and PT decreased from 78 to 62% (normal

Continued on next page)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
COLAZIDE (balsalazide).

20. DID REACTION ABATE AFTER STOPPING DRUG? ☒ YES ☐ NO ☐ NA

15. DAILY DOSE(S)
6750 mg

16. ROUTE(S) OF ADMINISTRATION
ORAL, CAPSULE

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

17. INDICATION(S) FOR USE
COLITIS ULCEROSA

18. THERAPY DATES (from/to)
26-JUL-1999 Stopdate unknown

19. THERAPY DURATION
Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

FRED-CLYSMA	(prednisolone sodium phosphate)	Startdate unknown Stopdate unknown
ORAL CONTRACEPTIVE NOS	(oral contraceptive nos)	Startdate unknown Stopdate unknown

23. OTHER RELEVANT HISTORY (e.g. diagnoses, allergies, pregnancy with last menstrual period, etc.)
-

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
AstraZeneca R&D Lund
S-221 87 LUND
Sweden

COMMENTS
Report from the authorities in Sweden.

REFERENCE	24b. MFR CONTROL NO.
-	57-99
24c. DATE RECEIVED BY ASTRA 19-APR-2000	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL
DATE OF THIS REPORT 19-APR-2000	25a. REPORT TYPE ☒ INITIAL ☐ FOLLOW-UP

* Approximated date

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year	24b. MFR CONTROL NO.
Unknown	SWEDEN	-	-	-	30	F	22	JUL	1999	57-99

13 DESCRIBE REACTION(S) (Continued)

alues:70-130%). Serology tests for viral hepatitis and autoantibodies were egative. Treatment with Colazide and contraceptives were discontinued. The atient was hospitalised for 13 days and was considered recovered about one onth later.

APPEARS THIS WAY
ON ORIGINAL

APPENDIX 4

APPEARS THIS WAY
ON ORIGINAL

EUROCAT

Prevalence of some congenital anomalies

Table A03 : Congenital anomalies
Prevalence rate (per 10,000 births) in 25 EUROCAT registries, 1990-1996

Registry	LB		LB + FD		IA		LB + FD + IA	
	N	Rate	N	Rate	N	Rate	N	Rate
Glasgow (UK)	1994	241.3	2078	250.0	263	31.6	2341	281.6
Dublin (Ir)	3184	242.7	3322	252.3	*	*	3322	252.3
Odense (DK)	775	187.3	813	195.5	75	18.0	888	213.5
Northern Netherlands	3130	232.1	3218	237.3	189	13.9	3407	251.2
Southwestern Netherlands	2026	131.2	2071	133.4	81	5.2	2152	138.6
Antwerp (B)	1306	238.5	1333	243.2	70	12.8	1403	255.9
Hainaut-Namur (B)	2112	236.9	2180	243.2	238	26.6	2418	269.8
Paris (F)	6771	264.9	6995	272.0	2076	80.7	9071	352.7
Strasbourg (F)	2735	293.3	2788	297.4	427	45.5	3215	342.9
Bouches-du-Rhone (F)	2608	165.3	2764	174.2	663	41.8	3427	215.9
Switzerland	6131	162.4	6256	165.1	771	20.3	7027	185.4
Tuscany (I)	2756	195.9	2803	198.5	342	24.2	3145	222.7
Emilia Romagna (I)	3055	171.1	3072	171.4	26	1.5	3098	172.8
North-East Italy (I)	3248	93.3	3278	93.9	882	25.3	4160	119.2
Malta	786	220.3	803	223.8	*	*	803	223.8
Basque Country (E)	1807	162.5	1849	165.5	341	30.5	2190	196.0
Asturias (E)	982	199.2	1010	203.7	143	28.8	1153	232.5
Barcelona (E)	687	109.5	721	114.3	202	32.0	923	146.4
El Valles (E)	436	153.5	459	161.0	133	46.7	592	207.7
Southern Portugal	623	134.8	673	144.6	29	6.2	702	150.8
Mainz (D)	986	367.8	1022	375.5	60	22.0	1082	397.5
Saxony-Anhalt (D)	1400	225.5	1429	229.0	100	16.0	1529	245.1
Styrian (Au)	2793	304.6	2858	310.6	176	19.1	3034	329.7
Zagreb (Cr)	800	175.5	802	175.1	3	0.7	805	175.7
Sofia (Bu)	184	187.3	199	200.8	10	10.1	209	210.9

APPENDIX 5

APPEARS THIS WAY
ON ORIGINAL

Table 20: Outcomes of Pregnancies

Patient	Date	Outcome	Balsalazide Use
	1 Feb 93	Healthy boy	51 mo. to wk 15 of gestation
	21 Sep 90 Jul 91 9 Jun 94	Miscarriage Healthy boy Healthy girl	20 mo. to wk 6 of gestation none none
	17 Sep 90 24 Apr 93	Healthy Healthy	to wk 6 of gestation none
	Oct 85 19 Dec 89	Boy w/ Down's syndrome Healthy boy	none 18.5 mo. to week 10 gestation
	26 Dec 90	Healthy boy	8 mo. to week 9 gestation
	unknown	Elective termination	3 wks to 19 Feb 92
	25 May 95	Healthy girl	9 wks to wk 6 gestation
	30 Apr 87	Boy, thriving w/ bifed kidney	week 12 of gestation & continuing
	27 Jun 89 31 Aug 91	Miscarriage Miscarriage[a]	14 mo. to miscarriage >10 mo. to miscarriage
	Jul 95	Healthy girl	13 wks to 2 mo. prior to conception
[redacted]	Unknown	Elective termination	6 wks to wk 2 of gestation

a: Husband found to have oligoasthenoteratozoospermia
Source: 0028/Pregnancy report

Since the first Safety Update, Salix has received two reports from the UK of congenital abnormalities after two females received balsalazide either immediately before and/or during the first month of pregnancy. Both reports were filed to [redacted] (see Section 10.1). In both cases, too little information was available to make any causality assessment. Three male patients with infertility due to sulfasalazine were treated with Balsalazide in 1983. At entry, sperm counts and sperm motility was below normal. These improved in the first two patients. The third patient did not provide additional sperm samples yet his wife became pregnant during the third month in the trial (outcome unknown).

Balsalazide appears to have no effects on human reproduction and may restore fertility to males with sulfasalazine-induced infertility.