

MEMORANDUM

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

Control #: 2007-2198

DATE: February 14, 2008

TO: Lisa L. Mathis, M.D., Associate Director
Pediatric and Maternal Health Staff (PMHS)
Office of New Drugs (OND), CDER
and
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Office of Pediatric Therapeutics (OPT), OC

FROM: Ann Corken Mackey, RPh, MPH, Safety Evaluator
Division of Drug Risk Evaluation

THROUGH: Ann McMahon, M.D., MS, Acting Deputy Director
for
Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation

SUBJECT: 1-year Post-Pediatric Exclusivity Postmarketing Adverse Event Review
Drug: Balsalazide (Colazal)
Pediatric Exclusivity Approval Date: August 22, 2006

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1. Executive Summary

This document summarizes balsalazide (Colazal) pediatric adverse event reports identified in the Adverse Event Reporting System (AERS) database. The Office of Pediatric Therapeutics requested this information in preparation for the Pediatric Advisory Committee (PAC) meeting scheduled for Spring 2008.

Balsalazide was approved in the US on July 18, 2000. Balsalazide is an anti-inflammatory agent (5-aminosalicylate [5-ASA]) with local effects; it is indicated for the treatment of mildly to moderately active ulcerative colitis in patients 5 years of age and older.

The AERS database was searched for reports of adverse events (serious and non-serious) occurring with the use of balsalazide in pediatric patients. Up to the "data lock" date of September 22, 2007, AERS contained 172 cases for balsalazide (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent approximately 4.7% of the total (8/172). DDRE was asked to focus on the 1-year period following the approval of pediatric exclusivity, August 22, 2006 to September 22, 2007. We used an AERS data lock date of September 22, 2007, to allow time for reports received up to August 22, 2007, to be entered into AERS. During the first 13 months after pediatric exclusivity was granted, AERS received a total of 34 cases (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent approximately 8.8% of the total number of cases (3/34). We will refer to this 13-month interval as the pediatric exclusivity period in the remainder of this review.

The two pediatric cases received during the pediatric exclusivity period involved children who developed flares in their underlying ulcerative colitis while taking balsalazide (cases coded as drug ineffective, drug effect decreased); the third case was miscoded and is not included in this review. Neither patient died; both were hospitalized. These cases are described below (see *Review of Postmarketing Pediatric Adverse Event Reports* and *Case description/Discussion of Cases Received*). See *Case description/Discussion* section below for a summary of the five AERS reports identified in children since initiation of marketing for balsalazide up to the exclusivity period.

The review of the two balsalazide reports received during the exclusivity period in the AERS database did not identify adverse events unique to the pediatric population as compared to the adult population. Based on these data, no clear signals were found. However the review was limited by the few number of reports.

In adults, the most commonly-reported adverse events (per AERS reports) associated with balsalazide therapy involved GI symptoms (e.g., diarrhea, nausea, abdominal pain), blood dyscrasias, renal failure, myocarditis, pericarditis, and pancreatitis. All of these events are labeled for adults taking other 5-ASA products (i.e., sulfasalazine, mesalamine, olsalazine)^{1, 2, 3} but not for balsalazide. DDRE has submitted a review of these adverse events to the Division of Gastrointestinal Products (see Attachment 1).

¹ Azulfidine EN-tabs (sulfasalazine) product label, Pharmacia, September 2001.

² Pentasa (mesalamine) product label, Shite US Inc, July 2004.

³ Dipentum (olsalazine) product label, UCB Pharma Limited, May 2006.

It is estimated that upwards of 100,000 children and adolescents in the US are affected by inflammatory bowel disease (i.e., Crohn's disease, ulcerative colitis).⁴ The treatment for ulcerative colitis depends on the severity of the disease. Therapies used for the treatment of ulcerative colitis in children include aminosalicylates (i.e., sulfasalazine, mesalamine, balsalazide, olsalazine), corticosteroids (e.g., prednisone, budesonide), immunomodulators (e.g., azathioprine, 6-mercaptopurine, methotrexate), antibiotics (e.g., metronidazole, ciprofloxacin), and biological therapy (e.g., infliximab, adalimumab).⁴

In conclusion, the effectiveness of balsalazide in children with ulcerative colitis has been documented.⁵ Some patients will develop flares of their conditions even though they are receiving appropriate therapy. It is likely that children will use balsalazide for many years and the safety profile for long-term use is not known. There are too few reported adverse events to make a conclusion regarding safety signals unique to the pediatric population. DDRE will continue to monitor this issue.

2. Products, Indications, Pediatric Labeling, and Pediatric Filing History

2.1 Balsalazide Products Available in the United States: Colazal (NDA# 20-610) available 750 mg capsules. The product was approved in the US on July 18, 2000.

2.2 Balsalazide Approved Indications: Balsalazide is an anti-inflammatory agent (5-aminosalicylate) with topical effects; it is indicated for the treatment of mildly to moderately active ulcerative colitis in patients 5 years of age and older. Safety and effectiveness of balsalazide beyond 8 weeks in children (ages 5 to 17 years) and 12 weeks in adults have not been established.⁵

2.3 Pediatric Labeling:

Pediatric Studies: A clinical trial was conducted comparing two doses (6.75 g/day and 2.25 g/day) of balsalazide in 68 pediatric patients (age 5 to 17, 23 males and 45 females) with mildly to moderately active ulcerative colitis, 28/33 (85%) patients randomized to 6.75 g/day and 25/35 (71%) patients randomized to 2.25 g/day completed the study. The primary endpoint for this study was the proportion of subjects with clinical improvement (defined as a reduction of at least 3 points in the Modified Sutherland Ulcerative Colitis Activity Index [MUCAI] from baseline to 8 weeks). Fifteen (45%) patients in the balsalazide 6.75 g/day group and 13 (37%) patients in the balsalazide 2.25 g/day group showed this clinical improvement. In both groups, patients with higher MUCAI total scores at baseline were likely to experience greater improvement.

Rectal bleeding improved in 64% of patients treated with balsalazide 6.75 g/day and 54% of patients treated with balsalazide 2.25 g/day. Colonic mucosal appearance upon endoscopy improved in 61% of patients treated with balsalazide 6.75 g/day and 46% of patients treated with balsalazide 2.25 g/day.

Pharmacokinetics (Pediatric Population): In studies of pediatric patients with mild-to-moderate active ulcerative colitis receiving three 750 mg balsalazide capsules 3 times daily (6.75 g/day) for 8 weeks, steady state was reached within 2 weeks, as observed in adult patients.

⁴ Carvalho R, Hyams JS. Diagnosis and management of inflammatory bowel disease in children. *Semin Pediatr Surg* 2007; 16: 164-71.

⁵ Colazal (balsalazide) product label, Salix Pharmaceuticals, 2007.

Likewise, the pharmacokinetics of balsalazide, 5-ASA, and N-Ac-5-ASA were characterized by very large inter-patient variability, which is also similar to that seen in adult patients.

The pro-drug moiety, balsalazide, appeared to exhibit dose-independent (i.e., dose-linear) kinetics in children, and the systemic exposure parameters (C_{\max} and AUC_{0-8}) increased in an almost dose-proportional fashion after the 6.75 g/day versus the 2.25 g/day doses. However, the absolute magnitude of these exposure parameters was greater relative to adults. The C_{\max} and AUC_{0-8} observed in pediatric patients were 26% and 102% greater than those observed in adult patients at the 6.75 g/day dosage level. In contrast, the systemic exposure parameters for the active metabolites, 5-ASA and N-Ac-5-ASA, in pediatric patients increased in a less than dose-proportional manner after the 6.75 g/day dose versus the 2.25 g/day dose. Additionally, the magnitude of these systemic exposure perspective, 5-ASA, the C_{\max} and AUC_{0-8} observed in pediatric patients were 67% and 64% lower than those observed in adult patients at the 6.75 g/day dosage level. Likewise, for N-Ac-5-ASA, the C_{\max} and AUC_{0-8} observed in pediatric patients were 68% and 55% lower than those observed in adult patients at the 6.75 g/day dosage level.

All pharmacokinetic studies with balsalazide are characterized by large variability in the plasma concentration versus time profiles for balsalazide and its metabolites, thus half-life estimates of these analytes are indeterminate.

Pregnancy: Pregnancy Category B. Reproduction studies were performed in rats and rabbits at oral doses up to 2 g/kg/day, 2.4 and 4.7 times the recommended human dose based on body surface area for the rat and rabbit, respectively, and revealed no evidence of impaired fertility or harm to the fetus due to balsalazide. There are no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether balsalazide is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when balsalazide is administered to a nursing mother.

Pediatric Use: A clinical trial of 68 patients ages 5 to 17 years has been conducted comparing two doses of balsalazide (6.75 g/day and 2.25 g/day) in pediatric patients with mild-to-moderately active Crohn's disease.

Dosage and Administration: The pediatric dose is EITHER: Three 750 mg capsules 3 times a day (6.75 g/day) with or without food for 8 weeks OR one 750 mg capsule 3 times a day (2.25 g/day) with or without food for up to 8 weeks. Use of balsalazide in the pediatric population for more than 8 weeks has not been evaluated in clinical trials.

Warnings and Precautions: In the pediatric clinical trials, 4 out of 68 patients reported exacerbation of the symptoms of ulcerative colitis.

Adverse Reactions: The most common adverse reactions reported in children included headache, abdominal pain, diarrhea, nausea, vomiting, pyrexia, respiratory infection and arthralgia.

Pediatric Filing History: Pediatric exclusivity was granted on August 22, 2006. On December 17, 2001, a Written Request letter was issued for balsalazide and the following study was requested: A single study to evaluate the pharmacokinetics, safety, and efficacy of balsalazide in no less than 40 pediatric patients, 5 to 17 years of age with mildly to moderately active ulcerative

colitis; eligible patients were to be randomized to two dose levels of balsalazide (6.7 g/day or 2.25 g/day) for 8 weeks.

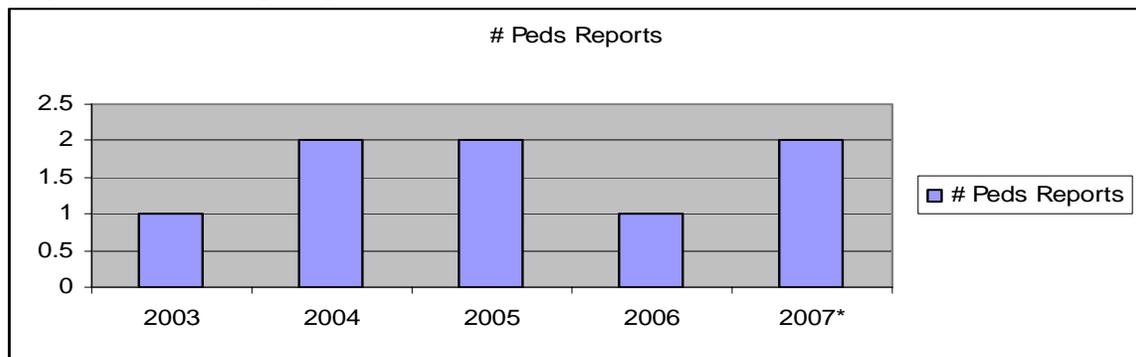
3. AERS Search Results: Balsalazide

3.1 Count of Reports: AERS Search including all sources - U.S. & foreign from marketing approval date (Table 1)

Table 1: Crude counts¹ of AERS Reports for All Sources from Marketing Approval Date (US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	103 (78)	92 (68)	11 (9)
Pediatrics (0-16 yrs.)	8 (6)	6 (5)	0 (0)
Age unknown (Null values)	61 (45)	39 (23)	1 (0)
Total	172 (129)	137 (96)	12 (9)

¹ May include duplicates
² Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.

Figure 1: Reporting trend for pediatric reports (ages 0 to 16 years) from approval date (July 18, 2000) through September 22, 2007.



* July 18, 2000 to September 22, 2007

3.2 Count of Reports: AERS Search including all sources - U.S. & foreign from Pediatric Exclusivity approval date (Table 2)

Table 2: Crude counts¹ of AERS Reports for All Sources from date Pediatric Exclusivity was Granted (US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	26 (19)	26 (19)	5 (5)
Pediatrics (0-16 yrs)	3 (2)	3 (2)	0 (0)
Age unknown (Null Values)	4 (2)	4 (2)	0 (0)
Total	33 (23)	33 (23)	5 (5)

¹ May include duplicates
² Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.

4. Postmarketing Review of All Pediatric Adverse Event Reports received during the one-year after a drug receives pediatric market exclusivity.

The AERS search identified 3 adverse event reports in children using balsalazide during the exclusivity period. One report has been excluded from the analysis below because it was miscoded (suspect drug was mesalamine; balsalazide was not mentioned in the report). The two remaining cases are described below.

4.1 Case Characteristics/Discussion for Two Cases Received during Exclusivity Period (Coded as Drug ineffective/Drug effect decreased):

A 14-year-old male with underlying ulcerative colitis was hospitalized due to a flare of his condition; he had been receiving **balsalazide 2.25 grams three times per day for 45 days** as well as prednisone taper, metronidazole, ciprofloxacin, and azathioprine (note that 2 months before initiating therapy with balsalazide, the patient's azathioprine prescription was misfilled with methotrexate--report does not state if patient actually took methotrexate). Balsalazide was discontinued and mesalamine and infliximab therapies were initiated and the patient's condition improved. He had a history of ulcerative colitis flares since his diagnosis 8 months before balsalazide was prescribed (**domestic report** submitted by an **attorney** in 2007, **event date=September 2007**).

A consumer reported that her **9-year-old son** with an underlying **history of Crohn's disease came out of remission** and was **hospitalized** when she started purchasing his balsalazide from a different pharmacy; his symptoms included growth retardation and poor weight gain. He had been taking **750 mg of balsalazide per day for approximately 17.5 months**. Concomitant medications included steroids and infliximab (**domestic report** submitted in 2006, **event date=July 2005**). (**Author note:** There is only one balsalazide product on the US marketplace.)

In addition, all cases where no age was reported were reviewed (n=61) in an attempt to determine if the patients who experienced adverse events were children. None of the cases stated that the patient was a child; several of the reports specified descriptions such as "patient in his 30s," reporter's "husband," or "18-year-old daughter."

Discussion of cases received during exclusivity period: The two pediatric cases received during the pediatric exclusivity period involved children who developed flares in their underlying ulcerative colitis while taking balsalazide (cases coded as drug ineffective, drug effect decreased); flares of underlying condition and hospitalizations are known to occur in patients with ulcerative colitis. Both patients were hospitalized; neither patient died. The Warnings/Precautions section and the Pediatric Adverse Event section of the balsalazide label lists exacerbation of symptoms of ulcerative colitis.

Case description/discussion of all adverse events in children from initiation of marketing to exclusivity period as reported to AERS: Because only two pediatric reports were received during the exclusivity period, all adverse event reports involving balsalazide use in children were reviewed. In addition to the cases described above, five additional reports were identified: hypothyroidism in an 11-day-old female whose mother had used balsalazide during pregnancy to treat ulcerative colitis (1); abdominal pain, bloody diarrhea, headache, overall aches, and facial swelling in a 15-year-old male (1); thrombocytopenia (1); pancreatitis (1); and pericarditis, pneumonia, and anemia (1). The latter 3 reports had a serious outcome (i.e., hospitalization) and are described in detail below.

A **9-year-old female** developed **thrombocytopenia** two years after initiating balsalazide therapy (750 mg two times per day) to treat ulcerative colitis. Her platelet count decreased from a baseline of 295,000 to 27,000 (nadir); unspecified "concomitant medications" were discontinued (balsalazide therapy was continued) and her platelets increased from 71,000 to 237,000. She was hospitalized for the event at some point. The patient experienced no unusual bleeding or bruising associated with thrombocytopenia. At the time of the report, the patient was undergoing a bone marrow biopsy to rule out idiopathic thrombocytopenic purpura (results not provided). She had a history of congenital adrenal hyperplasia; concomitant medications were listed as sulfamethoxazole and trimethoprim combination and 6-mercaptopurine (therapy dates not provided).

A **14-year-old male** developed **pericarditis and left lower lobe pneumonia** (per chest X-ray) while taking 6.75 mg of balsalazide per day for "several months" to treat ulcerative colitis. His symptoms included chest pain, rhinorrhea, fever, cough, and shortness of breath. In the hospital he was found to have **anemia**. Balsalazide was discontinued; the patient recovered. Medical history and concomitant medications were reported as "unknown."

A **6-year-old male** with a history of "colitis," convulsions, premature birth, hydrocephalus, and ventriculo-peritoneal shunt developed **pancreatitis** after taking balsalazide for 17 months (5 months after the dose was increased from 750 mg a day to 2250 mg per day). He was admitted to the hospital with elevated triglyceride (463 mg/dL), amylase ("in the 1000s"), and lipase ("in the 1000s") (baseline values not reported). Balsalazide was discontinued and the patient's condition was improving at the time of the report. The physician thought that the patient's elevated triglyceride values were related to concomitant prednisone use and that pancreatitis was related to balsalazide use. Additional concomitant medications included metronidazole, sodium valproate and valproic acid combination, and oxcarbazepine.

Discussion of pediatric cases from pre-exclusivity period: The case of hypothyroidism in the infant whose mother took balsalazide represents indirect exposure. Abdominal pain, hematochezia, headache, and inflammation (as specified in the second report listed above) are listed in the pediatric adverse events section of the balsalazide label. The patient who developed thrombocytopenia remained on balsalazide therapy and her condition improved when unspecified concomitant medications were discontinued. For two cases described above, the role of balsalazide in the patients' adverse events could be ruled out. The third case was not suggestive for a causal relationship because the patient's platelet count normalized while still on balsalazide (her two concomitant medications are known to cause thrombocytopenia).

In adults, the most commonly-reported adverse events (per AERS reports) associated with balsalazide therapy involved GI symptoms (e.g., diarrhea, nausea, abdominal pain), blood dyscrasias, renal failure, myocarditis, pericarditis, and pancreatitis. All of these events are labeled for adults taking other 5-ASA products (i.e., sulfasalazine, mesalamine, olsalazine),^{6, 7, 8} but not for balsalazide. DDRE has submitted a review of these adverse events to the Division of Gastrointestinal Products (see Attachment 1).

All deaths: The 12 deaths (adult patients) were reviewed. Of the 12 deaths, 6 reports were duplicates. The following causes were specified: underlying cardiac disease (2), sepsis (1), testicular infection leading to renal/liver failure (1), fibrosing alveolitis (1), and renal failure (1,

⁶ Azulfidine EN-tabs (sulfasalazine) product label, Pharmacia, September 2001.

⁷ Pentasa (mesalamine) product label, Shite US Inc, July 2004.

⁸ Dipentum (olsalazine) product label, UCB Pharma Limited, May 2006.

reported as part of a retrospective analysis; patient who died may have taken either sulfasalazine, mesalamine, olsalazine, or balsalazide [all 5-ASA products were analyzed together]); Fibrosing aveolitis and renal failure are labeled events for other 5-ASA products; the other patients appeared to have died of underlying conditions.

4.3. Published Case Reports: A Pubmed search using the term, balsalazide or Colalzal and limited to English, Child (0-18 years) identified no reported adverse event cases involving children.

5. Summary/Recommendations

The review of the few balsalazide pediatric reports in the AERS database did not identify adverse events unique to the pediatric population. Based on these data, no clear signals were found. However, the review was limited by the small number of reports.

In adults, the most commonly-reported adverse events (per AERS reports) associated with balsalazide therapy involved GI symptoms (e.g., diarrhea, nausea, abdominal pain), blood dyscrasias, renal failure, myocarditis, pericarditis, and pancreatitis. These events are labeled for adults taking other 5-ASA products (i.e., sulfasalazine, mesalamine, olsalazine),^{9, 10, 11} but not for balsalazide. DDRE has submitted a review of these adverse events to the Division of Gastrointestinal Products (see Attachment 1).

It is estimated that upwards of 100,000 children and adolescents in the US are affected by inflammatory bowel disease (i.e., Crohn's disease, ulcerative colitis).¹² The treatment for ulcerative colitis depends on the severity of the disease. Therapies used for the treatment of ulcerative colitis in children include aminosalicylates (i.e., sulfasalazine, mesalamine, balsalazide, olsalazine), corticosteroids (e.g., prednisone, budesonide), immunomodulators (e.g., azathioprine, 6-mercaptopurine, methotrexate), antibiotics (e.g., metronidazole, ciprofloxacin), and biological therapy (e.g., infliximab, adalimumab).⁴

In conclusion, the effectiveness of balsalazide in children with ulcerative colitis has been documented.⁵ Some patients will develop flares of their conditions even though they are receiving appropriate therapy. It is likely that children will use balsalazide for many years and the safety profile for long-term use is not known. There are too few reported adverse events to make a conclusion regarding safety signals unique to the pediatric population. DDRE will continue to monitor this issue.

⁹ Azulfidine EN-tabs (sulfasalazine) product label, Pharmacia, September 2001.

¹⁰ Pentasa (mesalamine) product label, Shite US Inc, July 2004.

¹¹ Dipentum (olsalazine) product label, UCB Pharma Limited, May 2006.

¹² Carvalho R, Hyams JS. Diagnosis and management of inflammatory bowel disease in children. *Sem Pediatr Surg* 2007; 16: 164-71.

Ann Mackey 1/22/2008

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Concur

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Team Leader

Appendix

Standard Searches:

- A. Adults (17 yrs and above)
 - 1. All outcomes from approval date (no set criteria)
 - 2. Serious outcomes from AP date
 - 3. Death as an outcome from AP date
 - 4. All outcomes from PE date to present or any desired date
 - 5. Serious outcomes from PE date to present or any desired date
 - 6. Death as an outcome from PE date to present or any desired date

- B. Ages 0-16 yrs ONLY
 - 1. Same as above 1-6
 - 2. Retrieve case reports for hands-on review

Drug Product Information

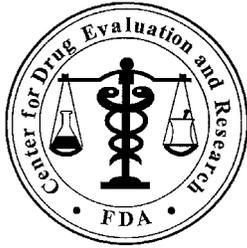
Cut and paste relevant pediatric labeling

Limitations of the Adverse Event Reporting System (AERS)

The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the U.S reflects underreporting and also duplicate reporting. For any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Therefore, counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing drug risk between drugs.

Other appendices (e.g., line listings, AERS printouts) up to the discretion of the reviewer

Attachment 1: Balsalazide: Serious adverse events



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: January 14, 2008
To: Daniel Shames, MD, Acting Director
Division of Gastrointestinal Products (DGP)
Thru: Mark Avigan, MD, CM, Director
Division of Drug Risk Evaluation
From: Ann Corken Mackey, RPh, MPH, Safety Evaluator, DDRE
Subject: Serious adverse events
Drug Name(s): Balsalazide (Colazal)

Application Type/Number: 20-610
Applicant/sponsor: Salix Pharmaceuticals, Inc.
OSE RCM #: 2007-2045

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

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EXECUTIVE SUMMARY

Based on adverse event reports submitted to the Adverse Event Reporting System (AERS) and the literature, balsalazide is associated with serious adverse events that are labeled for the other 5-aminosalicylates (5-ASA, i.e., sulfasalazine, mesalamine, olsalazine).^{13, 14, 15, 16}

DDRE recommends class labeling for the 5-ASA products (i.e., sulfasalazine, mesalamine, balsalazide, and olsalazine) and myocarditis, pericarditis, vasculitis, pruritus, pleural effusion, pneumonia with and without eosinophilia, alveolitis, renal failure, interstitial nephritis (note that renal failure is considered an outcome of interstitial nephritis), and pancreatitis. The labeling for balsalazide should be updated to reflect that postmarketing reports for these events have been received.

Although evidence is limited (based on postmarketing reports), the following adverse events have been reported for other 5-ASA drugs and should be considered by DGP for inclusion in the balsalazide label: Interstitial lung disease, urticaria, pulmonary fibrosis, hemolytic uremic syndrome, angioedema, toxic epidermal necrolysis, pericardial effusion, leukopenia, and thrombocytopenia.

1 BACKGROUND

1.1 Introduction

Routine review of adverse event reports submitted to AERS identified serious adverse events that are not labeled for balsalazide, but are labeled events for other drugs in the class (5-aminosalicylates [5-ASA]) (i.e., sulfasalazine, mesalamine, olsalazine). Data for other 5-ASA products is included for information purposes.

1.2 Regulatory history

Balsalazide was approved in the US on July 18, 2000 for the treatment of mildly to moderately active ulcerative colitis (UC) in patients 18 years of age and older. In December 2006, the indication was expanded to include use in children 5 to 17 years of age for the same indication. The label states that safety and effectiveness of balsalazide beyond 8 weeks in children (ages 5 to 17 years) and 12 weeks in adults have not been established. Balsalazide is an oral anti-inflammatory agent (5-ASA) with local effects; other drugs in the same class include sulfasalazine, mesalamine, and olsalazine. It is available as a 750 mg capsule.

1.3 Product labeling

Sulfasalazine: *Warnings:* Hypersensitivity reactions, liver failure, renal failure, ***Adverse reactions section:*** Pneumonitis with or without eosinophilia, vasculitis, fibrosing alveolitis, pericarditis with or without tamponade, hepatitis; allergic myocarditis, pancreatitis, toxic nephrosis with oliguria and anuria, nephritis, hemolytic uremic syndrome, exfoliative dermatitis, proteinuria, anemia, epidermal necrolysis, serum sickness syndrome, serum vasculitis, pleuritis

¹³ Azulfidine EN-tabs (sulfasalazine) product label, Pharmacia, revised September 2001.

¹⁴ Asacol (mesalamine) product label, Procter & Gamble Pharmaceuticals, revised September, 2006.

¹⁵ Dipentum (olsalazine) product label, UCB Pharma Limited, revised December 2006.

¹⁶ Pentasa (mesalamine) product label, Shire US Inc, revised 2004.

Mesalamine: *Precautions:* Hypersensitivity; renal impairment including acute and chronic interstitial nephritis, and, rarely renal failure, ***Adverse Reactions section:*** Drug fever (rare), edema, lupus-like syndrome, pericarditis (rare), myocarditis (rare), pancreatitis, hepatotoxicity, hepatitis, eosinophilic pneumonia, interstitial pneumonitis, pleuritis, pulmonary infiltrates, urticaria, renal failure (rare), interstitial nephritis, minimal change nephropathy, fever, edema, vasodilation, ecchymosis, pruritus, thrombocytopenia, dyspnea, chest pain, nephritic syndrome, pneumonitis, interstitial pulmonary fibrosis without eosinophilia

Olsalazine: *Adverse Reactions section:* Chest pain, myocarditis, pericarditis, peripheral edema, pancreatitis, interstitial nephritis, nephrotic syndrome, ***Postmarketing:*** Interstitial lung disease, angioneurotic edema, interstitial nephritis

Balsalazide: *Postmarketing Experience:* Hepatotoxicity including elevated liver function tests, jaundice, cholestatic jaundice, cirrhosis, hepatocellular damage including liver necrosis and liver failure (some cases fatal).

2 METHODS AND MATERIALS

This section describes the conduct of literature searches, AERS searches, drug use searches, and case series selection.

2.1 AERS Selection of Cases

On October 25, 2007, a System Organ Class/Preferred Term (SOC/PT) printout was generated to identify hypersensitivity reactions and other serious adverse events reported for balsalazide.

2.2 Drug Use Data

Total dispensed prescriptions from outpatient retail pharmacies were obtained for oral dosage forms of sulfasalazine, mesalamine, balsalazide, and olsalazine using Verispan, LLC: Vector One[®]: National (VONA) for years 2003-2006 and year to date September 2007. A complete description of the database can be found in Attachment 1 of the Appendix.

2.3 Literature Search

PubMed was searched on October 25, 2007 using balsalazide as a search term.

3 RESULTS

3.1 Adverse events

The AERS search identified the following categories of adverse events: Cardiac, vasculitis, pulmonary, renal, serious skin, pancreatitis, and blood dyscrasias. The cases are included in the sections below based on the patients' primary/initial events; note that some patients experienced additional adverse events.

CARDIAC DISORDERS

The search identified a total of 9 cases reporting cardiac disorders associated with balsalazide use. Two cases reported as pericarditis provided very little information and are not included in the analysis; the remaining 7 cases are described below.

TABLE 1: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF CASES OF CARDIAC EVENTS ASSOCIATED WITH BALSALAZIDE USE REPORTED TO AERS FROM INITIATION OF MARKETING TO OCTOBER 25, 2007 (N=7)

Age (years): 30 mean, 28 median, 14 to 58 range (n=7)
Gender: Female (1), Male (6)
Source: Domestic (4), foreign (3)
Year: 2000 to 2002 (3), 2003 (2), 2005 to 2007 (2)
Indication for use: Crohn's disease (CD) (1), UC (2), "colitis" (1), not stated (3)
Dose: 550 mg (1), 4.5 g (1), 6.75 (5)
Onset: 14 days (1), 4 to 6 months (2), 1 year (1), "2 weeks after dose increased to 6.75 grams" (1), unk (2)
Dechallenge: 6
Event (as stated by reporter):[§] Myocarditis and pericarditis (2), myocarditis (3), pericarditis (2), interstitial lung disease (1), eosinophilia (1), pneumonia (2), dyspnea (2), chest pain (6), pyrexia (3), arthralgia (1), shortness of breath (1), cardiac murmur (1), myalgia (1), tachycardia (1), pleural effusion (1)
Outcome: Life-threatening (2), hospitalization (4)
Concomitant medications: 2*
Significant medical history: 2[†]

[§] Not mutually exclusive; nonserious adverse events (e.g., nausea/vomiting, cough, night sweats) are not included in the list above.

* Two patients were taking concomitant medications labeled for myocarditis and pericarditis, including sulfasalazine by mouth/mesalamine enema (1) and mesalamine enema (1).

[†] One patient experienced a hypersensitivity reaction (i.e., alveolitis) associated with previous use of mesalamine and one patient had a history of allergic reaction to penicillin.

Case descriptions: FDA# 5482162 (foreign) (2007) A 38-year-old male experienced **myocarditis** 14 days after mesalamine was switched to balsalazide (6.75 g per day) to treat UC (mesalamine had been discontinued due to a flare in UC symptoms). Tests revealed the following: cardiac troponin I elevated (3.02 microg/L), widespread T wave inversion per ECG, C-reactive protein elevated (43 mg/dL), posterior segment wall motion abnormality with no effusion per echocardiography, and normal epicardial vessels per angiography. Myocardial infarction was ruled out per MRI. Medical history and concomitant medications were not reported. Balsalazide therapy was discontinued and the symptoms resolved within 2 days. (this case also was reported in the medical literature.¹⁷)

FDA# 4127691 (Domestic) (2003) A 14-year-old male developed **pericarditis** and **left lower lobe pneumonia** (per chest X-ray) while taking 6.75 mg of balsalazide per day for

¹⁷ Robertson E, Austin D, Jamieson N, et al. Balsalazide-induced myocarditis. Internat J Cardiol 2007; 6: 33.

"several months" to treat UC. His symptoms included chest pain, rhinorrhea, fever, cough, and shortness of breath. In the hospital he was found to have **anemia** (per report, consistent with iron-deficiency anemia; no values reported). Balsalazide therapy was discontinued; the patient recovered. Medical history and concomitant medications were not reported.

VASCULITIS

The search identified a total of 3 cases reporting vasculitis; these cases are described below.

TABLE 2: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF CASES OF VASCULITIS ASSOCIATED WITH BALSALAZIDE USE REPORTED TO AERS FROM INITIATION OF MARKETING TO OCTOBER 25, 2007 (N=3)

Age (years): 23 (1), 49 (1), unk (1)
Gender: Female (2), Male (1)
Source: Domestic (2), foreign (1)
Year: 2003 (2), 2005 (1)
Indication for use: UC (2), not stated (1)
Dose: 6.75 grams (2), unk (1)
Onset: 5 days (1), 4 weeks (1), "number of months" (1)
Dechallenge: 3
Event (as stated by reporter):[†] Vasculitis (2), cellulitis/leucocytoclastic vasculitis (1), skin lesions/rash/urticaria (3), fever (1), proteinuria (1)
Outcome: Hospitalized (1)
Concomitant medications: 1*

[†] Not mutually exclusive.

* One patient experienced an episode of vasculitis one week after penicillin therapy was initiated and four weeks after balsalazide therapy was initiated (report did not mention previous exposure to penicillin).

Case description: Report #4549993 (Domestic) (2003) A 23-year-old female was hospitalized with **vasculitis** five days after initiating balsalazide therapy (6.75 grams per day) to treat UC. Her symptoms included ulcerated skin lesions, fever, and proteinuria (no value reported). Balsalazide was discontinued and her condition improved. She had no significant medical history and was taking oral contraceptives concomitantly. Six weeks after the event, the patient was hospitalized for a UC flare.

PULMONARY EVENTS

An AERS search identified 17 reports coded with respiratory adverse events; 4 reports were excluded for the following reasons: patient's events were due to a respiratory infection (1), patient experienced sore throat/larynx and loss of voice due to ingestion of balsalazide capsule with bitter taste (drug quality issue) (1), patient's pneumonia was bacterial in origin (patient eventually died of sepsis) (1), and report proved little information other than patient experienced an exacerbation of underlying asthma (1).

TABLE 3: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF CASES OF RESPIRATORY EVENTS ASSOCIATED WITH BALSALAZIDE USE REPORTED TO AERS FROM INITIATION OF MARKETING TO OCTOBER 25, 2007 (N=13)

Age (years): 57 mean, 53 median, 42 to 74 range (n=11); not stated (2)
Gender: Male (8), female (5)
Source: Domestic (10), foreign (3)
Year: 2002-2003 (5), 2004 (5), 2005-2006 (3)
Indication for use: UC (9), CD (1), "occasional bleeding from bowel" (1), not stated (2)
Dose: 6.75 grams (4), 6.25 grams (1), 6 grams (2), 3 grams (1), 2.25 grams (2), not stated (3)
Onset: 14 days (1), 25 to 37 days (4), 60 to 120 days (3), 9 months (1), 3 years (2), not stated (2)
Dechallenge: 7
Rechallenge: 3
Events (as stated by reporter):[†] Pleural effusion (1), chest pain (4), dyspnea (1), bronchitis obliterans organized pneumonia (1), pulmonary fibrosis (1), wheezing (1), blood gases abnormal (1), SOB (2), atrial fibrillation (1), increased heart rate (1), pneumonitis (2), eosinophilic pneumonia (2), mesothelial hyperplasia (1), caseating granuloma alveolitis (1), hypoxia (1), fibrosing alveolitis (1), pulmonary hemorrhage (1), respiratory failure (1)
Outcome: Death (1), life threatening (1), hospitalized (3), disability (1)
Significant medical history: 4[§]
Concomitant medications: 1*
[†] Not mutually exclusive; nonserious adverse events (e.g., nausea, myalgia, fatigue, abdominal pain) are not included in the list above.
[§]Four patients had pulmonary-related medical history as follows: history of chest pain or pneumonia associated with mesalamine use (2), history of mild asthma attacks (1), history of recurrent pneumonia/chronic small airway disorder (1)
* One patient was using rectal mesalamine concomitantly.

Case descriptions: FDA# 4430307 (Foreign) (2004) A 64-year-old male developed **dyspnea** and **fibrosing alveolitis** (per CT pulmonary angiogram) and **died** approximately 3 years after taking 2.25 grams of balsalazide per day to treat UC. He was hospitalized two months after reporting dyspnea and balsalazide was discontinued; the patient died one month later (per report, probable cause was fibrosing alveolitis). The report states that there were no other causes for the patient's event. No additional medical history was reported; concomitant medications included mesalamine (1 gram rectally at bedtime), diphenoxyllate and atropine combination, prednisolone, and atorvastatin. (Alveolitis is labeled for sulfasalazine.)

FDA# 4062072 (Domestic) (2003) A 48-year-old female developed **chest pain**, **dyspnea**, and **pleural effusion** after taking 6.75 grams of balsalazide per day to treat UC (onset not stated). A thoracentesis removed approximately 100 mL of fluid from the pleural cavity. Balsalazide was discontinued and resumed at a later date. Upon re-exposure, the patient

developed **chest pain** and **dyspnea**. The patient was switched to 6-mercaptopurine. Additional medical history and concomitant medications were not reported. (Note, rechallenge case)

RENAL EVENTS

The search identified 7 cases of renal disorders associated with balsalazide use. Three cases have been excluded for the following reasons: patient developed a testicular infection leading to liver failure then renal failure due to hepatotoxicity from either drug use (acetaminophen, azathioprine, infliximab) or hepatitis B reactivation or rhabdomyolysis (1), patient had underlying end-stage cardiovascular disease and renal failure before initiating balsalazide (1 [patient died of cardiovascular disease]), and insufficient information provided (allopurinol reported as suspect drug for patient's renal failure). Note that renal failure is considered an outcome related to interstitial nephritis.

TABLE 4: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF CASES OF RENAL EVENTS ASSOCIATED WITH BALSALAZIDE USE REPORTED TO AERS FROM INITIATION OF MARKETING TO OCTOBER 25, 2007 (N=4)

Age (years): 41 mean, 34 median, 22 to 72 range (n=4)

Gender: Male (3), female (1)

Source: Domestic (2), foreign (2)

Year: 1998 (1), 1999 (1), 2001 (1), 2007 (1)

Indication for use: UC (3), CD (1)

Dose: 6.75 grams (3), 2.25 grams

Onset: 20 days (1), 60 days (1), 75 days (1), 6 months (1)

Dechallenge: 2

Events (as stated by reporter):[†] Acute renal failure (3), tubular necrosis (1), dehydration (1), interstitial nephritis (1), hemolytic uremic syndrome (1; anemia, thrombocytopenia, syncope, jaundice, rectal hemorrhage also reported)

Outcome (mutually exclusive): Life threatening (1), hospitalization (3)

Significant medical history: 1[§]

Concomitant medications: 2^{*}

Lab values:

Increased creatinine (3; one patient had baseline of 1.3 increased to 4.4;[‡] one patient had a creatinine of 5.7 [baseline not reported]; one patient had baseline of 134 increased to 223 [foreign values; units not provided]); creatinine value not reported for one patient.

Increased BUN (2; one patient had baseline 5.6 increased to 12.5 [foreign values, units not provided], one patient had a value of 48 [baseline not reported]); BUN not reported for 2 patients.

[†] Not mutually exclusive

[§] One patient had an underlying history of diabetes (type not specified) and ischemic heart disease.

^{*} One patient was taking lisinopril concomitantly (lisinopril is labeled for renal failure); the patient who developed hemolytic uremic syndrome was listed as using mesalamine concomitantly and had recently been switched from a "5-ASA derivative" (note that sulfasalazine is labeled for hemolytic uremic syndrome).

‡ This patient developed renal failure/tubular necrosis approximately 2 months after balsalazide initiation and 9 days after azathioprine initiation (reporter suspects adverse event related to balsalazide or azathioprine or combination of the two drugs [azathioprine is not labeled for renal failure or tubular necrosis]).

Case description: Report # 3681412 (Foreign) (1999) A 35-year-old male patient was switched from mesalamine (variable patient compliance reported) to balsalazide and was hospitalized with **interstitial nephritis (per biopsy) and renal failure** 6 months later. He was taking balsalazide 6.75 grams per day to treat UC. His baseline creatinine and BUN values were 134 and 5.6, respectively; at event, his baseline values were 223 and 12.5, respectively (note foreign values, units not provided). Balsalazide was discontinued and the patient's outcome continues. Medical history and concomitant medications were not reported.

SERIOUS SKIN EVENTS

TABLE 5: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF CASES OF SERIOUS SKIN EVENTS ASSOCIATED WITH BALSALAZIDE USE REPORTED TO AERS FROM INITIATION OF MARKETING TO OCTOBER 25, 2007 (N=3)

Age (years): 33 mean, 32 median, 31 to 37 range (n=3)

Gender: Female (2), Male (1)

Source: Domestic (2), foreign (1)

Year: 2003 (2), 2005 (1)

Indication for use: UC (2), idiopathic proctocolitis (1)

Dose: 6.75 grams (1), 7.5 grams (1), 3 grams (1)

Onset: 1 day (1), 2 days (1), 1.5 to 2 years (1)

Dechallenge: 2

Rechallenge: 2

Events (as stated by reporter):[†] Angioedema (1), pruritus (2), increased white blood cells (1), dysphagia (1), peripheral edema/swelling (2), dyspnea (1), toxic epidermal necrolysis (1), exanthema (1), skin lesions (1), respiratory failure (1)

Outcome: Life-threatening (1), hospitalized (1), ER visit (1)

Concomitant medications: 1*

[†] Not mutually exclusive; nonserious adverse events (e.g., nausea, diarrhea, abdominal pain) are not included in the list above.

* One patient-reporter experienced hypersensitivity reaction initially and upon rechallenged when balsalazide was taken with acetaminophen (he did not have a reaction when taking acetaminophen without balsalazide); one patient had a hypersensitivity reaction associated with sulfasalazine administration (see description below).

Case descriptions: FDA #5292699 (Domestic) (2007) A 32-year-old male who had been using balsalazide (7.2 grams per day) to treat UC for 1.5 to 2 years developed **angioedema, pruritus, erythema, and increased white blood cells** (12,000 cells per microliter). Initially he had noticed itchy feet after going on a hike, which progressed to angioedema. He was hospitalized and balsalazide was discontinued; he was treated with doxycycline and prednisone and his condition improved. While on doxycycline and prednisone, he resumed balsalazide use and once again he presented to the hospital with redness and swelling along with difficulty swallowing; he was admitted to the hospital for further evaluation.

FDA #5361141 (Foreign) (2007) A 31-year-old male developed **toxic epidermal necrolysis** two days after initiating 3 grams of balsalazide a day to treat idiopathic proctocolitis. The patient exhibited **exanthema** on the trunk and extremities, **aphthous lesions** in the mouth and pharynx, and **bullous lesions** in mucous membranes extending to 30% of the body surface. He was intubated due to **respiratory failure**; a chest x-ray showed bilateral pulmonary opacities. He was treated with steroids, antimycotics, and antibiotics. He was taking prednisone concomitantly. The patient was switched to azathioprine to treat his underlying condition. He was reported as having no history of food, pollen, or drug allergies; he had had a previous hypersensitivity reaction to sulfasalazine (i.e., purpuric exanthema, erythrodermic rash, angioedema, vesicular lesions, lymphadenopathy, splenomegaly, leukocytosis with hypereosinophilia, elevated liver function test and changes in coagulation parameters).

PANCREATITIS

The search identified a total of 6 cases reporting pancreatitis; 2 of these cases provided very little information and are not included in the case series. The remaining 4 cases are described below.

TABLE 6: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF CASES OF PANCREATITIS ASSOCIATED WITH BALSALAZIDE USE REPORTED TO AERS FROM INITIATION OF MARKETING TO OCTOBER 25, 2007 (N=4)

Age (years): 34 mean, 38 median, 6 to 54 range (n=4)
Gender: Female (3), Male (1)
Source: Domestic (4)
Year: 2002 (1), 2004 (1), 2005 (2)
Indication for use: CD (1), UC (2), "colitis" (1)
Daily Dose: 750 mg (1), 750 mg increased to 2250 mg (1), 6750 mg (2)
Onset: 13 days (1), 6 months (1), 17 months (1), unk (1)
Dechallenge: 4
Event (as stated by reporter): [†] Allergic pancreatitis (1), pancreatitis (2), necrotizing pancreatitis (1), increased triglycerides (1)
Outcome: Hospitalized (4)
Concomitant medications: 4*
Laboratory Values at Event (baselines not reported)
Amylase (U/L): 300 (1), "1000s" (1), 1363 (1), "increased" (1)

Lipase (U/L): 880 (1), "1000s" (1), 7293 (1), "increased" (1)

† Not mutually exclusive; nonserious adverse events (e.g., epigastric pain, nausea/vomiting, abdominal pain) are not included in the list.

* All 4 patients were taking concomitant medications known to cause pancreatitis, including mesalamine (2), mesalamine suppositories (1), and valproate/valproic acid combination (1).

Case descriptions: FDA# 3962209 (Domestic) (2002): A 54-year-old female developed **acute necrotizing pancreatitis with bleeding** 13 days after sulfasalazine was switched to balsalazide at a dose of 6750 mg per day to treat UC. The patient experienced **nausea/vomiting, epigastric pain, increased amylase (1363 U/L) and increased lipase (7293 U/L)**; baseline labs were not reported. An endoscopic retrograde cholangiography was unsuccessful. Pseudocyst became infected and a debridement of the pancreas was performed. She was hospitalized for 10 weeks. The patient had a history of cholecystectomy, hiatal hernia, hypercholesterolemia, uterine fibrosis, and ovarian cyst; she had had a recent flare of her UC. Concomitant medications included atorvastatin and mesalamine suppositories (mesalamine is labeled for pancreatitis).

FDA# 4397903 (Domestic) (2004) A 6-year-old male with a history of "colitis," convulsions, premature birth, hydrocephalus, and ventriculo-peritoneal shunt developed **pancreatitis** after taking balsalazide for 17 months (5 months after the dose was increased from 750 mg per day to 2250 mg per day). He was admitted to the hospital with elevated triglyceride (463 mg/dL), amylase ("in the 1000s"), and lipase ("in the 1000s"); baseline values not reported. Balsalazide was discontinued and the patient's condition was improving at the time of the report. The physician thought that the patient's elevated triglyceride values were related to concomitant prednisone use and that pancreatitis was related to balsalazide use. Additional concomitant medications included metronidazole, sodium valproate and valproic acid combination (labeled for pancreatitis; duration of use not specified), and oxcarbazepine.

BLOOD DYSCRASIAS

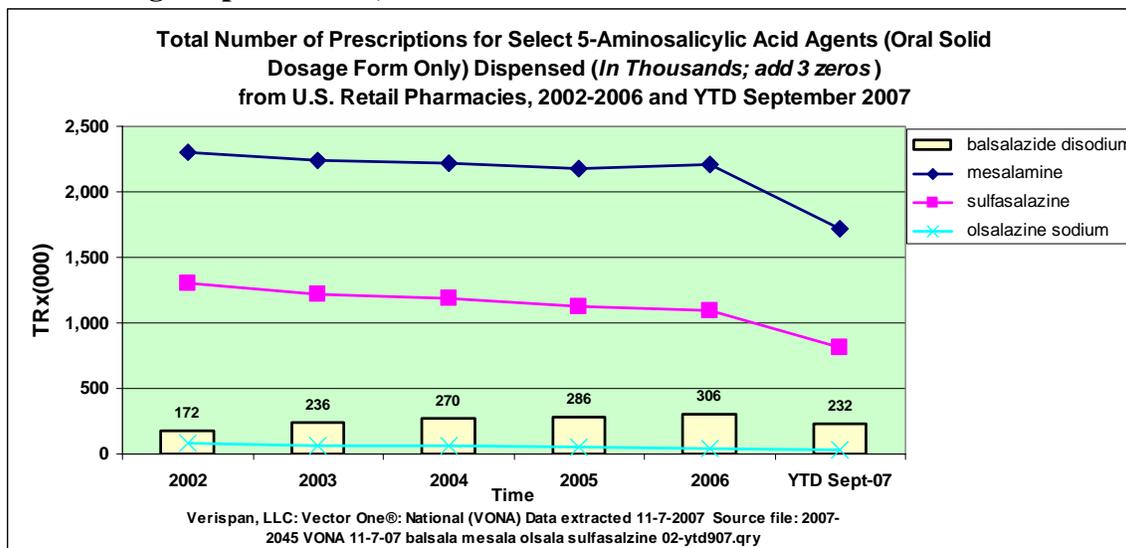
A search of AERS identified 5 cases reporting blood dyscrasias associated with balsalazide use as follows: pancytopenia (1), neutopenia (2), and thrombocytopenia (2). The patient who developed pancytopenia was later diagnosed with leishmaniasis, which was determine to be the reason for his pancytopenia (foreign case). Two cases reported neutropenia: one case provided very little clinical information and the other patient was taking mercaptopurine concomitantly; his WBC increased from 2.3 to 4.7 after treatment with filgastrim. Two cases reported thrombocytopenia: one patient had underlying chronic pancytopenia as well as other serious medical history and the other patient (a child) was receiving sulfamethoxazole/trimethoprim combination and mercaptopurine concomitantly (she remained on balsalazide; her condition improved when other medications were discontinued). Both mercaptopurine and sulfamethoxazole/trimethoprim combination are known to cause blood dyscrasias.

3.3 Drug Usage - Dispensed Prescriptions

A total of 1,502,000 prescriptions were dispensed for balsalazide from January 1, 2002 through September 30, 2007 by retail pharmacies (chain, independent, food stores, mass

merchandisers) in the U.S. (per Verispan, LLC: Vector One: National [VONA]).* Per chart below, total new prescriptions for sulfasalazine, mesalamine, and olsalazine also are depicted. Sulfasalazine was approved in the US on June 20, 1950; mesalamine was approved on January 31, 1992; olsalazine was approved on July 31, 1990; and balsalazide was approved on July 18, 2000.

Figure 1: Total Prescriptions Dispensed by Retail Pharmacies for Oral Dosage Forms of Sulfasalazine, Mesalamine, Balsalazide, and Olsalazine from January 1, 2002 through September 30, 2007.



* Data provided by Vicky Borders-Hemphill, Pharm.D., Drug Utilization Specialist, Lieutenant Commander, PHS, OSE Division of Surveillance, Research, and Communication.

3.2 Literature Search

A literature search identified two case reports of adverse events associated with balsalazide (i.e., **myocarditis** and **pericarditis/vasculitis**). The case involving **myocarditis** also was reported to AERS and is included in the analysis above. The other case involved a 59-year-old female who developed **pericarditis**, **vasculitis**, and **cholestatic liver disease** eight days after switching from sulfasalazine to balsalazide 6.75 grams per day to treat pancolitis.¹⁸ Initially, she was admitted to the hospital with **chest pain**, **shortness of breath**, **back pain**, **splinter hemorrhage on 2 fingernails**, and **raised jugular venous pressure**. Investigations found increased values for inflammatory markers (sed rate=122, C reactive protein=251) with mild **anemia** and **thrombocytosis**. A liver profile was indicative of **cholestasis** (alkaline phosphatase=472 U/mL, GGT=295 U/mL, ALT=50 U/mL, bilirubin=15 mg/dL). An electrocardiogram suggested **pericarditis** and **pericardial effusion**. Balsalazide was discontinued and the patient was treated with NSAIDs and prednisolone; she was switched to sulfasalazine and was reported to be doing well (foreign case).

¹⁸ Adhiyaman V, Vaishnavi A, Froese S, et al. Hypersensitivity reaction to balsalazide. *BMJ* 2001; 323: 489.

One study identified in the literature involved a retrospective and prospective analysis in the United Kingdom of cases of **nephrotoxicity** associated with 5-ASA products (i.e., sulfasalazine, mesalamine, balsalazide, and olsalazine).¹⁹ The authors identified 1 case of nephrotoxicity associated with balsalazide use in the retrospective study and 3 cases in the prospective study (202 total cases of nephrotoxicity for all 5-ASA products were reported in the retrospective study and 59 total cases were reported in the prospective study). In the retrospective study, 53 patients were diagnosed with interstitial nephritis per biopsy and 17 patients in the prospective study were diagnosed with interstitial nephritis per biopsy; note that not all patients received a biopsy. Because the patient data for all 5-ASA products were analyzed together, demographics and clinical outcomes are not available on the patients who were taking balsalazide. (The corresponding author was unable to provide details for the balsalazide cases.)

4 DISCUSSION

Balsalazide is an oral anti-inflammatory agent (5-aminosalicylate [5-ASA]) with local effects. Serious adverse events for 5-ASA medications are well known and many are labeled for other drugs in the same class (i.e., sulfasalazine, mesalamine, and olsalazine), but not for balsalazide. Many of the events described in this case series represent hypersensitivity reactions, pathologic processes that result from immunologically-specific interactions between antigens and antibodies.²⁰

There are fewer adverse events reported to AERS for balsalazide and olsalazine than for sulfasalazine and mesalamine; this could be because there are fewer prescriptions dispensed for balsalazide and olsalazine compared to sulfasalazine and mesalamine (see drug use data). See Attachment 2 in the Appendix for AERS counts of selected adverse events reported to AERS for sulfasalazine, mesalamine, and olsalazine.

Some patients in this case series had underlying conditions or were taking concomitant medications that could have contributed to their adverse events; however, the role of balsalazide could not be ruled out. Pharmacologically, the 5-ASA products are similar.²¹

It is thought that serious adverse reactions are related to the sulfa component of sulfasalazine.²² Even though mesalamine, balsalazide, and olsalazine do not contain a sulfa component, serious adverse reactions have been reported (see Product Labeling [above] and AERS Case Counts [Attachment 2]). Only two cases in this series reported patients' previous 5-ASA exposure (one patient received sulfasalazine and one patient

¹⁹ Muller AF, Stevens PE, McIntyre AS, et al. Experience of 5-aminosalicylate nephrotoxicity in the United Kingdom. *Aliment Pharmacol Ther* 2005; 21:1217-24. The authors queried physicians in the British Society of Gastroenterology and the Renal Association (1588 physicians total in both the retrospective and prospective studies [physicians queried every 6 months for 2 years in the prospective study]) and asked them to complete a questionnaire if they had treated patients for nephrotoxicity possibly associated with 5-ASA products. Other than interstitial nephritis, diagnoses in the retrospective study included the following: other histology included membranous nephropathy (n=1), end stage kidney disease (n=1), and chronic allograft nephropathy (n=1); other diagnoses in the prospective study included the following: other histology included glomerulosclerosis (n=1) and end stage kidney disease (n=1)

²⁰ Beers MH, Berkow R, editors. *The Merck Manual*, Merck Research Laboratories, West Point PA, 1999, pp 1041-53.

²¹ Facts and Comparisons (www.efactsweb.com), accessed on November 21, 2007.

²² Wilcox GM, Reynolds JR. Nephrotoxicity associated with olsalazine. *Am J Med* 1996; 100: 238-9.

received mesalamine); these two patients experienced a previous hypersensitivity reaction, indicating prior sensitization and cross reactivity. It is difficult to compare numbers of events for individual 5-ASA products because use varies depending on promotion of the product, number of years on the market, and other factors. However, there is evidence for a class phenomenon for 5-ASA use and the following adverse events: Myocarditis, pericarditis, vasculitis, pruritus, pleural effusion, pneumonia with and without eosinophilia, alveolitis, renal failure, interstitial nephritis, and pancreatitis. Drug use data indicate that use of balsalazide appears to be increasing slightly; therefore, more cases may be reported.

5 CONCLUSION

Balsalazide is associated with serious adverse events that are labeled for the other 5-ASA products (i.e., sulfasalazine, mesalamine, olsalazine).

6 RECOMMENDATIONS

DDRE recommends class labeling for the 5-ASA products (i.e., sulfasalazine, mesalamine, balsalazide, and olsalazine) and myocarditis, pericarditis, vasculitis, pruritus, pleural effusion, pneumonia with and without eosinophilia, alveolitis, renal failure, and interstitial nephritis (note that renal failure is considered an outcome of interstitial nephritis), and pancreatitis. The labeling for balsalazide should be updated to reflect that postmarketing reports for these events have been received.

Although evidence is limited (based on postmarketing reports), the following adverse events have been reported for other 5-ASA drugs and should be considered by DGP for inclusion in the balsalazide label: Interstitial lung disease, urticaria, pulmonary fibrosis, hemolytic uremic syndrome, angioedema, toxic epidermal necrolysis, pericardial effusion, leukopenia and thrombocytopenia.

APPENDICES

Attachment 1: Database Description

Verispan, LLC: Vector One: National (VONA)

Verispan's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One receives over 2 billion prescription claims, representing over 160 million unique patients.

Prescriptions are captured from a sample of approximately 54,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent approximately 50% of retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

Attachment 2: Counts of Selected Adverse Events for Sulfasalazine, Mesalamine, and Olsalazine as Reported to AERS from Initiation of Marketing to Present (note raw data, duplicates may exist)

	Sulfasalazine	Mesalamine	Olsalazine
Myocarditis	10	23	1
Pericarditis	12	70	3
Pericardial effusion	5	34	1
Pancreatitis	20	111	8
Interstitial Nephritis	10	93	2
Renal Failure	70	106	3
Hemolytic uremic syndrome	0	4	0
Proteinuria	6	27	1
Vasculitis	12	16	0
Peripheral edema	34	39	1
Pyrexia	413	282	11
Pleural effusion	31	42	0
Chest pain	25	103	4
Aveolitis	5	16	1
Pulmonary fibrosis	16	17	1
Dyspnea	87	102	9
Interstitial lung disease	41	41	0
Pneumonia	78	82	3
Eosinophilic pneumonia	8	29	0
Toxic epidermal necrolysis	29	3	0
Pruritus	67	49	3
Urticaria	29	30	2
Angioedema	10	7	2
Neutropenia	58	28	0
Thrombocytopenia	87	54	9
Leukopenia	129	60	7
Anemia	61	67	5
Bone marrow failure	48	14	3
Pancytopenia	61	31	3

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