

**One Year Post-Exclusivity  
Adverse Event Review:  
Balsalazide**

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# Background Drug Information

**Drug:** Colazal<sup>®</sup> (balsalazide)

**Therapeutic Category:** 5-aminosalicylate (5-ASA)

**Sponsor:** Salix Pharmaceuticals

**Original Market Approval:** July 18, 2000

**Pediatric Exclusivity Granted:** August 23, 2006

**Indication:** For the treatment of mildly to moderately active ulcerative colitis (UC)

# Drug Use Trends in Outpatient Settings

- 356,738 dispensed retail and mail order prescriptions for all age groups during the 12 month post-exclusivity period
  - 9,255 (2.7%) were dispensed for pediatric patients 0 to 16 years old
- 4% increase in retail prescriptions for all age groups between the 12 month pre- and post-exclusivity periods
  - 9% increase for the pediatric population

# Drug Use Trends in Outpatient Settings

- Gastroenterology was the most frequent prescriber specialty during the 12 month post-exclusivity period
  - Gastroenterology: 70% (250,000 total prescriptions)
  - Pediatrics: 2.6% (9,000 total prescriptions)
- No mention of balsalazide in association with a pediatric visit in an office-based physician practice survey

# **Pediatric Exclusivity Study: PK, Safety, and Efficacy Study**

## **Design**

Multi-center, randomized, double-blind, parallel-group, 8-week study of 2 balsalazide TID dosing regimens involving 68 pediatric patients, 5 to 17 years old, with mildly to moderately active UC

## **Dosing Regimen**

- High Dose: 6.75 g/day (n=33)
- Low Dose: 2.25 g/day (n=35)

# Pediatric Exclusivity Study

## PK Results (n=12)

Pediatric patients, 6 to 17 years old, had lower systemic exposure to the two key balsalazide metabolites (mesalamine and N-acetyl-5-aminosalicylic acid)

# Pediatric Exclusivity Study

## Primary Efficacy Endpoint

Proportion of patients with clinical improvement

- Clinical improvement defined as a reduction in the Modified Sutherland UC Index (MUCAI) total score by at least 3 points from baseline to Week 8
- MUCAI assessment items (score range of 0 – 12)
  - Stool frequency (0 – 3)
  - Rectal bleeding (0 – 3)
  - Mucosal appearance (0 – 3)
  - Physician's rating of disease activity (0 – 3)

# Pediatric Exclusivity Study

## Efficacy Results (n=68)

- Both doses showed reasonable improvement for the primary efficacy endpoint (but no statistically significant difference between the high and low doses)
  - High dose group: 15 patients (45%) improved
  - Low dose group: 13 patients (37%) improved
  - Normal placebo response rates for this class of drugs: ~20%
- High dose group had consistently better numerical scores compared to the low dose group for secondary endpoints (but no statistically significant difference between the high and low dose groups)
  - Rectal bleeding (64% vs. 54%)
  - Mucosal appearance (61% vs. 46%)

# Pediatric Exclusivity Study

## Safety Results (n=68)

- 0 deaths
- 4 patients with serious adverse reactions
- 4 patient withdrawals due to adverse events
- Two dose levels were generally safe and well tolerated

# Pediatric Exclusivity Study

## Safety Results (continued)

### Serious Adverse Events (n=4 patients)

- High dose group
  - UC flare (1)
  - Depression in a patient with a history of depression (1)
- Low dose group
  - UC flare (1)
  - Clostridial infection in a patient on prednisone, Imodium, and Levaquin (1)

# Pediatric Exclusivity Study

## Safety Results (continued)

### Withdrawals (n=4 patients)

- High dose group
  - Abdominal pain and urticaria (1)
- Low dose group
  - Frequent bowel movements (1)
  - Rectal hemorrhage (1)
  - UC flare (1)

# **Pediatric Exclusivity Study: Labeling Changes**

- Indications and Usage
- Dosage and Administration
- Warning and Precautions
- Adverse Reactions
- Use In Specific Populations – Pediatric Use
- Clinical Pharmacology – Pharmacokinetics
- Clinical Studies

# Pediatric Exclusivity Study: Labeling Changes (continued)

- Indications and Usage
  - Added an indication for pediatric patients 5 to 17 years old
- Dosage and Administration
  - Added pediatric dosing of three 750 mg capsules TID (6.75 g/d) OR one 750 mg capsule TID (2.25 g/d)
- Warning and Precautions
  - Added an Exacerbation of UC subsection and included data from the pediatric exclusivity study
- Adverse Reactions
  - Added a Pediatric UC subsection that describes the adverse events and patient withdrawals seen during the pediatric exclusivity study

# Pediatric Exclusivity Study: Labeling Changes (continued)

- Use In Specific Populations – Pediatric Use
  - Noted the other labeling sections that describe the pediatric exclusivity studies
  - Noted pediatric dosing of 6.75 or 2.25 g/d
  - Noted that safety and efficacy have not been established in pediatric patients < 5 years old
- Clinical Pharmacology – Pharmacokinetics
  - Added a Pediatric Population subsection that describes the PK findings from the pediatric exclusivity studies
- Clinical Studies
  - Added a Pediatric Studies subsection that describes the efficacy findings from the pediatric exclusivity studies

# Adverse Event Reports During the Post-Exclusivity Period

8/22/2006 – 9/22/2007

<b>Raw Counts*</b>	<b>All Reports (US)</b>	<b>Serious (US)</b>	<b>Death (US)</b>
<b>Adults (≥ 17)</b>	26 (19)	26 (19)	5 (5)
<b>Pediatrics (0 to 16)</b>	3 (2)	3 (2)	0 (0)
<b>Age unknown</b>	4 (2)	4 (2)	0 (0)
<b>All ages</b>	33 (23)	33 (23)	5 (5)

\*May include duplicate cases

Source: Adverse Event Reporting System, FDA

# Adverse Event Reports Since Marketing Approval

7/18/2000 – 9/22/2007

<b>Raw Counts*</b>	<b>All Reports (US)</b>	<b>Serious (US)</b>	<b>Death (US)</b>
<b>Adults (≥ 17)</b>	103 (78)	92 (68)	11 (9)
<b>Pediatrics (0 to 16)</b>	8 (6)	6 (5)	0 (0)
<b>Age unknown</b>	61 (45)	39 (23)	1 (0)
<b>All ages</b>	172 (129)	137 (96)	12 (9)

\*May include duplicate cases

Source: Adverse Event Reporting System, FDA

# Pediatric Adverse Events Since Market Approval

- 8 raw count cases
- 3 cases excluded
  - Miscoded as suspect drug was mesalamine (1)
  - Indirect exposure via maternal use (1)
  - Not a serious adverse event (1)
- 5 remaining cases
  - Deaths (0)
  - Serious adverse events (5)

# Serious Adverse Events Since Marketing Approval (n=5)

- Pericarditis, lower lobe pneumonia and anemia (1)  
Resolved after balsalazide was discontinued
- Pancreatitis (1)  
Resolved after balsalazide was discontinued
- UC flare (2)
- Thrombocytopenia (1)  
Resolved with discontinuance of unspecified concomitant medications while balsalazide treatment continued

Unlabeled events are underlined.

Source: Adverse Event Reporting System, FDA

# Warnings/Precautions and Adverse Reactions Labeling: Other 5-ASA Drugs

## Sulfasalazine

- Warnings: Hypersensitivity reactions, liver failure, renal failure
- Adverse reactions: **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

## Mesalamine

- Precautions: Hypersensitivity, renal impairment including acute and chronic interstitial nephritis, rarely renal failure
- Adverse reactions: 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 nephrotoxicity, fever, edema, vasodilation, ecchymosis, pruritus, thrombocytopenia, dyspnea, chest pain, nephritic syndrome, **pneumonitis**, interstitial pulmonary fibrosis without eosinophilia

## Olsalazine

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

# Requested Labeling Change: Balsalazide

## 6 Adverse Events

### 6.2 Postmarketing Experience

“The following adverse reactions have been identified during post-approval use of balsalazide:

myocarditis, **pericarditis**, vasculitis, pruritus, pleural effusion, **pneumonia** (with and without eosinophilia), alveolitis, renal failure, interstitial nephritis, **pancreatitis ...**”

# Summary: Balsalazide

- This completes the 1 year post-exclusivity AE reporting.
- The safety review identified postmarketing adverse reactions in pediatric and adult populations that are not listed in the balsalazide labeling but are listed in other 5-ASA drug labelings. Therefore, the FDA has requested that the identified adverse reactions be added to the balsalazide labeling.
- FDA will send the Advisory Committee a labeling update via email when the changes are complete.
- FDA also recommends routine monitoring of balsalazide for adverse events in all populations.

Does the Advisory Committee concur with this plan?

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