

# **Pediatric Focused Safety Review: Asacol, Asacol HD and Delzicol (mesalamine)**

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# Background Drug Information: Mesalamine Products

Trade Name	Initial Approval	Formulation*	Indication	Population†
Apriso	2008	Capsule, ER	Maintenance of remission of UC	Adults
Asacol‡	1992	Tablet, DR	Treatment of mildly to moderately active UC Maintenance of remission of mildly to moderately active UC	Age ≥ 5 years (treatment) Adults (maintenance)
Asacol HD	2008	Tablet, DR	Treatment of moderately active UC	Adults
Canasa	2001	Suppository	Treatment of active ulcerative proctitis (UP)	Adults
Delzicol	2013	Capsule, DR	Treatment of mildly to moderately active UC Maintenance of remission of UC	Age ≥ 5 years (treatment) Adults (maintenance)
Lialda	2007	Tablet, DR	Induction of remission in active, mild to moderate UC Maintenance of remission of UC	Adults
Mesalamine	2015	Suppository	Treatment of mild to moderately active UP	Adults
Pentasa	1993	Capsule, ER	Induction of remission and for the treatment of patient with mildly to moderately active UC	Adults
sfRowasa	1987	Enema	Treatment of active mild to moderate distal UC, proctosigmoiditis, or proctitis	Adults

\* Definitions: ER extended release, DR delayed release

† Asacol and Delzicol are the only mesalamine products indicated for the treatment of mildly to moderately active UC in patients five years of age and older

‡ Withdrawn by the sponsor, Warner Chilcott, from the US market March 2013

## Background Drug Information, cont'd. Asacol, Asacol HD and Delzicol (mesalamine)

- **Therapeutic Category:** aminosalicylate
- **Sponsor:** Allergan Pharmaceuticals International Limited
- **Indication:**
  - **Asacol and Delzicol**
    - Treatment of mildly to moderately active Ulcerative Colitis (UC) in **patients 5 years and older**
    - Maintenance of remission of mildly to moderately active UC in adults only
  - **Asacol HD**
    - Treatment of moderately active UC in adults only

# Background Drug Information, cont'd

## Asacol, Asacol HD and Delzicol (mesalamine)

- **Formulation:**
  - Asacol (400 mg), delayed-release tablets
  - Asacol HD (800 mg), delayed-release tablets
  - Delzicol (400 mg), delayed-release capsules (containing four 100 mg tablets)
- **Dosage and Administration: oral use**
  - Asacol and Delzicol
    - Treatment of mildly to moderately active UC
      - Adults: 800 mg three times daily for 6 weeks
      - **Pediatric patients 5 years or older: Total daily dosage is weight-based up to a maximum of 2.4 grams/day divided into two daily doses**
    - Maintenance of remission of mildly to moderately active UC
      - Adults: 1.6 grams daily in two to four divided doses
  - Asacol HD
    - Treatment of Moderately Active Ulcerative Colitis
      - Adults: 1600 mg three times daily for 6 weeks



# Regulatory History: Asacol, Asacol HD and Delzicol (mesalamine)

- **Original Market approval:**
  - Asacol: January 31, 1992
  - Asacol HD: May 9, 2008
  - Delzicol: February 1, 2013

## Regulatory History, cont'd.

### Asacol, Asacol HD and Delzicol (mesalamine), cont'd

- **Pediatric labeling changes:**

- Asacol: October 18, 2013\* and May 27, 2015
- Asacol HD: October 18, 2013\* and May 5, 2016
- Delzicol: April 28, 2014\* and September 9, 2015
- **Asacol and Delzicol are approved for treatment of mildly to moderately active UC in patients 5 years of age and older.\***
- Safety and efficacy not established in pediatric patients for maintenance of remission of UC for Asacol or Delzicol, or for treatment of UC in Asacol HD.
- Pediatric study requirement outstanding for Delzicol for maintenance of remission of UC in patients 5 to 17 years of age due September 2020.

\*Prompted today's PAC presentation.

## **Prior Safety Activities: Asacol, Asacol HD and Delzicol (mesalamine)**

- March, 2009: Due to potential adverse reproductive and fetal developmental effects with dibutyl phthalate (DBP), an excipient in Asacol and Asacol HD, the FDA asked the sponsor to develop new phthalate-free formulations.
- February, 2013: Delzicol approved as a new phthalate-free formulation of Asacol.
- March, 2013: Asacol 400 mg tablets removed from the US market following the approval of phthalate-free Delzicol.
- May, 2016: A new phthalate-free formulation of Asacol HD approved.

## Prior Safety Activities: Asacol, Asacol HD and Delzicol (mesalamine)

- April, 2014: Division of Pharmacovigilance evaluated 53 postmarketing reports of difficulty swallowing and removal of the outer capsule related to difficulty swallowing Delzicol.
  - Recommendations:
    1. Update the Delzicol label to inform patients not to open the capsule before swallowing.
    2. Ask the sponsor to monitor postmarketing serious and non-serious adverse events related to difficulty swallowing the capsules if the pediatric supplement for the treatment of mildly to moderately active UC in patients 5 years of age and older was approved.
- July, 2015: Clinical review of Delzicol determined that following the approval of the current pediatric-appropriate Delzicol formulation (4 smaller tablets within one capsule), the potential safety concerns related to difficulty swallowing were no longer an issue.

## **Pediatric Efficacy and Safety Studies: Asacol, Asacol HD and Delzicol (mesalamine)**

### **Treatment of UC:**

- The safety and effectiveness of Asacol and Delzicol in patients for treatment of mildly to moderately active UC, ages 5 to 17 years, are supported by evidence from adequate and well controlled studies of Asacol in adults and a single study in of Asacol in 82 pediatric patients, age 5 to 17 years, in addition to demonstration of bioequivalence of Asacol to Delzicol.
- Bioequivalence of Asacol to Asacol HD has not been established.

# Pediatric Efficacy and Safety Studies: Asacol and Delzicol (mesalamine)

## Maintenance of UC:

- In a randomized, double-blind 26-week trial of two dosage levels for maintenance of remission of mildly to moderately active ulcerative colitis initiated in 39 patients aged 5 to 17 years, the safety and effectiveness of Asacol has not been established.
- Possible factors contributing to this outcome included the dose range studied and premature termination of the trial.

# Pediatric Labeling Changes: Asacol (mesalamine)

- **8.4 Use in Specific Populations, Pediatric Use**
  - The safety and effectiveness of Asacol in pediatric patients 5 to 17 years of age for treatment of mildly to moderately active ulcerative colitis have been established over a 6-week period. Use of Asacol in these age groups is supported by evidence from adequate and well controlled studies of Asacol in adults and a single study in 82 pediatric patients 5 to 17 years of age [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.1)].
  - The safety and effectiveness of Asacol for the maintenance of remission of mildly to moderately active ulcerative colitis in pediatric patients have not been established. Efficacy was not demonstrated in a randomized, double-blind 26-week trial of two dosage levels for maintenance of remission of mildly to moderately active ulcerative colitis initiated in 39 patients aged 5 to 17 years. Possible factors contributing to this outcome included the dose range studied and premature termination of the trial.

Pediatric information is included throughout labeling for treatment of UC for patients 5 years and older.

# Pediatric Labeling Changes: Delzicol (mesalamine)

- **8.4 Use in Specific Populations, Pediatric Use**
  - The safety and effectiveness of DELZICOL for the treatment of mildly to moderately active ulcerative colitis in pediatric patients 5 to 17 years of age has been established based on adequate and well-controlled studies using mesalamine delayed-release 400 mg tablets. Use of DELZICOL in these pediatric age groups is supported by evidence from adequate and well controlled studies of mesalamine delayed-release 400 mg tablets in adults and a single 6-week study in 82 pediatric patients 5 to 17 years of age [see Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.1)].
  - The safety and effectiveness of DELZICOL for the treatment of mildly to moderately active ulcerative colitis in pediatric patients below the age of 5 years have not been established. The safety and effectiveness of DELZICOL in the maintenance of remission of ulcerative colitis in pediatric patients have not been established.

Pediatric information is included throughout labeling for treatment of UC for patients 5 years and older.



# Pediatric Labeling Changes: Asacol HD (mesalamine)

- **8.4 Use in Specific Populations, Pediatric Use**
  - Safety and effectiveness of Asacol HD in pediatric patients have not been established. See the prescribing information for other approved mesalamine products for the safety and effectiveness of these products in pediatric patients.

## Additional Relevant Safety Labeling: Asacol, Asacol HD and Delzicol (mesalamine)

- **5 WARNINGS AND PRECAUTIONS**

- 5.1 Renal Impairment

Renal impairment, including minimal change nephropathy, **acute and chronic interstitial nephritis**, and renal failure, has been reported in patients taking products such as Asacol that contain mesalamine or are converted to mesalamine [*see Adverse Reactions (6.2)*].

- 5.2 Mesalamine-Induced Acute Intolerance Syndrome

- 5.3 Hypersensitivity Reactions

- 5.4 Hepatic Failure

- **6.2 Postmarketing Experience**

- **Renal:** Renal failure, **interstitial nephritis**, minimal change nephropathy [*see Warnings and Precautions (5.1)*].

## Drug Utilization: Asacol and Asacol HD

Nationally estimated number of patients with a dispensed prescription for Asacol HD and Asacol from U.S. outpatient retail pharmacies, stratified by patient age, October 1, 2014 – February 29, 2016

	Patients (N)	Share (%)
<b>Asacol HD Total Patients</b>	<b>197,338</b>	<b>100.0%</b>
<b>0 - 17 years</b>	<b>5,607</b>	<b>2.8%</b>
<b>0 - 4 year</b>	44	0.8%
<b>5 - 17 years</b>	5,570	99.3%
<b>18+ years</b>	192,023	97.3%
<b>Unknown Age</b>	2,064	1.0%
<b>Asacol Total Patients</b>	<b>3,732</b>	<b>100.0%</b>
<b>0 - 17 years</b>	<b>120</b>	<b>3.2%</b>
<b>0 - 4 year</b>	10	8.2%
<b>5 - 17 years</b>	110	91.6%
<b>18+ years</b>	3,611	96.7%
<b>Unknown Age</b>	6	0.2%

Source: IMS, Vector One®: Total Patient Tracker. Oct 2014 - Feb 2016. Extracted March 2016.

# Drug Utilization: Delzicol

Nationally estimated number of patients with a dispensed prescription for Delzicol from U.S. outpatient retail pharmacies, stratified by patient age, April 1, 2014 – February 29, 2016

	Patients (N)	Share (%)
<b>Delzicol Total Patients</b>	<b>188,466</b>	<b>100.0%</b>
<b>0 - 17 years</b>	<b>6,903</b>	<b>3.7%</b>
<b>0 - 4 year</b>	156	2.3%
<b>5 - 17 years</b>	6,774	98.1%
<b>18+ years</b>	181,491	96.3%
<b>Unknown Age</b>	1,899	1.0%

Source: IMS, Vector One®: Total Patient Tracker. Apr 2014 - Feb 2016. Extracted March 2016.



# Total Number\* of Mesalamine Adverse Event Reports Since Original Mesalamine Approval (December 24, 1987- February 23, 2016)

	All reports (US)	Serious (US)**	Death (US)
<b>Adults (≥ 17 yrs.)</b>	5127 (3315)	3598 (1817)	214 (107)
<b>Pediatrics (0-&lt;17 yrs.)</b>	535 (302)	<b>385 (155)</b>	<b>19 (2)†</b>

\*May include duplicates and transplacental exposures, and have not been assessed for causality  
\*\*For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.  
†Does not include null age death reports

# Selection of Serious Pediatric FAERS Cases

Total pediatric reports with a serious outcome reviewed (n=385)

- Pediatric reports with the outcome of death (n=19)

**Excluded Serious Reports (n= 381)  
(Including 19 deaths)\***

- Known adverse event (n=209)
- Transplacental (n=67)
- Duplicates (n= 49)
- Strong alternative cause (n=23 )
- Limited information (n=21)
- No adverse drug event (n= 12)

**Pediatric Case Series (n=4)  
(Including 0 Deaths )**

\*Reviewed and excluded from case series for the listed reasons.

## Summary of Serious Adverse Events (n=4): Mesalamine

- Nonfatal Serious Adverse Events (n=4)
  - Benign intracranial hypertension (n=2)
  - Nephrogenic diabetes insipidus (n=2)

Unlabeled events are underlined.

## Serious Non-Fatal Adverse Events (n=4): Mesalamine

- Benign intracranial hypertension (BIH, n=2)
  - A 15-year-old female developed torticollis-like cervical pain, headache and scotoma 1 month after starting 3 g daily of another oral mesalamine product for UC, and was diagnosed intracranial hypertension with papilledema. Most of her signs and symptoms resolved with reduction of mesalamine dose to 2 g daily with addition of acetazolamide; however, following a UC relapse, 3 months later mesalamine was discontinued and corticosteroids were started with persistence of scotoma.
  - An 11- year-old female developed worsening headaches 3 weeks after starting 3 g of an unspecified mesalamine product daily for Crohn’s Disease (CD) which were initially controlled with acetaminophen. Signs, symptoms, and clinical laboratory findings included “bilateral stage 1 optic disc edema without retinal hemorrhage”, “enlarged blind spots”, elevated erythrocyte sedimentation rate and “normal head CT”. Concomitant medications included other “silicates” and trimebutine for diarrhea. Symptoms partially resolved with discontinuation of mesalamine and treatment with corticosteroids.

## Serious Non-Fatal Adverse Events (n=4): Mesalamine

- Division of Neurology Products (DNP) reviewed these 2 pediatric cases and an additional literature case report of benign intracranial hypertension in a 23-year-old female who was receiving mesalamine.
- DNP was unable to distinguish between benign intracranial hypertension or cerebral venous thrombosis due to :
  - Insufficient neuroimaging information in the cases.
  - The response to acetazolamide in the first case and corticosteroids in the second case.
  - Both benign intracranial hypertension and cerebral venous thrombosis rarely occur in patients with inflammatory bowel disease.

Unlabeled events are underlined.

## Serious Non-Fatal Adverse Events (n=4): Mesalamine

- Nephrogenic diabetes insipidus (NDI) and interstitial nephritis (n=2)
  - A 14-year-old female experienced interstitial nephritis and NDI , confirmed with water deprivation/vasopressin testing, approximately 5 months after starting 2,250 mg/day of another oral mesalamine product for treatment of UC. Renal biopsy showed interstitial nephritis. NDI resolved completely and the interstitial nephritis partially improved with discontinuation of mesalamine and treatment with prednisolone. Drug-induced lymphocyte stimulation testing was positive for mesalamine.
  - A 9-year-old male developed interstitial nephritis (no histopathology) and NDI after increase of another oral mesalamine product from 1000 to 1250 mg daily and addition of a mesalamine rectal enema 1000 mg daily for the treatment of UC. Signs and symptoms resolved after drug discontinuation. Other drugs and treatments included prednisolone, icosapent ethyl, famotidine, and granulocytapheresis.

Unlabeled events are underlined.

## Serious Non-Fatal Adverse Events (n=4): Mesalamine

- The Division of Cardiovascular and Renal Products (DCRP) review concluded that NDI was likely drug related because of 1) temporal relationship of signs (including biopsy finding) and symptoms to drug exposure, 2) the fact that mesalamine is known cause tubulointerstitial nephritis, and 3) the reported concomitant medications are not associated with renal toxicity, and 4) response to treatment with mesalamine discontinuation and response to corticosteroids.
- DRCP recommends adding NDI to the list of adverse reactions in the postmarketing section of product labeling for those drugs labeled as causing tubulointerstitial nephritis (possibly noting that the cases have been reported with other members of the pharmacology class).
- DRCP recommends further consideration of: which mesalamine products to add labeling for NDI, the extent of systemic absorption, and whether cases of interstitial nephritis have been reported with these other mesalamine products.



## Summary Pediatric Focused Safety Review: Asacol, Asacol HD and Delzicol (mesalamine)

- This concludes the pediatric focused safety review.
- The safety review identified benign intracranial hypertension as a safety signal, but imaging was insufficient to distinguish the events from cerebral venous thrombosis.
- The safety review identified nephrogenic diabetes insipidus as a drug related safety signal.
- FDA recommends:
  - no change to product labeling for any mesalamine product regarding benign intracranial hypertension.
  - adding nephrogenic diabetes insipidus to the list of adverse reactions that have been reported in the postmarketing section of product labeling for mesalamine products.
  - continuing ongoing routine pharmacovigilance monitoring.
- Does the Committee concur?



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