



Therapeutic Class ReviewSM

GI – Mesalamine (Lialda[®])

February 2008

New Product for Review:
Mesalamine (Lialda[®]) [Shire]

Dossier Provided by Manufacturer: Yes
Dossier Evaluation: 2

- 1 - Dossier missing significant clinical trial(s).
- 2 - Mfg. provided all relevant trials; Missing pharmacoeconomic model.
- 3 - Mfg. provided all relevant trials and information.

Available Therapeutic Alternatives:

Preferred/Formulary	Non-Preferred/Non-Formulary
Mesalamine (Asacol [®]) [Proctor & Gamble]	Mesalamine (Lialda [®]) [Shire U.S.]
Mesalamine (Pentasa [®]) [Shire U.S.]	Balsalazide (Colazal [®]) [Salix]
Olsalazine (Dipentum [®]) [Pharmacia-Upjohn]	
Sulfasalazine (generic) [Various]	

Executive Summary

Ulcerative Colitis

- Ulcerative colitis is a chronic, relapsing and remitting disease of unknown etiology characterized by acute, non-infectious inflammation of the colonic mucosa. Disease severity and extent vary widely between individuals.
- The incidence of ulcerative colitis in the U.S. is about 11 in 100,000, with onset occurring most often between the ages of 15 and 30.¹
- Common clinical symptoms of active disease such as bloody diarrhea, urgency, tenesmus, and abdominal pain greatly reduce patients' quality of life.²

Treatment³

- Treatment is aimed at inducing and maintaining remission of disease.
- Initial treatment depends on the severity of disease and anatomical extent of intestinal involvement.
- Products containing mesalamine (5-aminosalicylic acid) are currently the standard of care for inducing and maintaining remission in mild-to-moderate ulcerative colitis.
 - Extensive disease requires treatment with oral 5-ASA agents, while distal disease can be treated with oral or rectal agents.

- A number of safe and effective 5-ASA compounds are currently available.
- Most oral dosing regimens involve taking 2 to 3 tablets/capsules 3 to 4 times a day.
- Delayed-release mesalamine (Lialda) requires taking 2 to 4 tablets once a day.

Lialda

- Delayed-release mesalamine (Lialda) is a new high-concentration, once-daily formulation of mesalamine that was approved by the FDA in January 2007 and became commercially available in March. It is indicated for induction of remission of active, mild-to-moderate ulcerative colitis.
 - Delayed-release mesalamine's (Lialda's) novel MMX Multi Matrix System™ formulation theoretically provides a very slow release of active drug throughout the colon using a core of hydrophilic and lipophilic excipients that form a viscous gel mass when the surrounding pH-dependent layer dissolves in the terminal ileum.
- Although delayed-release mesalamine (Lialda) is currently only indicated for induction of remission in active disease, it is likely that practitioners will also use this medication off-label as long-term maintenance therapy.

Evidence

*5-ASA agents*⁴

- The efficacy and safety of 5-ASA agents in the treatment of active ulcerative colitis is well-established.
- There is little evidence to show differences in efficacy between various 5-ASA products.

Lialda^{5,6}

- Both of the randomized, placebo-controlled trials evaluating delayed-release mesalamine (Lialda) for the treatment of mild-to-moderate ulcerative colitis were appraised as not useful (Grade X), primarily due to high drop-out rates.
 - Overall study drop-out rates were approximately 25% and differential drop-out rates were >20%.
 - Additionally, patients who had previously failed treatment with mesalamine >2 grams/day were excluded from the trials, creating a selection bias in favor of treatment.
- The majority of patients studied had disease of moderate severity and limited extent and were diagnosed within the past 2 years.
- Study results:
 - Patients taking delayed-release mesalamine (Lialda) had significantly higher rates of clinical and endoscopic remission (the composite primary endpoint in both trials) at week 8 than patients taking placebo.
 - Asacol, included as an active reference arm in one trial, was not significantly different from placebo in rate of clinical and endoscopic remission.
 - The proportion of patients in remission in the delayed-release mesalamine (Lialda) groups of one trial did not meet the authors' definition of a clinically worthwhile response (>25% improvement in remission rate over placebo).

- Patients who took 1.2 g delayed-release mesalamine (Lialda) twice daily had slightly higher rates of remission than patients who took 4.8 g once daily. This difference was not statistically significant, but it brings the optimal dosing regimen of delayed-release mesalamine (Lialda) into question.
- Adverse events reported with delayed-release mesalamine (Lialda) appeared similar to those expected with 5-ASA products. The trials were not powered to evaluate safety, however.
- **Consideration in subpopulations**
 - **Pediatrics:** Safety and effectiveness in pediatrics have not been established.
 - **Geriatrics:** An insufficient number of subjects ≥ 65 years of age were in clinical trials to determine any differences in response over younger subjects.
 - **Gender:** There is no information regarding differences in safety and effectiveness of delayed-release mesalamine (Lialda) between men and women.
 - **Race, ethnicity:** There is no information regarding differences in safety and effectiveness of delayed-release mesalamine (Lialda) between different races.

Expert opinion

Expert opinion was sought from 21 providers, including gastroenterologists and internal medicine. To date (January 24, 2008) we have received no responses.

Product Value

Delayed-release mesalamine (Lialda) provides another treatment option for patients with active, mild to moderate ulcerative colitis. Some patients may prefer the convenience of Lialda's once daily dosing regimen.

Conclusion

Delayed-release mesalamine (Lialda) is non-preferred/non-formulary because there is currently no reliable evidence to determine its efficacy or safety in comparison with therapeutic alternatives.

Products

Drug Products	FDA approval ^a	Patent expiration ^c	FDA approved indications	Usual Dose/Route	Cost per month ^b
Mesalamine (Lialda [®])	Jan/2007	June/2020	Induction of remission of active mild-to-moderate UC	2.4-4.8 g PO once daily x 8 wks 1.2 g tabs 2-4 tabs/day	Treatment \$273.75- \$547.50
Mesalamine (Asacol [®])	Aug/1997	July/2013	Treatment and maintenance of remission of mild-to-moderate UC	Treatment: 800 mg PO TID x 6 wks Maintenance: 1.6 g PO daily in divided doses 400 mg tabs 4-6 tabs/day	Treatment \$262.49 Maintenance \$175.00
Mesalamine (Pentasa [®])	May/1993 (250 mg) July/2004 (500 mg)	Expired	Induction of remission and treatment of active mild-to-moderate UC	1 g PO QID 250, 500 mg caps 8-16 caps/day	Treatment 500 mg caps: \$389.02 250 mg caps: \$431.00
Balsalazide (Colazal [®])	July/2000	Expired	Treatment of active mild-to-moderate UC	2.25 g PO TID x 8-12 wks 750 mg caps 9 caps/day	Treatment \$479.79
Olsalazine (Dipentum [®])	July/2000	Expired	Maintenance of remission of UC in patient intolerant to sulfasalazine	500 mg PO BID 250 mg caps 4 caps/day	Maintenance \$ 218.04
Sulfasalazine (Azulfidine [®])	Generic	Expired	Treatment and maintenance of remission of UC	Treatment: 1 g 3-4x/day Maintenance: 2 g/day in divided doses 500 mg tabs 4-8 tabs/day	Treatment \$18-\$24 Maintenance \$12

^a Date applies to approval date for the original brand name medication where there are now generics available.

^b Cost estimate based on AWP (average wholesale price) listed in First Data Bank as of 10/22/2007 for 1 month of therapy.

^c Based on patents listed in the Orange Book as of 10/10/2007.

References

1. Friedman S and Blumberg RS. Chapter 276: Inflammatory Bowel Disease. Harrison's Internal Medicine. Available at <http://www.accessmedicine.com>. Accessed 10/18/07.
2. Lichtenstein GR, Kamm MA, Boddu P, Gubergrits N, Lyne A, Butler T, et al. Effect of once- or twice-daily MMX mesalamine (SPD476) for the induction of remission of mild to moderately active ulcerative colitis. *Clin Gastroenterol Hepatol* 2007;5(1):95-102.
3. Kornbluth A and Sachar DB. Ulcerative Colitis Practice Guidelines in Adults (Update): American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2004;99(7):1371-1385.
4. Sutherland L and Macdonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database of Systematic Reviews* 2007, Issue 1. Art No.: CD000543. DOI: 10.1002/14651858.CE000543.pub2.

5. Kamm MA, Sandborn WJ, Gassul M, Schreiber S, Jackowski L, Butler T, et al. Once-daily, high-concentration MMX mesalamine in active ulcerative colitis. *Gastroenterology* 2007;132(1):66-75.
6. Lichtenstein GR, Kamm MA, Boddu P, Gubergrits N, Lyne A, Butler T, et al. Effect of once- or twice-daily MMX mesalamine (SPD476) for the induction of remission of mild to moderately active ulcerative colitis. *Clin Gastroenterol Hepatol* 2007;5(1):95-102.
7. Sandborn WJ, Kamm MA, Lichtenstein GR, Lyne A, Butler T and Joseph RE. MMX Multi Matrix System[®] mesalazine for the induction of remission in patients with mild-to-moderate ulcerative colitis: a combined analysis of two randomized, double-blind, placebo-controlled trials. *Aliment Pharmacol Ther* 2007;26:205-215.
8. Sutherland L and Macdonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database of Systematic Reviews* 2007, Issue 1. Art No.: CD000543. DOI: 10.1002/14651858.CE000543.pub2.
9. Kornbluth A and Sachar DB. Ulcerative Colitis Practice Guidelines in Adults (Update): American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2004;99(7):1371-1385.
10. Sutherland LR, Martin F, Greer S, Robinson M, Greenberger N, Saibil F, et al. 5-aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis, and proctitis. *Gastroenterology* 1987;92:1894-1898.
11. Lialda[™] (mesalamine) Prescribing Information. Shire US Inc., Wayne, PA; 2007.