Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Month/Year of Review: May 2014
PDL Class: Inflammatory Bowel Agents

Date of Last Review: September 2012
Source Document: OSU College of Pharmacy

Current Status of PDL Class:

- Preferred Agents: BALSALAZIDE DISODIUM, MESALAMINE SUPPOSITORIES (CANASA®), MESALAMINE CAPSULES ER 24H (APRISO®), MESALAMINE ENEMA, MESALAMINE TABLET DR (LIALDA®), OLSALAZINE SODIUM CAPSULE (DIPENTUM®), SULFASALAZINE TABLET DR, SULFASALAZINE TABLET
- Non-preferred Agents: MESALAMINE TABLET DR (ASACOL®), MESALAMINE TABLETS DR HIGH DOSE (ASACOL HD®), MESALAMINE CAPSULE DR (DELZICOL®), MESALAMINE CAPSULES (PENTASA®), MESALAMINE ENEMAS SULFITE-FREE (SFROWASA®), MESALAMINE WITH CLEANSING WIPES KIT, BALSALAZIDE SODIUM TABLET (GIAZO®)

Current PA Criteria: The generic non-preferred drugs in PDL classes prior authorization criteria is in place to support preferred PDL ulcerative colitis agents and to cover for OHP above the line diagnoses only.

Research Questions:

- Does any the new information change previous conclusions regarding effectiveness and safety of inflammatory bowel agents?
- Are there unique patients or situations where agents may be more effective or safer than currently available agents?

Previous Conclusions Recommendations:

- Evidence does not support a difference in efficacy/effectiveness between the aminosalicylates.
- Evidence does not support a difference in harms/adverse events between the aminosalicylates.
- Olsalazine can cause secretory diarrhea and is only indicated for maintenance therapy.
- Include different formulations as preferred products on the PDL, including a long-acting and rectal option.

Conclusions:

- There is high quality evidence that 5-aminosalicylic acid is superior to placebo in inducing clinical remission (RR 0.86; 95% CI 0.81 to 0.91; NNT 9) and relapse (RR 0.69; 95% CI 0.62 to 0.77; NNT 5-8). [1,2]
- There is moderate quality evidence of no difference between 5-aminosalicylate products and sulfasalazine in failure to induce clinical remission (RR 0.90; 95% CI 0.77 to 1.04) and high quality evidence of superiority of sulfasalazine in maintaining clinical remission (RR 1.14; 95% CI 1.03 to 1.27), with a higher rate or relapse associated with aminosalicylates. [1,2] However, when including only the studies with

outcomes at 12 months or taking the olsalazine trials out of the analysis, there was no difference between sulfasalazine and aminosalicylic acid in maintenance of clinical remission.

- There is moderate quality evidence of less withdrawals due to adverse events with oral 5-aminosaylciates compared to sulfasalazine (RR 0.40; 95% CI 0.24 to 0.69).[1]
- There is moderate quality evidence of no difference between once daily dosing and conventional dosing in failure to induce clinical remission, maintaining clinical remission or adverse events and withdrawals due to adverse events. [1]
- There is moderate quality evidence of no difference between different formulations of oral aminosayliclates in induction of clinical remission (RR 0.94; 95% CI 0.86 to 1.02) or adverse events and withdrawals due to adverse events (RR 0.94; 95% CI 0.57 to 1.54), and low quality evidence of no difference in maintaining clinical remission (RR 1.01; 95% CI 0.80 to 1.28). [1,2]
- There is evidence that higher doses (≥ 3g/day) of aminosalicylate are more likely to induce clinical remission than lower doses. [1]
- There is low quality evidence of no difference in maintenance of remission between rectal and oral formulations of 5-aminosalicylic acid (RR 1.24; 95% CI 0.92 to 1.66; p=0.15) for distal ulcerative colitis.

Recommendations:

- Continue to maintain topical and oral options as preferred on the PDL.
- No further review of research needed at this time and review comparative costs.

Reason for Review:

Routine scan of the literature for new developments.

Background:

Ulcerative colitis is an inflammatory disorder of the gastrointestinal tract that also affects the colorectum.[3] It is a chronic disease that if untreated has a relapsing and remitting course. The goals of treatment are to induce remission and prevent relapse of disease activity, improving quality of life, and avoiding long term consequences. In addition to remission, endoscopic mucosal healing is commonly used as an endpoint in RCTs due to evidence that it is associated with a lower likelihood of disease relapse or colectomy.[3] Mild to moderate flares are often treated with oral or topical aminosalicylates or oral steroids. Evidence has shown that aminosalicylates can induce remission in mild to moderately active disease (NNT 6) and they are the main drugs used to prevent relapse. It is unclear which preparations are most effective and there is insufficient evidence directly comparing the different formulations. The newer 5-aminosalicylic acid preparations were intended to avoid the adverse effects of the older sulfasalazine therapy while maintaining its therapeutic benefits.[1] Overall, they are safe and well tolerated with the most common side effects being headache, abdominal pain, nausea, vomiting, skin rash, and diarrhea. [3] It has also been demonstrated that doses of 2 g or more are more effective in achieving remission compared to doses under 2 g (NNT 11). In patients whose disease is limited to the rectum, topical aminosalicylates can be a useful approach. Guidelines from……. Recommend topical treatment as first line in patients, however; adherence and patient preference should be part of the decision on treatment modality. More severe disease requires treatment with intravenous glucocorticosteriods and biological agents such as infliximab and adalimumab. [3]

Crohn's disease is another type of inflammatory bowel disease. Aminosalicylates are also used to treat Crohn's disease, although they are not FDA approved for this indication. Medical therapy in Crohn's disease targets intestinal inflammation with the intent of altering the progression of disease and biologics are a mainstay in treatment.[4] However, there is controversy over when biologics should be introduced in the disease course. A top-down therapy approach starts with immunomodulators and biologics early, as opposed to taking them after use of aminosalicylates and corticosteroids (step-up therapy). Further research is needed to review the benefits and harms of step-up versus top-down treatment strategies.

Methods:

A Medline literature search ending March 2014 Week 4 for meta-analyses or randomized active-controlled trials (RCT's) comparing aminosalicylates to each other or to other drugs for the treatment of ulcerative colitis was performed. The Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs (VA), Clinical Evidence, UpToDate, Dynamed and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for relevant systematic reviews. The FDA website was searched for background information from advisory committees, new indications, and safety alerts. The AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. Randomized controlled trials will be emphasized only if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

A recent systematic review from AHRQ compared the efficacy and safety of agents in the treatment of Crohn's disease through an evaluation of the literature through June 2011.[4] Most of the data were comparing biologic agents to each other or placebo. Five trials evaluated the effectiveness of aminosalicylates as monotherapy to induce remission and 14 trials compared aminosalicylates to placebo in maintaining remission. Overall, there was low strength evidence that aminosalicylates (mesalamine at least 3.2 g daily or sulfasalazine) were more effective than placebo in inducing remission at weeks 16-17. There was also low strength of evidence of a benefit in remission with sulfasalazine compared to placebo at week 104 (risk difference 14%) and that sulfasalazine was more effective than placebo in healing fistulas. For maintaining remission, there was low strength of evidence that mesalamine at 3 to 4 g daily was more efficacious than placebo to maintain remission, and moderate strength of evidence that mesalamine at 2 g daily was not more efficacious than placebo. There was moderate strength of evidence of no difference between olsalazine and placebo in maintaining remission. A pooled analysis comparing aminosalicylates with placebo in remission at weeks 48 to 54 showed no significant difference between sulfasalazine (RR 1.0; 95% CI 0.8 to 1.2), mesalamine (RR 1.1; 95% CI 1.0 to 1.3), mesalamine controlled-release (RR 1.2; 95% CI 1.0 to 1.5) or olsalazine (RR 1.0; 95% CI 0.9 to 1.2).

There was limited evidence evaluating overall safety. There was moderate strength of evidence favoring a combination of prednisone and sulfasalazine over prednisone along for infections (RR 0.3). Overall, there were a number of medications that were effective in inducing and maintaining remission in Crohn's disease, no single medication or class was found to be most effective, provided the best quality of life, or had the best safety profile. Infliximab was the only medication that was consistently more effective than placebo across a number of outcomes for both induction and maintenance of remission.

Two systematic reviews from the Cochrane Collaboration assessed the efficacy and safety of oral aminosalicylates; one for induction of remission in active ulcerative colitis and the other for maintenance of remission.[1,2] A total of 49 studies were identified that measured induction of remission in RCTs and most were of high methodological quality.[1] A random effects analysis demonstrated high quality evidence that fewer patients in the treatment group failed to enter remission compared to placebo (72% vs. 85%;RR 0.86; 95% CI 0.81-0.91; I2=38%; p<0.001) and there was a trend towards greater efficacy with higher doses with

a statistically significant benefit for the 2 to 2.9 g/day (RR 0.87; 95% CI 0.79 to 0.96) and the 3 g or greater per day (RR 0.81; 95% CI 0.74 to 0.88). There was moderate quality evidence of no difference between 5-aminosalicylates and sulfasalazine in failure to entre remission (RR 0.90; 95% CI 0.77 to 1.04; p=0.15). There was moderate quality evidence of no difference in remission between once daily and conventional dosing (RR 0.95; 95%CI 0.82 to 1.10; p=0.49), and no difference in medication adherence (RR 1.36; 95% CI 0.64 to 2.86; p=0.42). When comparing different preparations, there was no statistically significant difference in failure to enter clinical remission between various formulations of 5-aminosalicylate (Balsalzide, Pentasa, Olsalazine, micropellets) and comparator formulations (Asacol, Claversal, and Salofalk), with a RR of 0.95 (95% CI 0.86 to 1.02; p=0.11).

A total of 37 studies were included in the second analysis evaluating maintenance of remission.[2] Similar to previous results, there was high quality evidence of fewer patients failing to maintain remission in the aminosalicylate group compared to placebo (41% vs. 58%; RR 0.69; 95% CI 0.62 to 0.77; p<0.0001; I^2=15%). Sulfasalazine was significantly superior to 5-aminosalicylic acid in the failure to maintain remission (48% vs. 43%; RR 1.14; 95% CI 1.03 to 1.27; p=0.01; NNT -17), based on high quality evidence. When this analysis was limited to studies that measured at 12 months, there was no significant difference (RR 1.10; 95% CI 0.98 to 1.23). Sulfasalazine was shown to be superior to olsalazine in clinical remission (OR 1.20; 95% CI 1.04 to 1.38). There was moderate quality evidence of no difference between once daily and conventional dosing in failure to maintain clinical remission at 6 months (RR 1.02; 95% CI 0.85 to 1.23) and 12 months (RR 0.92; 95% CI 0.83 to 1.03). There was low quality evidence of no difference between different formulations in maintenance of clinical remission at 12 months (RR 1.01; 95% CI 0.80 to 1.28).

There was no statistically significant difference in the incidence of adverse events between treatment and placebo groups (R 0.97; 95% CI 0.85 to 1.11; p=0.65), and no difference in withdrawals due to adverse events (RR 0.88; 95% CI 0.62 to 1.24; p=0.39). However, 5 trials comparing olsalazine to placebo showed a higher proportion of olsalazine patients withdrawn due to adverse events (8.8% vs. 3.3%; RR 2.58; 95% CI 1.16 to 5.70). Patients taking sulfasalazine were more likely to experience an adverse event compared to those on a 5-aminosalicylate (29% vs. 15%; RR 0.48; 95% CI 0.37 to 0.63) and more likely to withdraw due to adverse events (13% vs. 5%; RR 0.40; 95% CI 0.24 to 0.69). However, in the studies measuring maintenance of remission, there was no difference in adverse events or withdrawals due to adverse events (RR 1.27; 95% CI 0.87 to 1.87). There was no overall difference in adverse events or withdraws due to adverse events between the different formulations of mesalamine.

Another Cochrane Collaboration systematic review assessed the efficacy and safety of rectal 5-aminosalicylic acid for maintaining remission of distal ulcerative colitis.[5] Nine studies met inclusion criteria and 6 were rated as low risk of bias. Three studies were rated as high risk of bias due to blinding. There was low quality evidence that rectal delivery was significantly superior compared to placebo for maintenance of remission over 12 months (62% vs. 30%; RR 2.22; 95% CI 1.26 to 3.90; I2=67%; p<0.01). There was also low quality evidence of no significant difference between rectal and oral 5-aminosalicylic acid for remission over 6 months (RR 1.24; 95% CI 0.92 to 1.66; I2=0%; p=0.15). There was no statistically significant difference in the proportion of patients with at least one adverse event or withdrawals due to adverse events (RR 1.04; 95% CI 0.23 to 4.70; p=0.96). There were no trials available comparing rectal aminosalicylic acid to other therapies such as rectal steroids.

New Guidelines:

In 2013, NICE released a clinical guideline for the treatment of ulcerative colitis in adults, children and young people.[6] The following recommendations related to aminosalicylates were provided:

Inducing remission: step 1 therapy for mild to moderate disease:

- For proctitis or proctosigmoiditis:
    - Topical aminosalicylate alone (suppository or enema)
    - Consider adding an oral aminosalicylate to a topical agent OR
    - Consider an oral aminosalicylate alone, based on the person's preferences and explaining that this is not as effective as a topical aminosalicylate alone or combined treatment
- For left-sided or extensive ulcerative colitis:
    - Offer a high induction dose of an oral aminosalicylate or oral aminosalicylate in children and young people
    - Consider adding a topical aminosalicylate or oral beclometasone

Maintaining Remission:

- Consider a once-daily dosing regimen for oral aminosalicylates when used for maintaining remission.

Recent FDA warnings:

None

New Formulations:

A new delayed release formulation of mesalamine 400mg delayed release capsules (Delzicol®) was approved in February 2013 intended to replace mesalamine delayed release (Asacol®). Delzicol was formulated without dibutyl phthalate (DBP), which is associated with safety concerns. Evidence from animal studies suggests that DBP is associated with external and skeletal malformations and adverse effects on the male reproductive system. There is no relevant human safety information available. Delzicol is approved for the treatment of mild to moderate active ulcerative colitis and for the maintenance of remission. Approval was based on a pharmacokinetic and bioavailability study demonstrating bioequivalence to the old formulation. Postmarketing studies in pediatric patients was requested.[7]

Balsalazide (Giazo®) is a new formulation of the oral product balsalzide approved in February 2012 and indicated for mild to moderately active ulcerative colitis in male patients 18 years of age and older. Safety and effectiveness of giazo beyond 8 weeks in adults have not been established and effectiveness in female patients was not demonstrated in clinical trials.[8] This is the only balsalzide product dosed twice daily. It was approved based on two, randomized, double-blind trials; one placebo-controlled and one non-inferiority trial. These have not been published and cannot be assessed for quality. In the first placebo-controlled trial (n=250), the primary endpoint was clinical improvement at 8 weeks, based on the Modified Mayo Disease Activity Index (MMDAI). Clinical improvement was defined by at least a 3 point improvement in MMDAI. There was a significantly greater number of total patients with clinical improvement in the treatment group compared to placebo (55% vs. 40%; p=0.024). However, there was a higher response rate in the placebo arm when looking at female patients only; 54% of female patients in the balsalazide group achieving clinical response and 58% of females in the placebo group. This was significantly different than the treatment effect seen in males (57% in

balsalzide vs. 30% in placebo group; p<0.001). There was also no improvement seen in clinical remission or mucosal healing in the female subset of patients with balsalazide versus placebo. [8]

A second RCT was a non-inferiority study with mesalamine (Asacol) with the primary endpoint again being a reduction of at least 3 points in MMDAI (clinical improvement). In the per-protocol population, 61.7% of patients in the balsalzide group achieved clinical response at week 6 compared to 60.8% in the mesalamine group; with a difference of 0.9%. Results were similar in the modified Intention to treat population as well. FDA reviewers recommended a post marketing trial of female patients to adequately assess the gender differences observed. [8]

Randomized Controlled Trials:

Study information	Comparison	Patient Population	Primary Outcome	Results
D'Haens et al.[9] RCT, DB, non-inferiority trial	Mesalamine once daily (Lialda) vs. twice daily delayed release mesalamine (Asacol) (n-826)	Patients with ulcerative colitis in remission for ≥ 30 days on a stable dose of mesalamine or equivalent of sulfasalazine	Endoscopic remission at 6 months	Endoscopic Remission: Lialda: 83.7% Asacol: 81.5% 95% CI -3.9% to 8.1% Time to Relapse: Lialda: 12.8% Asacol: 14.6% HR 0.87; p=0.5

References:

1. Feagan BG, Macdonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2012;10:CD000543. doi:10.1002/14651858.CD000543.pub3.

2. Feagan BG, Macdonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2012;10:CD000544. doi:10.1002/14651858.CD000544.pub3.

3. Ford AC, Moayyedi P, Hanauer SB. Ulcerative colitis. *BMJ*. 2013;346:f432.

4. Hutfless S, Almashat S, Berger Z, et al. *Pharmacologic Therapies for the Management of Crohn's Disease: Comparative Effectiveness*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014. Available at: http://www.ncbi.nlm.nih.gov/books/NBK192961/. Accessed April 14, 2014.

5. Marshall JK, Thabane M, Steinhart AH, Newman JR, Anand A, Irvine EJ. Rectal 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2012;11:CD004118. doi:10.1002/14651858.CD004118.pub2.

6. National Institute for Health and Clinical Excellence. Ulcerative colitis: Management in adults, children and young people. NICE clinical guideline 166. *NICE*. 2013. Available at: guidance.nice.org.uk/cg166.

7. FDA Center for Drug Evaluation and Research. Application Number: 204412Orig1s000. Delzicol (mesalamine) Summary Review. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204412Orig1s000SumR.pdf. Accessed March 15, 2014.

8. FDA Center for Drug Evaluation and Research. Application Number: 022205Orig1s000. Balsalazide (Giazo) Summary Review. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022205Orig1s000SumR.pdf. Accessed March 26, 2014.

9. D'Haens G, Sandborn WJ, Barrett K, Hodgson I, Streck P. Once-daily MMX(®) mesalamine for endoscopic maintenance of remission of ulcerative colitis. *Am J Gastroenterol*. 2012;107(7):1064-1077. doi:10.1038/ajg.2012.103.

Author: Megan Herink, Pharm.D.

May 2014