

Ulcerative Colitis: The Value of Persistence in Therapy

*A review of the impact of ulcerative colitis on patients
and the health care system*

Supplement to

M A N A G E D
Care

Volume 17, No. 2
Supplement 1
February 2008

This publication is supported by Shire Pharmaceuticals

Ulcerative Colitis: The Value of Persistence in Therapy

Ulcerative colitis is a chronic inflammatory disease that may significantly affect a person's health and quality of life. This *Clinical Brief* discusses a once-daily oral dosing option to limit pill burden and potentially increase the likelihood of compliance with medication therapy.

Ulcerative colitis is a chronic condition that causes inflammation and ulceration of the colon's inner lining. This inflammation occurs typically in the rectum and lower part of the colon, but can affect the entire organ. Ulcerative colitis is distinguished by an inappropriately aggressive T-cell response to a subset of commensal enteric bacteria (Turnbough 2007). Genetic predisposition has been suggested as a possible trigger for ulcerative colitis, as have certain environmental factors, such as residence in an urban area versus a rural setting (Cohen 2006, Loftus 2000).

The symptoms of ulcerative colitis include abdominal pain, bloody diarrhea, bloating, fecal urgency, and incontinence. For the majority of patients, the disease will fluctuate between periods of remission and relapse; these patients require constant therapy to prolong periods of remission (Turnbough 2007). Because it is a chronic condition, treatment for ulcerative colitis must continue indefinitely to help prevent relapses and long-term complications (Kane 2003).

Incidence and prevalence

According to a population study by Loftus (2000), the adjusted incidence rate during the last decade studied (1984 to 1993) was 8 cases per 100,000 person-years, with 35 years as the median age at diagnosis. Incidence rates were higher in men versus women ($P < .003$) and in urban residents versus rural residents ($P < .0001$) (Loftus 2000). Loftus also looked at prevalence rates and found that as of Jan. 1, 1991, after adjusting for age and gender, there were 229 cases of ulcerative colitis per 100,000 persons. With the presumption of a stable incidence rate and a median survival rate of 40 years after diagnosis, prevalence should stabilize at roughly 320 cases per 100,000, 40 percent higher than in 1991 (Loftus 2000). It is estimated that between 479,000 and 550,000 people in the United States are diagnosed with the disease (Loftus 2000).

Socioeconomic impact

Although the prevalence of ulcerative colitis in the general population may be relatively small, the chronic nature of the disease generally necessitates indefinite treatment, along with significant lifestyle changes that affect education, work, social interactions, and personal relationships (Turnbough 2007). As ulcerative colitis primarily affects a young, working-age population, patients may experience a considerable financial burden over time

if they must pay for their own medications, hospitalizations, and general medical bills. During periods of disease relapse, the inability to work due to illness, along with increased clinic visits, also may result in a loss of net earnings (Turnbough 2007).

Cost data. Whether patients are compliant and/or persistent with their prescribed ulcerative colitis therapy has been shown to play a large role in associated health care costs.

Shaya (2006) conducted a retrospective, longitudinal pharmacy and medical claims database analysis of 4,313 ulcerative colitis patients and found that 78 percent of patients were nonpersistent with their medication regimen, resulting in substantially higher costs for hospital admissions, outpatient visits, and physician office visits compared with patients who were persistent with their medication regimen. On average, nonpersistent patients incurred an additional \$1,973 and \$1,875 in annual medical and total health care expenditures, respectively (Shaya 2006). After adjusting for confounding factors, mean medical costs incurred by persistent patients were 54 percent lower than those costs incurred by patients who discontinued their therapy (Shaya 2006).

The study also found that mean pharmacy costs incurred by persistent patients — who tend to consume more medications — were 6.9 percent higher than those incurred by nonpersistent patients (Shaya 2006). This increase, however, was more than offset by the decrease in mean costs for admissions, outpatient visits, and office visits, resulting in substantially lower mean medical costs and total costs for persistent patients versus those who discontinued their therapy (Shaya 2006).

Treatment modalities

The severity and extent of ulcerative colitis is determined by clinical and endoscopic findings. Patients with mild-to-moderate distal colitis may be treated with 5-aminosalicylate (5-ASA) therapy, considered to be the current standard of care (Kamm 2007). They also may be treated with topical mesalamine or topical steroids (Kornbluth 2004). Available 5-ASA formulations vary in their delivery modalities, and include high-dose tablets, micro-pellets, suppositories, and enemas (Cohen 2006). Oral formulations come in different dosages, influencing the number and frequency of pills that must be taken by patients, and, thus, are likely to have an effect on compliance (Kamm 2007).

To establish patients' perception of their disease and also gauge their satisfaction with currently prescribed therapy, Loftus (2006) conducted a large Internet-based survey of members of the Crohn's and Colitis Foundation of America. These members were prescribed a range of aminosalicylates for their ulcerative colitis. Of the 4,034 useable questionnaires obtained, only 35 percent of respondents stated that they consistently took their prescribed 5-ASA medications (Loftus 2006).

Several reasons were cited for noncompliance to a prescribed treatment regimen, including the need to take too many pills, frequency of dosing, and the perceived inconvenience of the medication. The majority (90 percent) of 944 noncompliant patients "just forgot" to take their medication (Loftus 2006).

An earlier study found that a history of previous ulcerative colitis relapse showed the closest correlation with another relapse, indicating the cyclical nature of the disease (Riley 1990). Indeed, 75 percent of ulcerative colitis patients surveyed in Loftus' study experienced disease relapse within the previous year, and approximately two thirds of patients were found to be noncompliant with their treatment regimens (Loftus 2006). Researchers suggest that treatment satisfaction is closely linked to both disease activity and treatment efficacy (Loftus 2006). Patient considerations, therefore, may be critical when selecting an appropriate ulcerative colitis therapy (Table).

Value of compliance

Kamm (2007) suggests that it would be beneficial for the treatment of acute ulcerative colitis if 5-ASA therapy could be delivered in a formulation that limits daily pill burden, that is, the number and frequency of tablets that need to be taken on a daily basis. In addition, the delivery of 5-ASA throughout the entire colon may result in fast symptom relief and mucosal healing, along with improved treatment success (Loftus 2006).

Newer formulations of 5-ASA with easier dosing regimens may be a treatment option. A novel, once-daily, oral formulation of 5-ASA that utilizes MMX Multi Matrix System (MMX) tech-

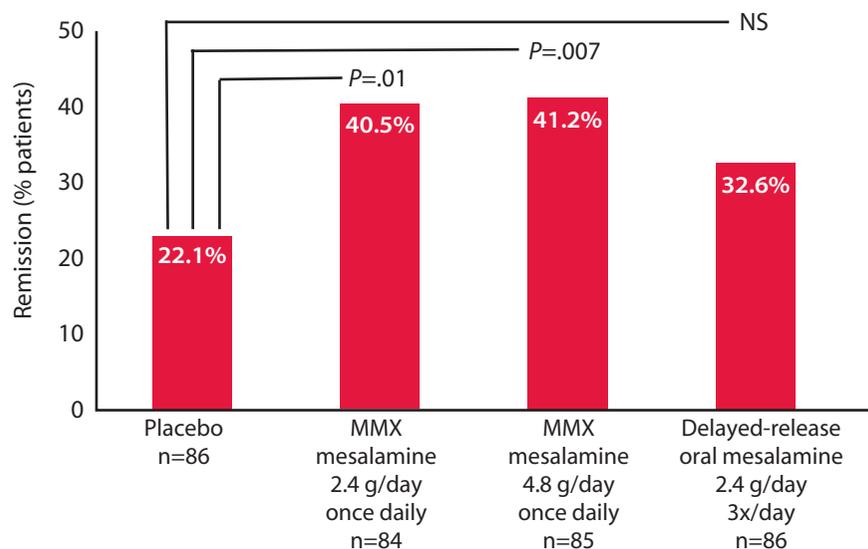
TABLE
Patient-viewed important characteristics for ulcerative colitis treatment

<i>% of patients who categorized this characteristic as "very important"*</i>	
Effectiveness	97
Limited side-effect profile	74
Doctor visit unnecessary	50
Shots or intravenous injection unnecessary	46
Rectal application unnecessary	36
Convenience	34
Limited pills	23
Low cost	23
Taken only a few times per day	23

*Patients were able to choose more than one factor.
SOURCE: LOFTUS 2006

nology, MMX mesalamine (Lialda), delivers the active drug directly to the colon, offering a useful mechanism of delivery (Baker 2006). MMX mesalamine is indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis. The drug's patented poly-

FIGURE 1
Patients who achieved remission defined by clinical and endoscopic measures at week 8*



Delayed-release oral mesalamine 2.4g/day was included in this study as a reference arm only.
- The study was not designed as a comparative head-to-head trial of MMX mesalamine versus delayed-release oral mesalamine.
- Delayed-release oral mesalamine tablets are indicated for the treatment of mildly to moderately active ulcerative colitis, not induction of remission, in patients with ulcerative colitis.

*Patients with active, mild to moderate ulcerative colitis were included in 2 separate 8-week, randomized, double-blind, placebo-controlled trials. Induction of remission was the primary endpoint in these trials. Remission was calculated using a modified Ulcerative Colitis Disease Activity Index (UC-DAI) score ≤ 1 with a score of 0 for rectal bleeding and stool frequency, a combined Physician's Global Assessment (PGA) and a sigmoidoscopy score < 1 with a sigmoidoscopy score reduction of 1 point or more from baseline.

NS=Not statistically significant.

SOURCES: KAMM 2007 (FIGURE USED WITH PERMISSION), ASACOL PACKAGE INSERT

meric matrix is designed to permit a consistent distribution along the ascending, transverse, and descending colon, including the sigmoid flexure and rectum, and allows for its prolonged release in the colon (Prantera 2005).

MMX mesalamine is contraindicated in patients with hypersensitivity to salicylates (including mesalamine) or to any component of MMX mesalamine. Caution should be exercised with patients who have pyloric stenosis or who are allergic to sulfasalazine.

Pivotal trials

Two phase 3, randomized, placebo-controlled, global trials were conducted to determine the efficacy of MMX mesalamine in 517 adult patients (262 patients in Kamm's study and 255 patients in Lichtenstein's study) with active mild-to-moderate ulcerative colitis (Lichtenstein 2007, Kamm 2007). In both studies, MMX mesalamine doses of 2.4 g/day (1.2 g twice daily in Lichtenstein's study and 2.4 g once daily in Kamm's study) and 4.8 g/day were compared with placebo. Delayed-released mesalamine (Asacol) 2.4 g/day was included in Kamm's study as a reference arm only, as the study was not designed as a comparative head-to-head trial. Treatment in both studies lasted for 8 weeks.

Primary endpoints were clinical and endoscopic remission rates at the completion of the treatment period. To increase stringency, researchers utilized a modified ulcerative colitis disease activity index (UCDAI) score of ≤ 1 , with a score of 0 for rectal bleeding and stool frequency and at least a 1-point baseline reduction in sigmoidoscopy score (Kamm 2007). Patients found to have any degree of mucosal friability (bleeding) were assigned a sigmoidoscopy score of ≥ 2 .

Both doses of MMX mesalamine showed superior efficacy over placebo for the induction of remission (defined as symptom control and improved mucosal appearance) after 8 weeks of treatment (Figure 1, page 3). In Kamm's study, mucosal healing (defined as endoscopic remission, which was a modified sigmoidoscopy score of ≤ 1 [with no mucosal friability] at week 8) was achieved in more than two thirds of patients on MMX mesalamine 4.8 g once daily (Kamm 2007). Lichtenstein's study also confirmed that MMX mesalamine achieved mucosal healing superior to placebo (Lichtenstein 2007). In both studies, a broad range of patients achieved complete remission.

MMX mesalamine 2.4 g or 4.8 g once daily was well tolerated. In clinical trials (N=535), the majority of adverse events were mild to moderate in severity. The most common treatment-related adverse effects were headache and flatulence. Pancreatitis occurred in fewer than 1 percent of patients during clinical trials and resulted in the discontinuation of MMX mesalamine therapy.

Mesalamine has been associated with an acute intolerance syndrome (3 percent of patients in clinical trials

with mesalamine or sulfasalazine) that may be difficult to distinguish from a flare of inflammatory bowel disease. If acute intolerance syndrome is suspected, prompt withdrawal is required. Mesalamine-induced cardiac hypersensitivity reactions (myocarditis and pericarditis) have been reported. Reports of renal impairment have been associated with mesalamine medications. In patients with renal impairment, caution should be exercised, and MMX mesalamine should be used only if the benefits outweigh the risks. No information is available for patients with hepatic impairment.

The safety and effectiveness of MMX mesalamine beyond 8 weeks have not yet been established.

Conclusion

Patients with ulcerative colitis tend to be nonadherent with their therapy as a result of undesired dosing regimens, heightening the risk of relapse. New drugs with simpler dosing routines may present an attractive option for patients. MMX mesalamine may be a beneficial treatment for patients with ulcerative colitis, possibly increasing medication adherence and reducing associated health care costs.

References

- Asacol package insert. Cincinnati: Procter & Gamble Pharmaceuticals. 2004.
- Baker DE. MMX mesalamine. *Rev Gastroenterol Disord*. 2006;6:146–152.
- Cohen RD. Review article: Evolutionary advances in the delivery of aminosaliculates for the treatment of ulcerative colitis. *Aliment Pharmacol Ther*. 2006;24:465–474.
- Kamm MA, Sandborn WJ, Gassull M, et al. Once-daily, high-concentration MMX mesalamine in active ulcerative colitis. *Gastroenterol*. 2007;12:66–75.
- Kane S, Huo D, Aikens J, Hanauer S. Medication nonadherence and the outcomes of patients with quiescent ulcerative colitis. *Am J Med*. 2003;114:39–43.
- Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults (update): American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol*. 2004;1371–1385.
- Lichtenstein GR, Kamm MA, Boddu P, 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;5:95–102.
- Loftus EV. A practical perspective on ulcerative colitis: patients' needs from aminosaliculate therapies. *Inflamm Bowel Dis*. 2006;12: 1107–1113.
- Loftus EV, Silverstein MD, Sandborn WJ, et al. Ulcerative colitis in Olmstead County, Minnesota, 1940–1993: incidence, prevalence, and survival. *Gut*. 2000;46:336–343.
- Prantera C, Viscido A, Biancone L, et al. A new oral delivery system for 5-ASA: preliminary clinical findings for MMX. *Inflamm Bowel Dis*. 2005;11:421–427.
- Riley SA, Mani V, Goodman MJ, Lucas S. Why do patients with ulcerative colitis relapse? *Gut*. 1990;31:179–183.
- Shaya FT, El Khoury AC, Wong W, et al. Persistence with pharmacotherapy for gastrointestinal disease: associated costs of health care. *P&T*. 2006;31:657–665.
- Turnbough L, Wilson L. Take your medicine: nonadherence issues in patients with ulcerative colitis. *Gastroenterol Nursing*. 2007;30:212–217.

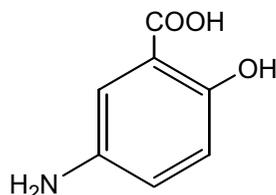
MMX Multi Matrix System technology was developed by Cosmo S.p.A. Italy. Lialda is a trademark of Shire Pharmaceuticals, Wayne, Pa. Asacol is a registered trademark of Medeva Pharma Schweiz AG.

Please see attached Full Prescribing Information on adjacent pages.

LIALDA™ (mesalamine)
Delayed Release Tablets

DESCRIPTION

Each **LIALDA** delayed release tablet for oral administration contains 1.2g 5-aminosalicylic acid (5-ASA; mesalamine), an anti-inflammatory agent. Mesalamine also has the chemical name 5-amino-2-hydroxybenzoic acid and its structural formula is:



Molecular formula: $C_7H_7NO_3$
Molecular weight: 153.14

The tablet is coated with a gastro-resistant pH dependent polymer film, which breaks down at or above pH 7, normally in the terminal ileum where mesalamine then begins to be released from the tablet core. The tablet core contains mesalamine with hydrophilic and lipophilic excipients.

The inactive ingredients of **LIALDA** tablets are sodium carboxymethylcellulose, carnauba wax, stearic acid, silica (colloidal hydrated), sodium starch glycolate (type A), talc, magnesium stearate, methacrylic acid copolymer types A and B, triethylcitrate, titanium dioxide, red ferric oxide and polyethyleneglycol 6000.

CLINICAL PHARMACOLOGY

The mechanism of action of mesalamine is not fully understood, but appears to be topical. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase and lipoxygenase pathways, is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin production in the colon. Recent data also suggest that mesalamine can inhibit the activation of NFκB, a nuclear transcription factor that regulates the transcription of many genes for pro-inflammatory proteins.

Pharmacokinetics

Absorption: The total absorption of mesalamine from **LIALDA** 2.4g or 4.8g given once daily for 14 days to healthy volunteers was found to be approximately 21-22% of the administered dose.

Gamma-scintigraphy studies have shown that a single dose of **LIALDA** 1.2g (one tablet) passed intact through the upper gastrointestinal tract of fasted healthy volunteers. Scintigraphic images showed a trail of radio-labeled tracer in the colon, suggesting that mesalamine had distributed throughout this region of the gastrointestinal tract.

In a single dose study, **LIALDA** 1.2g, 2.4g and 4.8g were administered in the fasted state to healthy subjects. Plasma concentrations of mesalamine were detectable after 2 hours and reached a maximum by 9-12 hours on average for the doses studied. The pharmacokinetic parameters are highly variable among subjects (Table 1). Mesalamine systemic exposure in terms of area under the plasma concentration-time curve (AUC) was slightly more than dose proportional between 1.2g and 4.8g **LIALDA**. Maximum plasma concentrations (C_{max}) of mesalamine increased approximately dose proportionately between 1.2g and 2.4g and sub-proportionately between 2.4g and 4.8g **LIALDA**, with the dose normalized value at 4.8g representing, on average, 74% of that at 2.4g based on geometric means.

Table 1: Mean (SD) PK Parameters for Mesalamine Following Single Dose Administration of LIALDA Under Fasting Conditions

Parameter ¹ of Mesalamine	LIALDA 1.2g (N=47)	LIALDA 2.4g (N=48)	LIALDA 4.8g (N=48)
AUC _{0-t} (ng.h/mL)	9039 ⁺ (5054)	20538 (12980)	41434 (26640)
AUC _{0-∞} (ng.h/mL)	9578 [•] (5214)	21084 (13185)	44775 [#] (30302)
C_{max} (ng/mL)	857 (638)	1595 (1484)	2154 (1140)
T_{max}^* (h)	9.0 ^{**} (4.0-32.1)	12.0 (4.0-34.1)	12.0 (4.0-34.0)
T_{lag}^* (h)	2.0 ^{**} (0-8.0)	2.0 (1.0-4.0)	2.0 (1.0-4.0)
$T_{1/2}$ (h) (Terminal Phase)	8.56 (6.38)	7.05 [§] (5.54)	7.25 [#] (8.32)

¹ Arithmetic mean of parameter values are presented except for T_{max} and T_{lag} .

* Median (min, max); ⁺N=43, [•]N=27, [§]N=33, [#]N=36, ^{**}N=46

Administration of a single dose of **LIALDA** 4.8g with a high fat meal resulted in further delay in absorption and plasma concentrations of mesalamine were detectable 4 hours following dosing. However, high fat meal increased systemic exposure of mesalamine (mean C_{max} : ↑ 91%; mean AUC: ↑ 16%) compared to results in the fasted state. **LIALDA** was administered with food in the Phase 3 trials.

In a single and multiple dose pharmacokinetic study of **LIALDA** 2.4g or 4.8g was administered once daily with standard meals to 28 healthy volunteers per dose group. Plasma concentrations of mesalamine were detectable after 4 hours and were maximal by 8 hours after the single dose. Steady state was achieved generally by 2 days after dosing. Mean AUC at steady state was only modestly greater (1.1- to 1.4-fold) than predictable from single dose pharmacokinetics.

Distribution: Mesalamine is approximately 43% bound to plasma proteins at the concentration of 2.5 µg/mL.

Metabolism: The major metabolite of mesalamine (5-aminosalicylic acid) is N-acetyl-5-aminosalicylic acid. Its formation is brought about by N-acetyltransferase activity in the liver and intestinal mucosa.

Elimination: Elimination of mesalamine is mainly via the renal route following metabolism to N-acetyl-5-aminosalicylic acid (acetylation). However, there is also limited excretion of the parent drug in urine. Of the approximately 21-22% of the dose absorbed, less than 8% of the

dose was excreted unchanged in the urine, compared with greater than 13% for N-acetyl-5-aminosalicylic acid. The apparent terminal half-lives for mesalamine and its major metabolite after administration of **LIALDA** 2.4g and 4.8g were, on average, 7-9 hours and 8-12 hours, respectively.

Special Populations

Geriatrics: No pharmacokinetic information is available in patients who are 65 years or older (see **PRECAUTIONS**).

Pediatrics: No pharmacokinetic information is available in patients who are less than 18 years of age (see **PRECAUTIONS**).

Gender: No consistent trend on gender effect was observed in the clinical trials.

Renal Insufficiency: No information is available in patients with mild, moderate, and severe renal impairment (see **PRECAUTIONS**).

Hepatic Insufficiency: No information is available for patients with hepatic impairment (see **PRECAUTIONS**).

Race: No pharmacokinetic information is available which examines **LIALDA** in different races.

Drug-Drug Interaction

There are no data available on interactions between **LIALDA** and other drugs. However, there have been reports of interaction between other mesalamine medications and other drugs (see **PRECAUTIONS**).

CLINICAL TRIALS

Active, Mild to Moderate Ulcerative Colitis

Two similarly designed, randomized, double blind, placebo-controlled trials were conducted in 517 adult patients with active, mild to moderate ulcerative colitis. The study population was primarily Caucasian (80%), had a mean age of 42 years (6% age 65 years or older), and was approximately 50% male. Both studies used **LIALDA** doses of 2.4g/day and 4.8g/day administered once daily for 8 weeks except for the 2.4g/day group in Study 1, which was given in two divided doses (1.2g BID). The primary efficacy end-point in both trials was to compare the percentage of patients in remission after 8 weeks of treatment for the **LIALDA** treatment groups vs placebo. Remission was defined as an Ulcerative Colitis Disease Activity Index (UC-DAI) of ≤ 1 , with scores of zero for rectal bleeding and for stool frequency, and a sigmoidoscopy score reduction of 1 point or more from baseline.

In both studies, the **LIALDA** doses of 2.4g/day and 4.8g/day demonstrated superiority over placebo in the primary efficacy endpoint (Table 2). Both **LIALDA** doses also provided consistent benefit in secondary efficacy parameters, including clinical improvement, treatment failure, clinical remission, and sigmoidoscopic improvement. **LIALDA** 2.4g/day and 4.8g/day had similar efficacy profiles.

Table 2: Patients in Remission at Week 8

Dose	Study 1	Study 2
	(n=262)	(n=255)
	n/N (%)	n/N (%)
LIALDA 2.4g/day	30/88 (34.1)	34/84 (40.5)
LIALDA 4.8g/day	26/89 (29.2)	35/85 (41.2)
Placebo	11/85 (12.9)	19/86 (22.1)

INDICATIONS AND USAGE

LIALDA tablets are indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis. Safety and effectiveness of **LIALDA** beyond 8 weeks has not been established.

CONTRAINDICATIONS

LIALDA is contraindicated in patients with hypersensitivity to salicylates (including mesalamine) or to any of the components of **LIALDA**.

PRECAUTIONS

General: Patients with pyloric stenosis may have prolonged gastric retention of **LIALDA**, which could delay mesalamine release in the colon.

The majority of patients who are intolerant or hypersensitive to sulfasalazine can take mesalamine medications without risk of similar reactions. However, caution should be exercised when treating patients allergic to sulfasalazine.

Mesalamine has been associated with an acute intolerance syndrome that may be difficult to distinguish from a flare of inflammatory bowel disease. Although the exact frequency of occurrence has not been determined, it has occurred in 3% of patients in controlled clinical trials of mesalamine or sulfasalazine. Symptoms include cramping, acute abdominal pain and bloody diarrhea, sometimes fever, headache and rash. If acute intolerance syndrome is suspected, prompt withdrawal is required.

Mesalamine-induced cardiac hypersensitivity reactions (myocarditis and pericarditis) have been reported with other mesalamine medications. Caution should be taken in prescribing this medication to patients with conditions predisposing to the development of myocarditis or pericarditis.

Renal: Reports of renal impairment, including minimal change nephropathy, and acute or chronic interstitial nephritis have been associated with mesalamine medications and pro-drugs of mesalamine. For any patient with known renal dysfunction, caution should be exercised and **LIALDA** should be used only if the benefits outweigh the risks. It is recommended that all patients have an evaluation of renal function prior to initiation of therapy and periodically while on treatment. In animal studies with mesalamine, a 13-week oral toxicity study in mice and 13-week and 52-week oral toxicity studies in rats and cynomolgus monkeys have shown the kidney to be the major target organ of mesalamine toxicity. Oral daily doses of 2400 mg/kg in mice and 1150 mg/kg in rats produced renal lesions including granular and hyaline casts, tubular degeneration, tubular dilation, renal

infarct, papillary necrosis, tubular necrosis, and interstitial nephritis. In cynomolgus monkeys, oral daily doses of 250 mg/kg or higher produced nephrosis, papillary edema, and interstitial fibrosis.

Hepatic Impairment: No information is available on patients with hepatic impairment, and therefore, caution is recommended in these patients.

Information for Patients: Patients should be instructed to swallow **LIALDA** tablets whole, taking care not to break the outer coating. The outer coating is designed to remain intact to protect the active ingredient, mesalamine, and ensure its availability throughout the colon.

Drug Interaction: No investigations have been performed between **LIALDA** and other drugs. However, the following are reports of interactions between mesalamine medications and other drugs. The concurrent use of mesalamine with known nephrotoxic agents, including non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of renal reactions. In patients receiving azathioprine or 6-mercaptopurine, concurrent use of mesalamine can increase the potential for blood disorders.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 104-week dietary carcinogenicity study in CD-1 mice, mesalamine at doses up to 2500 mg/kg/day was not tumorigenic. This dose is 2.2 times the maximum recommended human dose (based on a body surface area comparison) of **LIALDA**. Furthermore, in a 104-week dietary carcinogenicity study in Wistar rats, mesalamine up to a dose of 800 mg/kg/day was not tumorigenic. This dose is 1.4 times the recommended human dose (based on a body surface area comparison) of **LIALDA**.

No evidence of mutagenicity was observed in an *in vitro* Ames test or an *in vivo* mouse micronucleus test.

No effects on fertility or reproductive performance were observed in male or female rats at oral doses of mesalamine up to 400 mg/kg/day (0.7 times the maximum recommended human dose based on a body surface area comparison). Semen abnormalities and infertility in men, which have been reported in association with sulfasalazine, have not been seen with other mesalamine products during controlled clinical trials.

Pregnancy:

Teratogenic Effects: Pregnancy Category B

Reproduction studies with mesalamine have been performed in rats at doses up to 1000 mg/kg/day (1.8 times the maximum recommended human dose based on a body surface area comparison) and rabbits at doses up to 800 mg/kg/day (2.9 times the maximum recommended human dose based on a body surface area comparison) and have revealed no evidence of impaired fertility or harm to the fetus due to mesalamine. There are, however, 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. Mesalamine is known to cross the placental barrier.

Nursing Mothers: Low concentrations of mesalamine and higher concentrations of its N-acetyl metabolite have been detected in human breast milk. While there is limited experience of lactating women using mesalamine, caution should be exercised if **LIALDA** is administered to a nursing mother, and used only if the benefits outweigh the risks.

Pediatric Use: Safety and effectiveness of **LIALDA** tablets in pediatric patients who are less than 18 years of age have not been studied.

Geriatric Use: Clinical trials of **LIALDA** did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concurrent disease or other drug therapy.

ADVERSE REACTIONS

LIALDA tablets have been evaluated in 655 ulcerative colitis patients in controlled and open-label trials.

In two 8-week placebo-controlled clinical trials involving 535 ulcerative colitis patients, 356 received 2.4g/day or 4.8g/day **LIALDA** tablets and 179 received placebo. More treatment emergent adverse events occurred in the placebo group (119) than in each of the **LIALDA** treatment groups (109 in 2.4g/day, 92 in 4.8g/day). A lower percentage of **LIALDA** patients discontinued therapy due to adverse events compared to placebo (2.2% vs 7.3%). The most frequent adverse event leading to discontinuation from **LIALDA** therapy was exacerbation of ulcerative colitis (0.8%).

The majority of adverse events in the double blind, placebo-controlled trials were mild or moderate in severity. The percentage of patients with severe adverse events was higher in the placebo group (6.1% in placebo; 1.1% in 2.4g/day; 2.2% in 4.8g/day). The most common severe adverse events were gastrointestinal disorders which were mainly symptoms associated with ulcerative colitis. Pancreatitis occurred in less than 1% of patients during clinical trials and resulted in discontinuation of therapy with **LIALDA** in patients experiencing this event.

Overall, the percentage of patients who experienced any adverse event was similar across treatment groups. Treatment related adverse events occurring in **LIALDA** or placebo groups at a frequency of at least 1% in two Phase 3, 8-week, double blind, placebo-controlled trials are listed in Table 3. The most common treatment related adverse events with **LIALDA** 2.4g/day and 4.8g/day were headache (5.6% and 3.4%, respectively) and flatulence (4% and 2.8%, respectively).

Table 3. Treatment Related Adverse Events in Two Phase 3 Trials Experienced by at Least 1% of the LIALDA Group and at a Rate Greater than Placebo

Event	LIALDA 2.4g/day (n = 177)	LIALDA 4.8g/day (n = 179)	Placebo (n = 179)
Headache	10 (5.6%)	6 (3.4%)	1 (0.6%)
Flatulence	7 (4%)	5 (2.8%)	5 (2.8%)
Increased alanine aminotransferase	1 (0.6%)	2 (1.1%)	0
Alopecia	0	2 (1.1%)	0
Pruritis	1 (0.6%)	2 (1.1%)	0

The following treatment-related adverse events, presented by body system, were reported infrequently (less than 1%) by **LIALDA**-treated ulcerative colitis patients in controlled trials.

Cardiovascular and Vascular: tachycardia, hypertension, hypotension

Dermatological: acne, prurigo, rash, urticaria

Gastrointestinal Disorders: abdominal distention, diarrhea, pancreatitis, rectal polyp, vomiting

Hematologic: decreased platelet count

Hepatobiliary Disorders: elevated total bilirubin

Musculoskeletal and Connective Tissue Disorders: arthralgia, back pain

Nervous System Disorders: somnolence, tremor

Respiratory, Thoracic and Mediastinal Disorders: pharyngolaryngeal pain

General Disorders and Administrative Site Disorders: asthenia, face edema, fatigue, pyrexia

Special Senses: ear pain

DRUG ABUSE AND DEPENDENCY

Abuse: None reported.

Dependency: Drug dependence has not been reported with chronic administration of mesalamine.

OVERDOSAGE

There have been no reports of overdose with **LIALDA**. **LIALDA** is an aminosalicylate, and symptoms of salicylate toxicity may include tinnitus, vertigo, headache, confusion, drowsiness, sweating, hyperventilation, vomiting, and diarrhea. Severe intoxication may lead to disruption of electrolyte balance and blood-pH, hyperthermia, and dehydration.

Although there has been no direct experience with **LIALDA**, conventional therapy for salicylate toxicity may be beneficial in the event of acute overdose. This includes prevention of further gastrointestinal tract absorption by emesis and, if necessary, by gastric lavage. Fluid and electrolyte imbalance should be corrected by the administration of appropriate intravenous therapy. Adequate renal function should be maintained.

DOSAGE AND ADMINISTRATION

The recommended dosage for the induction of remission in adult patients with active, mild to moderate ulcerative colitis is two to four 1.2g tablets to be taken once daily with meal for a total daily dose of 2.4g or 4.8g. Treatment duration in controlled clinical trials was up to 8 weeks.

HOW SUPPLIED

LIALDA tablets are available as red-brown ellipsoidal film coated tablets containing 1.2g mesalamine, and debossed on one side with S476.

NDC 54092-476-12 Bottle of 120 tablets

Store at room temperature 15°C to 25°C (59°F to 77°F); excursions permitted to 30°C (86°F). See USP Controlled Room Temperature.

Manufactured for **Shire US Inc.**, 725 Chesterbrook Blvd., Wayne, PA 19087, USA.
© 2007 Shire US Inc.
U.S. Patent No. 6,773,720. by license of Giuliani S.p.A., Milan, Italy.

476 1207 002B
N7600A
Rev. 1/07