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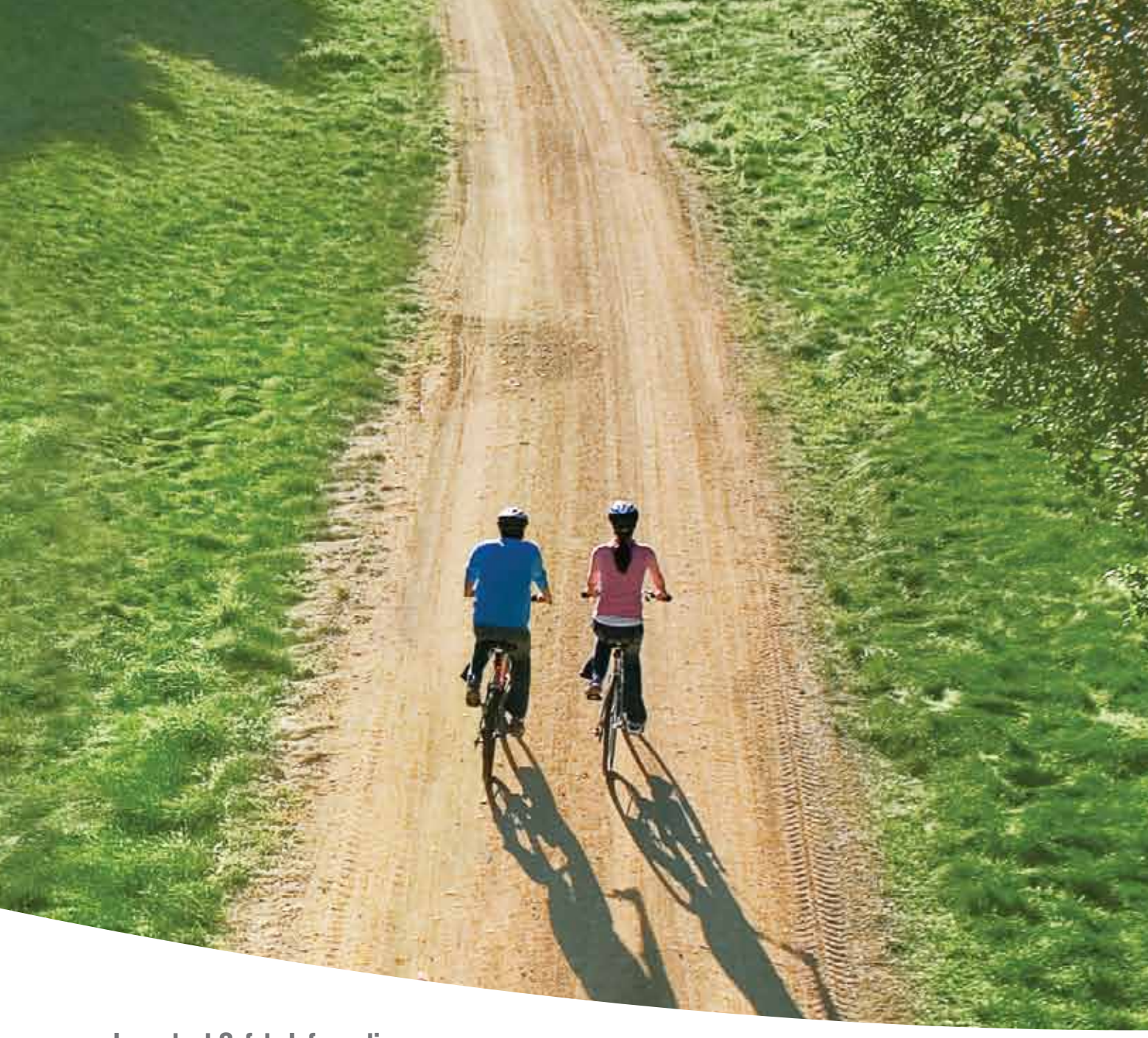
THE GASTRO & HEP REPORT

Presentation summaries in:

Comprehensive Reports on the Latest Advances in Gastroenterology and Hepatology from:

- The 2008 American College of Gastroenterology Annual Scientific Meeting
  October 3–8, 2008
  Orlando, Florida
- The 59th Annual Meeting of the American Association for the Study of Liver Diseases
  October 31–November 4, 2008
  San Francisco, California
- The 2008 Advances in IBD/Crohn's & Colitis Foundation's Clinical & Research Conference
  December 5–7, 2008
  Hollywood, Florida



Important Safety Information

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 have not been established.

Lialda is contraindicated in patients with hypersensitivity to salicylates (including mesalamine) or to any of the components of Lialda. Caution should be exercised when treating patients with pyloric stenosis or those allergic to sulfasalazine. Mesalamine has been associated with an acute intolerance syndrome (3% 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 Lialda should be used only if the benefits outweigh the risks. No information is available for patients with hepatic impairment.

Lialda is generally well tolerated. The majority of adverse events in the double-blind, placebo-controlled trials were mild or moderate in severity. In clinical trials (N=535), the most common treatment-related adverse events with Lialda 2.4g/day, 4.8g/day and placebo were headache (5.6%, 3.4% and 0.6%, respectively) and flatulence (4%, 2.8% and 2.8%, respectively). Pancreatitis occurred in less than 1% of patients during clinical trials and resulted in discontinuation of therapy with Lialda.

Turn acute ulcerative colitis flares into complete remission*†

Lialda® with Multi Matrix System Technology (MMX®) goes beyond symptom control to induce complete remission, a stringent treatment standard comprised of both clinical and endoscopic remission[1,2]

*Clinical Criteria:
- No rectal bleeding
- No excessive stool frequency
- Physician's Global Assessment score ≤1

†Endoscopic Criteria:
- No friability (no bleeding upon contact)
- Sigmoidoscopic (mucosal) appearance must have improved

According to prescription data
Lialda is the fastest-growing mesalamine[3]

Please see brief summary of Full Prescribing Information on back page.

References: 1. Kamm MA, Sandborn WJ, Gassull M, et al. Once-daily, high-concentration MMX mesalamine in active ulcerative colitis. *Gastroenterology*. 2007;132:66-75. **2.** 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. **3.** IMS Health, NPA *Plus*™, Q1 08-Q2 08, TRXs.

Visit Lialda.com to learn about the fastest-growing mesalamine

ONCE-DAILY
Lialda™ with MMX®
(mesalamine) 1.2g
delayed release tablets
The path to complete remission

LIA-00524 12/08

ONCE-DAILY

Lialda™ with MMX

(mesalamine)1.2g

delayed release tablets

BRIEF SUMMARY: Consult the Full Prescribing Information for complete product information.

LIALDA™ (mesalamine) Delayed Release Tablets **Rx only**

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 overdosage 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 overdosage. 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.

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. U.S. Patent No. 6,773,720. by license of Giuliani S.p.A., Milan, Italy. Made in Italy. 476 1207 002B

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Table of Contents

Included in EMBASE

Presentations in Endoscopy

Endoscopic Therapy Offers Alternative to Surgery in Patients With Barrett Esophagus and Early-stage Esophageal Cancer

Two studies showed that endoscopic therapy may offer an alternative to surgery for patients with Barrett esophagus and mucosal (T1a) esophageal adenocarcinoma or high-grade dysplasia or intramucosal carcinoma. Dr. Ganapathy A. Prasad and colleagues from Mayo Clinic reported that despite the low likelihood of lymph-nodal metastases, the long-term outcomes of patients with Barrett esophagus treated endoscopically for T1a esophageal adenocarcinoma remain unknown. In a retrospective review, they examined the history of patients treated in this fashion at Mayo Clinic in Minnesota between 1995 and 2007. A total of 135 patients with mucosal adenocarcinoma were treated (median age, 71 years; 84% males). Of these, 83% were treated with the Olympus endoscopic mucosal resection cap and 17% with the Duette kit; 57% received photodynamic therapy. After a mean follow-up of 42 months, 15 patients (13.5%) had recurrent carcinoma, with a median time to recurrence of 16 months. All recurrent tumors were intramucosal carcinomas, with 13 managed endoscopically and the remainder undergoing esophagectomy, which confirmed T1a disease without lymph-node metastases. At 5 years, cancer-free survival and overall survival were 79% and 83%, respectively. Prasad and colleagues concluded that endoscopic therapy is viable as an alternative to surgical resection for patients with Barrett esophagus and T1a adenocarcinoma. Higher risk of recurrence is associated with incident cancers, longer segments of Barrett esophagus, and multiple remission-induction treatments.

In related findings, complete Barrett eradication endoscopic mucosal resection (CBE-EMR) has the curative intent of eliminating high-grade dysplasia or intramucosal carcinoma via removal of all Barrett epithelium. Dr. Jennifer Chennat and associates from the University of Chicago Medical Center retrospectively reviewed a total of 48 patients with histologically confirmed Barrett esophagus, including 23 patients who underwent CBE-EMR for Barrett esophagus with high-grade dysplasia or intramucosal carcinoma. Twenty-eight patients had short segment BE, and 30 had visible lesions. A total of 104 endoscopic mucosal resection procedures were performed. On initial resection, 3 patients had superficial submucosal invasion and 2 patients had intramucosal carcinoma with lymphatic channel invasion. These patients were referred for esophagectomy, but 2 chose continued endoscopic management and had no evidence of residual or recurrent carcinoma. Surveillance biopsies showed normal squamous epithelium in 19 of 23 patients (82.6%) who underwent CBE-EMR (mean remission time, 17 months; range, 3–54 months). Three patients had nondysplastic Barrett esophagus and 1 had residual high-grade dysplasia. Six patients had subsquamous Barrett epithelium on surveillance. CBE-EMR upstaged preresection pathology results in 8 patients and downstaged 13 patients. A total of 14 of 48 patients (29%) developed symptomatic esophageal stenosis after a mean of one session and 28.6 days, but all were amenable to endoscopic treatment. No perforations or uncontrolled bleeding occurred. The researchers concluded that this study showed CBE-EMR with close endoscopic surveillance to be an effective treatment modality for Barrett esophagus with high-grade dysplasia or intramucosal carcinoma. CBE-EMR's role in patients with lymphatic invasion or superficial submucosal invasion remains to be elucidated.

Retrograde Colonoscope Provides Ability to Detect Otherwise Unseen Polyps

Although colonoscopy is the widely used standard for screening patients for evidence of colorectal cancer, lesions in the proximal aspect of the haustral folds or behind the ileococal valve can be missed using standard technology. The Third Eye Retroscope (TER), which offers a retrograde view, complements the forward view on a standard colonoscope. A prospective study, by Dr. Douglas Rex and coworkers, enrolling 214 subjects, evaluated the efficacy of the device for detection of polyps typically missed using standard technology. After cecal intubation, the TER is inserted through the instrument channel of the colonoscope. Upon emergence from the channel, the distal tip rotates 180 degrees to provide a retrograde view. In the study, the endoscopist indicated whether a polyp was visible through the standard colonoscope or the TER. A total of 203 polyps were identified with the standard technology, and an additional 27 polyps were detected with the TER, a 13% increased rate of detection ($P<.0001$). Additionally, 105 adenomas were detected with the standard technology, and an additional 13 adenomas detected with the TER, for a 12% increase ($P<.0001$). The mean size of lesions detected was similar with both devices. In

21 patients (9.8%), at least 1 additional polyp was found due to the TER, and in 7 (3%), the only polyp detected was found with the TER. In every case, the polyp found using the TER was subsequently located and removed with the standard colonoscope. Thus, the TER was considered to be effective in the detection of polyps in regions otherwise inaccessible to the endoscopist using standard technology.

Narrow Band Imaging Compared to White Light Imaging in a Randomized, Controlled Trial

Narrow band imaging (NBI) technology allows a better definition of mucosal microcapillaries by increasing the contrast of adenomas as compared to the surrounding mucosa with the goal of reducing missed lesions. NBI's ability to increase detection of colonic neoplasms was evaluated by researchers from Como, Italy, in a study of the routine use of NBI in the withdrawal phase of the procedure. The researchers hypothesized that NBI compared to white light (WL) enhances the detection of polypoid and nonpolypoid (flat or depressed) lesions in patients undergoing screening colonoscopy by 20% (P=.05). Once reaching the cecum with adequate cleaning conditions of the colon, the patients were assigned a WL or NBI retraction phase on a randomized basis. A total of 215 subjects were included (mean age, 60 years; 54% male). High-grade dysplasia or invasive carcinoma was diagnosed in 13 of 49 (26.5%) flat or depressed lesions and in 52 of 333 (15.6%) polypoid lesions (P=.057). The researchers concluded that routine use of NBI during the retraction phase of colonoscopy does not seem to increase the adenoma detection rate. However, the researchers contended that nonpolypoid adenomas are substantially prevalent, and NBI is useful for detecting these more aggressive lesions.

Capsule Endoscopy Has Predictive Value For Diagnosis of Suspected Crohn's Disease

Researchers from Beth Israel Deaconess Medical Center in Boston, Mass., studied 102 patients with abdominal pain, diarrhea, or suspected Crohn's disease who underwent capsule endoscopy in order to determine the predictive value of this method of diagnosis of Crohn's disease. Patients with a previous diagnosis of Crohn's disease were excluded. The indications for capsule endoscopy were: abdominal pain (41%), diarrhea (14%), pain and diarrhea (41%), and suspected Crohn's disease (67%). Prior to capsule endoscopy, 92% and 99% of patients had undergone computed tomography/small bowel follow through and colonoscopy, respectively. Abnormal findings that suggested Crohn's disease were found in 39 patients, and these included aphthous ulcers, erosions, or inflammation. The prevalence of Crohn's disease in the study population was 13%. The sensitivity of capsule endoscopy for the diagnosis of Crohn's disease was 92%; the specificity was 71%; the positive predictive value was 32%; and the negative predictive value was 98%. When the strict criterion of "more than 3 ulcers" was used as the definition of abnormal results of capsule endoscopy, the positive predictive value increased to 52%. The researchers concluded that, in this population, the positive predictive value of capsule endoscopy for the diagnosis of Crohn's disease ranges from 32% to 67% depending on the criteria used to define an abnormal test result.

Video Capsule Endoscopy Comparable to Standard Upper Endoscopy for Risk Stratification

A study enrolling 20 patients was intended to determine if real-time video capsule endoscopy can be used to stratify patients with upper gastrointestinal bleeding according to risk as effectively as standard upper endoscopy. Researchers from Beth Israel Medical Center, in New York, NY, performed real-time video capsule endoscopy within 24 hours of presentation, and standard upper endoscopy was performed after the duodenum was reached. Images were reviewed and results were blinded from each other. Subjects answered questionnaires on tolerability and satisfaction after the procedures. The goal was to evaluate whether real-time video capsule endoscopy can produce similar Rockall scores, a marker of bleeding risk, in comparison to standard upper endoscopy. A total of 70% of patients had comorbidities, and 30% had a history of upper gastrointestinal bleeding. Additionally, 70% were receiving high-risk medication, and 100% were receiving proton pump inhibitors prior to the procedure. Video capsule endoscopy reached the duodenum in 85% of subjects; in the remainder, hiatal hernia, equipment malfunction, or gastroparesis interfered. Overall, Rockall scores for the two methods matched in 70% of cases and were within a single unit in 90%. There was no difference in terms of patient discomfort between the two methods, but more subjects preferred video capsule endoscopy and would prefer to undergo that procedure over standard upper endoscopy in the future.

Presentations in IBS

Probiotics Appear Effective in Analysis of Prior Trials in Patients With IBS

Bacteria is thought to be important in the pathogenesis of irritable bowel syndrome (IBS). As a result, clinicians have attempted to alter the microbial environment with administration of probiotics to ameliorate the disease. Dr. Paul Moayyedi and colleagues conducted a systematic review of previous randomized, controlled trials that have produced conflicting evidence. The minimum acceptable criteria for inclusion in the review were that the trials included parallel groups in a randomized, placebo-controlled design with at least 1 week of therapy with probiotics or else no treatment in patients with no evidence of IBS. Outcome measures had to include improvement in abdominal pain or global IBS symptoms. A total of 19 trials comprising 1,628 patients were included in the analysis. Among trials that reported outcomes as a dichotomous variable, probiotics were statistically significantly better than placebo (relative risk of no improvement, 0.67; 95% confidence interval [CI], 0.49–0.91). Among trials reporting outcomes as a continuous variable, there was a statistically significant effect of probiotics in ameliorating IBS symptom score. The four trials that evaluated *lactobacillus* alone showed no significant benefit over placebo alone, but nine trials that used combinations of probiotics (8 including bifidobacterium) suggested a significant improvement of IBS symptom score with active treatment. The conclusions drawn by the authors suggested that probiotic combinations including bifidobacterium may be efficacious in the treatment of IBS, but because many of the trials included in the analysis were small, it is possible that the efficacy of these agents has been overstated.

A multicenter, randomized, double-blind, placebo-controlled study produced related results, as reported by Dr. Gerald Friedman. A total of 84 patients with diarrhea-predominant IBS received either a multistrain probiotic or placebo if they qualified for study participation according to Rome II criteria, with the primary objective of reducing the frequency of diarrheal episodes. The probiotic contained at least 2 billion colony-forming units each of *Lactobacillus acidophilus* LA-5, bifidobacterium BB-12, *Lactobacillus paracasei* CRM-431, and *Streptococcus thermophilus* STY-31. The probiotic was well-tolerated, with no significant side effects. It was found that 28 days' administration of the probiotic achieved significant decrease in diarrheal episodes as compared to placebo, with a faster decrease from day 1 to day 16.

Antidepressants Effective in Treatment of IBS According to Meta-analysis

A systematic review and meta-analysis by Dr. Alexander Ford and associates showed that selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) offer a benefit in the treatment of IBS, which has not been seen in prior analyses. Thirteen trials, with a total of 789 patients, were included in the analysis, eight using TCAs, four SSRIs, and 1 both classes. The effect of antidepressants on IBS symptoms compared with placebo was reported as the relative risk (RR) of remaining symptomatic. Ford and associates showed that 42.1% of the patients treated with antidepressants had persistent or unimproved IBS symptoms, compared with 64.7% of 357 who received placebo. Overall, the RR of IBS symptoms persisting after treatment with antidepressants versus placebo was 0.66 (95% confidence interval [CI], 0.57–0.78). In the nine TCA trials, 41.4% of subjects receiving TCAs had persistent symptoms after treatment compared with 59.8% receiving placebo. The RR of IBS symptoms persisting was 0.68 (95% CI, 0.56–0.83). In the five SSRI trials, 44.2% of patients receiving SSRIs had persistent symptoms following therapy compared with 70.9% receiving placebo. The RR of IBS symptoms persisting with SSRIs versus placebo was 0.62 (95% CI, 0.45– 0.87). Dr. Ford remarked, "Biologically, you would think it would be better to use tricyclics in diarrhea-predominant patients and it would be better to use SSRIs in constipated-predominant ones. Unfortunately, the studies that have been published that we have identified don't actually break down their patients according to the predominant symptoms and subgroups. It was emphasized that careful counseling of patients was necessary in order to help them understand that the antidepressants are being used to ameliorate symptoms of IBS rather than treat any coexisting psychological conditions.

Diet Very Low in Carbohydrates Associated With Relief of Symptoms in Diarrhea-predominant IBS

A study was initiated to substantiate anecdotal reports that a diet very low in carbohydrates can improve symptoms among patients with diarrhea-predominant IBS because carbohydrate-laden foods act as a trigger for symptoms. Dr. Gregory Austin and coworkers enrolled 17 overweight and obese patients (ie, body mass index >25 kg/m^2) with

Rome II diarrhea-predominant moderately severe IBS (>36 Functional Bowel Disorder Severity Index score). Participants were given a standard diet for 2 weeks, followed by a diet very low in carbohydrates (ie, 20 g/day of carbohydrates) for 4 weeks, with the primary outcome of adequate relief as measured by a weekly questionnaire. Stool frequency and consistency was recorded using the Bristol Stool Scale (BSS). Additional quality of life measures were recorded. During the first week, 1 patient dropped out, and during the third week, 3 dropped out (2 due to intolerance of the very low–carbohydrate diet and 1 due to emotional symptoms). The remaining 13 patients all achieved adequate response at week 4 of the modified diet. Additionally, 10 of 13 reported adequate relief during all 4 weeks and on at least 90% of the days therein. Stool frequency decreased from a mean of 2.6/day to 1.4/day ($P<.001$), with an improvement in stool consistency on the BSS of 5.3 to 3.8 ($P<.001$). Clinically meaningful improvement in pain scores and quality-of-life measures were observed as well. Moreover, although weight loss was observed, clinical improvement was independent of weight loss. In conclusion, Austin and coworkers found a diet very low in carbohydrates to be associated with adequate relief of IBS symptoms, with improvements in abdominal pain, stool frequency and consistency, and quality of life.

SmartPill Used to Measure Gastrointestinal Transit Parameters Among Patients With Constipation

Dr. Irene Sarosiek and colleagues reported results from a multicenter study of 63 patients with chronic constipation whose gastric emptying time (GET), small bowel transit time (SBTT), colon transit time (CTT), and whole gut transit time (WGTT) were assessed using the SmartPill wireless pH/pressure recording capsule. A group of 39 healthy women comprised the controls. Enrolled patients, who met Rome II criteria, had a mean age of 49 years (range 21–79), and 55 were women. Functional, idiopathic constipation was diagnosed in 45 (73%) and constipation-predominant IBS in 18 (27%). Fasting was followed by a standard meal, and the SmartPill capsule was swallowed immediately after the meal. Diary records of meals and symptoms were kept by the patients, and a recording system took measurements from the SmartPill. WGTT was measured from time of ingestion until the system's signal was abruptly lost. Time from ingestion to rise of pH level over 4.0 was the definition of GET, and a sudden drop of 1 pH unit in less than 5 minutes was classified as ileocecal arrival time. SBTT and CTT were calculated by subtracting GET from the ileocecal arrival time. The median WGTT was similar in patients with IBS and functional constipation ($P=.958$), and it was significantly longer than in the control group ($P<.05$). CTT was not statistically significant between the symptomatic patient groups but was statistically significantly slower than in the control group ($P<.05$). SBTT and CTT were similar across both symptomatic groups and the controls. The overall conclusions of the study were that WGTT and CTT are both abnormally prolonged in patients with functional constipation and constipation-predominant IBS, but GET and SBTT are normal and similar in both groups. Because of the similarities in WGTT and CTT in patients with functional constipation and constipation-predominant IBS, findings based on these measures do not separate etiologies of constipation.

Baseline Symptom Severity Associated With Level of Relief Rifaximin Achieves

A recent study by Dr. Mark Pimentel and associates was accompanied by a supplementary investigation into the relationship between baseline severity of IBS symptoms and clinical response to rifaximin (Xifaxan, Salix). It was noted that trials of therapies for IBS often include patients with a range of severities, and therapeutic interventions may have different effects across this spectrum. The primary investigation involved patients with Rome II diarrhea-predominant IBS who received rifaximin 550 mg twice daily or placebo on a randomized basis for 14 days followed in both groups by placebo for another 14 days. The study assessed patients' relief of global IBS symptoms and IBS-associated bloating; clinical response was defined as adequate relief for at least 3 of the second, third, and fourth weeks of the treatment. The researchers evaluated severity of baseline IBS symptoms, which was characterized as mild/moderate or severe on a 7-point scale based on bloating and abdominal pain. The study concluded that a significantly greater proportion of patients receiving rifaximin versus placebo achieved adequate relief of IBS symptoms (52% vs 44%; $P=.03$) and bloating (46% vs 40%; $P=.04$). Patients with severe baseline abdominal pain or bloating did not achieve significant improvement in global IBS symptoms or bloating with rifaximin or placebo. It was noted, however, that patients with mild/moderate abdominal pain achieved a greater degree of relief of IBS symptoms and bloating with rifaximin than placebo (50% vs 39%; $P=.04$ and 44% vs 35%; $P=.09$, respectively). Patients with mild/moderate bloating achieved relief of global IBS symptoms at a higher rate with rifaximin than with placebo (56% vs 41%; $P=.006$); their bloating was significantly reduced with the study drug versus placebo as well (47% vs 36%; $P=.03$). Pimentel and associates thus concluded that severity of baseline symptoms affected patient outcomes: those with mild/moderate IBS symptoms were more likely to achieve relief of these symptoms with rifaximin.

*Please see full Indication, including **boxed WARNINGS,** and Important Safety Information for VIREAD on following pages.*
Safety and effectiveness in patients less than 18 years of age have not been established.

INDICATION AND USAGE

VIREAD® (tenofovir disoproxil fumarate) is indicated for the treatment of chronic hepatitis B in adults. The following points should be considered when initiating therapy with VIREAD for the treatment of HBV infection:

- This indication is based on data from one year of treatment in primarily nucleoside-treatment-naïve adult patients with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease
- The numbers of patients in clinical trials who were nucleoside-experienced or who had lamivudine-associated mutations at baseline were too small to reach conclusions of efficacy
- VIREAD has not been evaluated in patients with decompensated liver disease

WARNINGS: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT EXACERBATION OF HEPATITIS

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, in combination with other antiretrovirals**
- **Severe acute exacerbations of hepatitis have been reported in HBV-infected patients who have discontinued anti-hepatitis B therapy, including VIREAD. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy, including VIREAD. If appropriate, resumption of anti-hepatitis B therapy may be warranted**

Please see additional Important Safety Information for VIREAD on the following pages.

Viread® 300 mg tablets
tenofovir disoproxil fumarate

GILEAD | HEPATIChealth

My VIREAD for

POTENT VIRAL SUPPRESSION

93% **of HBeAg- patients (n = 250) achieved viral suppression at 48 weeks (1 year)[1]**

76% **of HBeAg+ patients (n = 176) achieved viral suppression at 1 year[1]**

Patients had compensated liver function and were primarily treatment-naïve.*

In two phase 3, randomized, double-blind, active-controlled studies for chronic hepatitis B in adult patients, VIREAD 300 mg was compared to adefovir dipivoxil 10 mg in 375 HBeAg- (anti-HBe+) patients (Study 102), and 266 HBeAg+ patients (Study 103), with a primary endpoint of complete response as defined by HBV DNA <400 copies/mL + histological response.

*Please see full Indication and Important Safety Information for VIREAD, including **boxed WARNING** information about **lactic acidosis, severe hepatomegaly with steatosis,** and **post treatment exacerbation of hepatitis,** on preceding page.*

WARNINGS AND PRECAUTIONS

- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Assess creatinine clearance (CrCl) before initiating treatment with VIREAD. Monitor CrCl and serum phosphorus in patients at risk. Avoid administering VIREAD with concurrent or recent use of nephrotoxic drugs, including HEPSERA® (adefovir dipivoxil)
- Products with same active ingredient: Do not use with other tenofovir-containing products (e.g., ATRIPLA® (efavirenz/emtricitabine/tenofovir disoproxil fumarate) and TRUVADA® (emtricitabine/tenofovir disoproxil fumarate))
- VIREAD should not be administered in combination with HEPSERA
- HIV testing: HIV antibody testing should be offered to all HBV-infected patients before initiating therapy with VIREAD. VIREAD should only be used as part of an appropriate antiretroviral combination regimen in HIV-infected patients with or without HBV coinfection
- Decreases in bone mineral density (BMD): Observed in HIV-infected patients. Consider monitoring BMD in patients with a history of pathologic fracture or who are at risk for osteopenia. The bone effects of VIREAD have not been studied in patients with chronic HBV infection

DRUG INTERACTIONS

- Didanosine: Coadministration increases didanosine concentrations. Use with caution and monitor for evidence of didanosine toxicity (e.g., pancreatitis, neuropathy). Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions. In adults weighing >60 kg, the didanosine dose should be reduced to 250 mg when it is coadministered with VIREAD. Data are not available to recommend a dose adjustment of didanosine for patients weighing <60 kg
- Atazanavir: Coadministration decreases atazanavir concentrations and increases tenofovir concentrations. Use atazanavir with VIREAD only with additional ritonavir; monitor for evidence of tenofovir toxicity
- Lopinavir/ritonavir: Coadministration increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity

My VIREAD for

NO RESISTANCE AT 1 YEAR

0% **HBV resistance at 1 year[1]**

Out of 426 HBeAg- and HBeAg+ patients, 39 had serum HBV DNA >400 copies/mL at 48 weeks. Genotypic data from paired baseline and on-treatment isolates were available for 28 of the 39 patients.[1]

*The numbers of patients in clinical trials who were nucleoside-experienced or who had lamivudine-associated mutations at baseline were too small to reach conclusions of efficacy.

ADVERSE REACTIONS

- In HBV-infected patients: Most common adverse reaction (all grades) was nausea (9%). Other treatment-emergent adverse reactions reported in >5% of patients treated with VIREAD included: abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain, and skin rash

DOSAGE AND ADMINISTRATION

- Recommended dose for the treatment of chronic hepatitis B: 300 mg once daily taken orally without regard to food. In the treatment of chronic hepatitis B, the optimal duration of treatment is unknown
- Dose recommended in renal impairment: Creatinine clearance 30-49 mL/min: 300 mg every 48 hours. Creatinine clearance 10-29 mL/min: 300 mg every 72 to 96 hours. Hemodialysis: 300 mg every 7 days or after approximately 12 hours of dialysis

  The pharmacokinetics of tenofovir have not been evaluated in non-hemodialysis patients with creatinine clearance <10 mL/min; therefore, no dosing recommendation is available for these patients

Please see next page for brief summary of full Prescribing Information, including ***boxed WARNINGS.***

Reference: 1. VIREAD (tenofovir disoproxil fumarate) Prescribing Information. Foster City, CA: Gilead Sciences, Inc.; November 2008.

PREGNANCY CATEGORY B RATING[1]

There are no adequate and well-controlled studies in pregnant women. VIREAD should be used during pregnancy only if clearly needed.

PREFERENTIAL TIERING STATUS AMONG THE MAJORITY OF MANAGED CARE PLANS

My liver. My fight. My VIREAD.

Viread® 300mg tablets
tenofovir disoproxil fumarate

VIREAD®
(tenofovir disoproxil fumarate) Tablets
Brief summary of full prescribing information. Please see full prescribing information including Boxed WARNINGS. Rx only

WARNINGS: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT EXACERBATION OF HEPATITIS
- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, in combination with other antiretrovirals *(See Warnings and Precautions).***
- **Severe acute exacerbations of hepatitis have been reported in HBV-infected patients who have discontinued anti-hepatitis B therapy, including VIREAD. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy, including VIREAD. If appropriate, resumption of anti-hepatitis B therapy may be warranted *(See Warnings and Precautions).***

INDICATIONS AND USAGE: VIREAD is indicated for the treatment of chronic hepatitis B in adults. The following points should be considered when initiating therapy with VIREAD for the treatment of HBV infection:
- This indication is based on data from one year of treatment in primarily nucleoside-treatment-naïve adult patients with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease.
- The numbers of patients in clinical trials who were nucleoside experienced or who had lamivudine-associated mutations at baseline were too small to reach conclusions of efficacy.
- VIREAD has not been evaluated in patients with decompensated liver disease.

DOSAGE AND ADMINISTRATION: For the treatment of chronic hepatitis B, the dose of VIREAD is 300 mg once daily taken orally, without regard to food. The optimal duration of treatment is unknown. **Dose Adjustment for Renal Impairment:** Significantly increased drug exposures occurred when VIREAD was administered to patients with moderate to severe renal impairment. Therefore, the dosing interval of VIREAD should be adjusted in patients with baseline creatinine clearance <50 mL/min using the recommendations in Table 1. These dosing interval recommendations are based on modeling of single-dose pharmacokinetic data in non-HIV and non-HBV infected subjects with varying degrees of renal impairment, including end-stage renal disease requiring hemodialysis. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated in patients with moderate or severe renal impairment, therefore clinical response to treatment and renal function should be closely monitored in these patients *(See Warnings and Precautions)*. No dose adjustment is necessary for patients with mild renal impairment (creatinine clearance 50–80 mL/min). Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients with mild renal impairment *(See Warnings and Precautions).*

Table 1.
Dosage Adjustment for Patients with Altered Creatinine Clearance

	Creatinine Clearance (mL/min)[a]			Hemodialysis Patients
	≥50	30–49	10–29	
Recommended 300 mg Dosing Interval	Every 24 hours	Every 48 hours	Every 72 to 96 hours	Every 7 days or after a total of approximately 12 hours of dialysis[b]

a. Calculated using ideal (lean) body weight.
b. Generally once weekly assuming three hemodialysis sessions a week of approximately 4 hours duration. VIREAD should be administered following completion of dialysis.

The pharmacokinetics of tenofovir have not been evaluated in non-hemodialysis patients with creatinine clearance <10 mL/min; therefore, no dosing recommendation is available for these patients.

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS: Lactic Acidosis/Severe Hepatomegaly with Steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with VIREAD should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations). **Exacerbation of Hepatitis after Discontinuation of Treatment:** Discontinuation of anti-HBV therapy, including VIREAD, may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue VIREAD should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted. **New Onset or Worsening Renal Impairment:** Tenofovir is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of VIREAD *(See Adverse Reactions)*. It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with VIREAD. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment. Dosing interval adjustment of VIREAD and close monitoring of renal function are recommended in all patients with creatinine clearance <50 mL/min *(See Dosage and Administration)*. No safety or efficacy data are available in patients with renal impairment who received VIREAD using these dosing guidelines, so the potential benefit of VIREAD therapy should be assessed against the potential risk of renal toxicity. VIREAD should be avoided with concurrent or recent use of a nephrotoxic agent. **Coadministration with Other Products:** VIREAD should not be used in combination with the fixed-dose combination products TRUVADA® (emtricitabine/tenofovir disoproxil fumarate) or ATRIPLA® (efavirenz/emtricitabine/tenofovir disoproxil fumarate) since tenofovir disoproxil fumarate is a component of these products. VIREAD should not be administered in combination with HEPSERA® (adefovir dipivoxil) *(See Drug Interactions)*.

Patients Coinfected with HIV-1 and HBV: Due to the risk of development of HIV-1 resistance, VIREAD (tenofovir disoproxil fumarate) should only be used in HIV-1 and HBV coinfected patients as part of an appropriate antiretroviral combination regimen. HIV-1 antibody testing should be offered to all HBV-infected patients before initiating therapy with VIREAD. It is also recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B before initiating treatment with VIREAD. **Decreases in Bone Mineral Density:** Bone mineral density (BMD) monitoring should be considered for patients who have a history of pathologic bone fracture or are at risk for osteopenia. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained. In HIV-infected patients treated with VIREAD in Study 903 through 144 weeks, decreases from baseline in BMD were seen at the lumbar spine and hip in both arms of the study. At Week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in patients receiving VIREAD + lamivudine + efavirenz (-2.2% ± 3.9) compared with patients receiving stavudine + lamivudine + efavirenz (-1.0% ± 4.6). Changes in BMD at the hip were similar between the two treatment groups (-2.8% ± 3.5 in the VIREAD group vs. -2.4% ± 4.5 in the stavudine group). In both groups, the majority of the reduction in BMD occurred in the first 24–48 weeks of the study and this reduction was sustained through Week 144. Twenty-eight percent of VIREAD-treated patients vs. 21% of the stavudine-treated patients lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 patients in the VIREAD group and 6 patients in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide) in the VIREAD group relative to the stavudine group, suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in the VIREAD group. Except for bone-specific alkaline phosphatase, these changes resulted in values that remained within the normal range. The effects of VIREAD-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Cases of osteomalacia (associated with proximal renal tubulopathy and which may contribute to fractures) have been reported in association with the use of VIREAD *(See Adverse Reactions)*. The bone effects of VIREAD have not been studied in patients with chronic HBV infection.

ADVERSE REACTIONS: Clinical Trials in Patients with Chronic Hepatitis B: Treatment-Emergent Adverse Reactions: In controlled clinical trials in patients with chronic hepatitis B, more patients treated with VIREAD experienced nausea: 9% with VIREAD versus 2% with HEPSERA (adefovir dipivoxil). Other treatment-emergent adverse reactions reported in >5% of patients treated with VIREAD included: abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain, and skin rash. Grade 3/4 laboratory abnormalities identified in ≥1% of VIREAD-treated patients in studies 0102 and 0103 (0-48 weeks) included: any ≥ Grade 3 laboratory abnormality, 19%; elevated creatine kinase, 2% (M: >990 U/L; F: >845 U/L); elevated serum amylase, 4% (>175 U/L); glycosuria, 3% (urine glucose ≥3+); elevated AST, 4% (M: >180 U/L; F: >170 U/L); and elevated ALT, 10% (M: >215 U/L; F: >170 U/L). The overall incidence of on-treatment ALT elevations (defined as serum ALT >2 × baseline and >10 × ULN, with or without associated symptoms) was similar between VIREAD (2.6%) and HEPSERA (2%). ALT elevations generally occurred within the first 4–8 weeks of treatment and were accompanied by decreases in HBV DNA levels. No patient had evidence of decompensation. ALT flares typically resolved within 4 to 8 weeks without changes in study medication. **Postmarketing Experience:** The following adverse reactions have been identified during postapproval use of VIREAD. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: allergic reaction, lactic acidosis, hypokalemia, hypophosphatemia, dyspnea, pancreatitis, increased amylase, abdominal pain, hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT), rash, rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy, acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria, asthenia. The following adverse reactions listed above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia. **DRUG INTERACTIONS: Didanosine:** Coadministration of VIREAD and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions. Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions. When administered with VIREAD, C_{max} and AUC of didanosine (administered as either the buffered or enteric-coated formulation) increased significantly. The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis and neuropathy. Suppression of $CD4^+$ cell counts has been observed in patients receiving tenofovir disoproxil fumarate (tenofovir DF) with didanosine 400 mg daily. In adults weighing >60 kg, the didanosine dose should be reduced to 250 mg when it is coadministered with VIREAD. Data are not available to recommend a dose adjustment of didanosine for patients weighing <60 kg. When coadministered, VIREAD and didanosine EC may be taken under fasted conditions or with a light meal (<400 kcal, 20% fat). Coadministration of didanosine buffered tablet formulation with VIREAD should be under fasted conditions. **Atazanavir:** Atazanavir has been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving atazanavir and VIREAD should be monitored for VIREAD-associated adverse reactions. VIREAD should be discontinued in patients who develop VIREAD-associated adverse reactions. VIREAD decreases the AUC and C_{min} of atazanavir. When coadministered with VIREAD, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Atazanavir without ritonavir should not be coadministered with VIREAD. **Lopinavir/Ritonavir:** Lopinavir/ritonavir has been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving lopinavir/ritonavir and VIREAD should be monitored for VIREAD-associated adverse reactions. VIREAD should be discontinued in patients who develop VIREAD-associated adverse reactions. **Drugs Affecting Renal Function:** Since tenofovir is primarily eliminated by the kidneys, coadministration of VIREAD with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to cidofovir, acyclovir, valacyclovir, ganciclovir, and valganciclovir. Drugs that decrease renal function may also increase serum concentrations of tenofovir. In the treatment of chronic hepatitis B, VIREAD (tenofovir disoproxil fumarate) should not be administered in combination with HEPSERA (adefovir dipivoxil).

USE IN SPECIFIC POPULATIONS: Pregnancy: *Pregnancy Category B:* Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, VIREAD should be used during pregnancy only if clearly needed. *Antiretroviral Pregnancy Registry:* To monitor fetal outcomes of pregnant women exposed to VIREAD, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263. **Nursing Mothers:** Studies in rats have demonstrated that tenofovir is secreted in milk. It is not known whether tenofovir is excreted in human milk. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving VIREAD. Pediatric Use:** Safety and effectiveness in patients less than 18 years of age have not been established. **Geriatric Use:** Clinical studies of VIREAD did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. **Patients with Impaired Renal Function:** It is recommended that the dosing interval for VIREAD be modified in patients with creatinine clearance <50 mL/min or in patients with end-stage renal disease (ESRD) who require dialysis *(See Dosage and Administration)*.

NONCLINICAL TOXICOLOGY: Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose. Tenofovir disoproxil fumarate was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus assay, tenofovir disoproxil fumarate was negative when administered to male mice. There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil fumarate was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats.

PATIENT COUNSELING INFORMATION: Information for Patients
Patients should be advised that:
- VIREAD is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using VIREAD.
- The use of VIREAD has not been shown to reduce the risk of transmission of HIV-1 or HBV to others through sexual contact or blood contamination.
- The long-term effects of VIREAD are unknown.
- VIREAD Tablets are for oral ingestion only.
- VIREAD should not be discontinued without first informing their physician.
- If you have HIV-1 infection, with or without HBV coinfection, it is important to take VIREAD with combination therapy.
- It is important to take VIREAD on a regular dosing schedule and to avoid missing doses.
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Treatment with VIREAD should be suspended in any patient who develops clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity (including nausea, vomiting, unusual or unexpected stomach discomfort, and weakness) *(See Warnings and Precautions).*
- Patients with HIV-1 should be tested for hepatitis B virus (HBV) before initiating antiretroviral therapy *(See Warnings and Precautions).*
- Severe acute exacerbations of hepatitis have been reported in patients who are infected with HBV or coinfected with HBV and HIV-1 and have discontinued VIREAD *(See Warnings and Precautions).*
- In patients with chronic hepatitis B, it is important to obtain HIV antibody testing prior to initiating VIREAD *(See Warnings and Precautions).*
- Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported. VIREAD should be avoided with concurrent or recent use of a nephrotoxic agent *(See Warnings and Precautions).* Dosing interval of VIREAD may need adjustment in patients with renal impairment *(See Dosage and Administration).*
- VIREAD should not be coadministered with the fixed-dose combination products TRUVADA (emtricitabine/tenofovir disoproxil fumarate) and ATRIPLA (efavirenz/emtricitabine/tenofovir disoproxil fumarate) since it is a component of these products *(See Warnings and Precautions).*
- VIREAD should not be administered in combination with HEPSERA *(See Warnings and Precautions).*
- Decreases in bone mineral density have been observed with the use of VIREAD in patients with HIV. Bone mineral density monitoring should be considered in patients who have a history of pathologic bone fracture or at risk for osteopenia *(See Warnings and Precautions).*
- In the treatment of chronic hepatitis B, the optimal duration of treatment is unknown. The relationship between response and long-term prevention of outcomes such as hepatocellular carcinoma is not known.

For detailed information, please see full prescribing information. To learn more: call 1-800-GILEAD-5 (1-800-445-3235) or visit www.VIREAD.com.

Reference: 1. VIREAD (tenofovir disoproxil fumarate) Prescribing Information. Foster City, CA: Gilead Sciences, Inc.; November 2008.

GILEAD

Presentations in Hepatology

Lamivudine Resistance Mutations Lead to Treatment Failure Among Patients With Hepatitis B Virus

The prevalence of genetic mutation leading to lamivudine resistance is high among patients with hepatitis B virus (HBV), resulting in treatment failure, according to the results of a study by Dr. Scott Fung and coworkers. The study was conducted to determine the role of a patient's genetic profile in influencing the efficacy of treatment for HBV, with the hope of documenting the incidence of antiviral resistance mutations among treatment-naive patients. Fung and coworkers remarked that they expected to observe a low level of natural resistance among the cohort of 209 patients (mean age, 38 years; male, 69%). The mean HBV DNA level among these patients was 5.7 $\log_{10}$ IU/mL, with a rate of cirrhosis of 15%. The range of HBV genotypes was: type A (8%), type B (32%), type C (47%), and type D (10%). Patients' antiviral resistance mutations were the following: rtL180M (10%), rtM204V/I (12%), rtL80V/I (9%), and rtV173L (3%), with rtA181V/T and rtN236T both reported to have 0% incidences. Of the patients with antiviral resistance mutations, 6 received nucleoside therapy, 3 received lamivudine 100 mg daily for a mean of 11 months, and 3 received adefovir (Hepsera, Gilead) 10 mg or tenofovir (Viread, Gilead) 300 mg daily for a mean of 7 months. Of the 3 treated with lamivudine, 1 did not achieve a primary response and the remainder exhibited breakthrough infection. In comparison, the patients treated with adefovir or tenofovir achieved undetectable levels of HBV DNA. A total of 21 patients (10%) had lamivudine resistance at baseline, and males with a high viral load were at greater risk of having antiviral resistance mutations. The researchers concluded that patients with antiviral resistance mutations achieved better results with adefovir or tenofovir than with lamivudine, and, therefore, development of a genetic profile for antiviral resistance would be beneficial in the development of therapeutic regimens. Dr. Fung suggested that agents with no known resistance should be used at baseline in treatment-naive patients.

Tenofovir Shows Efficacy and Lack of Resistance in Two-Year Extension Treating Chronic Hepatitis B

After showing superiority to adefovir in a 1-year head-to-head study to treat chronic HBV infection, tenofovir disoproxil fumarate was utilized in an open-label extension to treat both hepatitis B e antigen (HBeAg)-positive and -negative patients in simultaneous studies conducted by Drs. Marcellin, Heathcote, and associates. Among HBeAg-negative patients, response to tenofovir remained high, both in those who received tenofovir from the beginning of the study and those who switched from adefovir at the beginning of the open-label period. This held true in both patients who were stable on adefovir (HBV DNA <400 c/mL at week 48) and those who had suboptimal response to adefovir (HBV DNA≥400 c/mL at week 48). After 96 weeks, 89% of the overall population switching from adefovir were maintaining HBV DNA levels below 400 c/mL. Of patients receiving tenofovir throughout the 96 weeks, 90% maintained levels under 400 c/mL. An alternative combination therapy of tenofovir plus emtricitabine was offered at 72 weeks for patients with lost response to tenofovir monotherapy and was utilized by only approximately 1% of patients.

In a similarly designed study of HBeAg-positive patients, 78% of those switched from adefovir and 77% of those receiving tenofovir from study entry had HBV DNA levels below 400 c/mL at 96 weeks. Switching to tenofovir produced HBV DNA suppression in 82% of patients whose levels had risen above 400 c/mL while on adefovir. The authors concluded that tenofovir produced potent, continuous viral suppression and was well tolerated after 2 years.

In a related analysis of both studies, no phenotypic resistance mutations related to tenofovir were detected in any patients and rare cases of viral breakthrough were associated with lack of adherence. Annual resistance surveillance is planned through year 8 of follow-up in these studies.

Five-Year Mortality Among Liver Transplantation Recipients Reduced by Early Access Despite Differences in Donor Quality

Dr. Michael Goldstein and colleagues conducted an analysis of the United Network for Organ Sharing (UNOS) waitlist as well as adults who had received liver transplantation in order to determine the optimal strategy for timing of liver transplantation. The UNOS waitlist analysis comprised 43,497 patients; 22,863 adult recipients of transplantation were also analyzed. The analysis consisted of calculations of the relative waitlist mortality and posttransplant survival for recipients who received

organs from living donors or organs from deceased donors with both high– and low–donor index risk. The primary conclusion of the research was that a benefit accrued to patients who had early access to transplantation regardless of donor type that offset the detriment of the increase in posttransplant mortality due to differences in donor type. Patients on the UNOS waitlist are assessed according to the Mayo Model for End-stage Liver Disease (MELD), which scores disease severity and prognosis assessment. Patients enter the waitlist based on MELD score and other medical criteria. It is estimated that between 5% and 10% of patients on the waitlist die before transplantation, and MELD scores vary among those who die. The national median wait times, listed according to MELD scores, were: 1,868 days for those with scores under 10; 642 days for MELD 11–18; 105 days for MELD 19–24; and 19 days for MELD over 25. The researchers found MELD-dependent mortalities of patients on the waitlist at the time of MELD-allocated deceased donor transplantation to be 19.7%, 18.25%, 15.57%, and 21.48%, respectively, from low to high scores. Five-year mortality from time of entry on the waitlist for low–donor risk index recipients was 19.7%, 35.5%, 43.5%, and 53.3%, respectively, from low to high scores. Recipients of early living-donor transplantation had an increased mortality risk if their MELD scores were below 10 or above 25, whereas those with MELD scores of 11–18 and 19–24 had a decreased mortality risk. Benefit was not observed for high–donor risk index recipients with MELD scores below 10, and a modest potential benefit was observed for such recipients with MELD scores over 25. Therefore, the mortality reduction in high–donor risk index recipients was found only among those with MELD scores of 11–18 and 19–24, dependent on early timing of transplantation. Thus, Dr. Goldstein and colleagues concluded that living-donor and high–donor risk index allografts are best utilized in patients with middle-range MELD scores, and their benefit accrues when utilized early. It was further concluded that recipients whose MELD scores are below 10 do not achieve a 5-year benefit in mortality from any type of transplantation.

Lifestyle Intervention Leads to Significant Weight Loss Among Patients With Nonalcoholic Steatohepatitis

Nonalcoholic steatohepatitis (NASH), a chronic progressive liver disease that currently lacks an approved medical therapy, is strongly associated with obesity and insulin resistance. In order to assess the efficacy of weight reduction, which is typically recommended for patients with NASH, a randomized, controlled trial was conducted by Dr. Kittichai Pomrat and associates. The trial used a weight-reduction strategy involving a lifestyle intervention program. A total of 31 patients with biopsy-proven NASH received, on a randomized basis, either a lifestyle intervention with diet, exercise, and behavior modification, or standard nutrition counseling. The goal of the intervention was a weight loss of 7–10%. After 48 weeks, those receiving the lifestyle intervention experienced a mean weight reduction of 9.3% (±SD, 7.5%), as compared to 0.2% (±SD, 6.1%) for those receiving only standard nutrition counseling. A greater reduction in the mean degree of NASH was also associated with the lifestyle intervention (from 1.8 to 0.8 vs 1.9 to 1.6; P=.02). Additionally, a significant reduction in mean overall nonalcoholic fatty liver disease activity score was observed in those receiving lifestyle intervention in comparison to the control group (from 4.3 to 2.0 vs 4.9 to 3.5; P=.05). Other histologic features of NASH, including hepatocellular ballooning, lobular inflammation, and fibrosis, were not significantly different between the two groups. A significant decrease in mean alanine aminotransferase was also observed among patients receiving lifestyle intervention. It was, therefore, concluded that an aggressive lifestyle intervention program is associated with greater weight reduction among patients with NASH, leading to a significant improvement in degree of disease, liver chemistry, and histology.

Rifaximin With Lactulose Reduces Hospitalizations and Their Length in Patients With Hepatic Encephalopathy

The standard treatment for hepatic encephalopathy (HE), a potentially reversible neuropsychiatric abnormality in patients experiencing end-stage liver disease, is lactulose. The addition of rifaximin (Xifaxan, Salix), a semisynthetic antibiotic, to lactulose results in a significant reduction in the number of hospitalizations and reduces the length of hospital stay, according to the results of a retrospective review of patients at Methodist Dallas Medical Center, Dallas, Tex., by Dr. Parvez S. Mantry and colleagues. Of 213 patients whose records were reviewed, 65 patients received rifaximin (400–1,200 mg/day) plus lactulose for a mean of 14 months after receiving lactulose monotherapy for a mean of 21 months; 58 patients received lactulose monotherapy for a mean of 24 months. Of the patients who received combination therapy followed by adjunctive rifaximin, 30 (46%) were hospitalized previously for HE (mean, 2.6 hospitalizations). Of the 58 patients who received lactulose monotherapy, 50 patients (86%) had a history of HE and 19 (33%) had been hospitalized previously (mean, 1.2 hospitalizations). The researchers

found that the risk of hospitalization for HE was 87% lower among patients receiving adjunctive rifaximin treatment than during the preceding period of lactulose monotherapy. There was a total of 17 hospitalizations with combination therapy, in contrast to 60 with monotherapy. The mean number of hospitalizations per patient was 0.26 with rifaximin plus lactulose versus 0.95 with lactulose alone (odds ratio, 0.13; *P*<.001). Additionally, patients receiving adjunctive rifaximin had shorter stays in the hospital in comparison to those receiving lactulose monotherapy (1.1 vs 2.4 days; *P*=.04). It was found that 23% of patients who received lactulose monotherapy had multiple hospitalizations, but of these patients, 6% had multiple hospitalizations during adjunctive rifaximin therapy (*P*<.001). In comparison, 5% of patients who received lactulose alone had multiple hospitalizations. The researchers found that treatment, age, and MELD score were independent predictors of hospitalization for HE (*P*<.02). They concluded that prospective studies are warranted to determine the potential therapeutic and economic benefits of the reduction of hospitalization, and, potentially, morbidity, due to HE by administration of rifaximin.

Increasing Insulin Sensitivity With Metformin Improves Antiviral Response Rates in Hepatitis C

Dr. Manuelo Romero-Gomez and associates conducted a prospective, multicenter, double-blind, placebo-controlled trial in 125 patients with chronic hepatitis C virus (HCV) genotype 1 infection and insulin resistance. Many patients with chronic HCV infection have insulin resistance, which inhibits response to antiviral therapy. Patients received placebo or metformin 425 mg thrice daily during the first month, followed by metformin 850 mg thrice daily from weeks 4 to 48. All patients received standard pegylated interferon (PEG-IFN) alfa-2a 180 mcg/week and ribarivin 1,000–1,200 mg/day. The study was intended to determine whether metformin, an insulin sensitizer, added to PEG-IFN results in improved viral response rates. The mean age was 47 years in the study group and 48 years in the control group was. Baseline viral loads were 6.33 and 6.48 log10 IU/mL in the study and control groups, respectively. Viral response was assessed at 4, 12, 24, and 72 weeks in an intent-to-treat analysis. Dr. Romero-Gomez and associates found that 54.2% of metformin-treated patients experienced viral clearance, in comparison to 48.4% of patients receiving standard therapy only. At 24 weeks, approximately 75% of both groups showed viral clearance. At 72 weeks, the sustained viral response rates were 52.5% in patients receiving metformin and 42.2% in patients receiving only standard therapy. Women experienced a better response to the addition of metformin than men, with viral clearance at week 12 occurring in 57.7% of women versus 39.3% of men. At week 24, 80.8% of women and 71.4% of men had viral clearance, with sustained viral response rates of 57.7% at week 72 among women and 28.6% among men (*P*=.031). The viral load decreased 4.18 $\log_{10}$ IU/mL in women versus 4.02 $\log_{10}$ IU/mL in men (*P*=.044). The combination of metformin and standard therapy was tolerated well, with mild diarrhea in 34.1% in metformin-receiving patients versus 11.4% in patients receiving standard therapy alone. Although insulin sensitivity was increased among patients receiving metformin, particularly women, who have more fat stored than men, the overall response rate of 57.7% leaves room for further improvement.

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[1] Vakil N, Fendrick M. How to test for *Helicobacter pylori* in 2005. *Cleve Clin J Med.* 2005; 72 (Suppl 2): S8–S13.

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Urea Breath Test for H. pylori
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Brief Summary

Intended Use:

The BreathTek™ UBT Collection Kit is intended for use in the qualitative detection of urease associated with *Helicobacter pylori* in the human stomach and as an aid in the initial diagnosis and post-treatment monitoring of *H. pylori* infection in adult patients. The test may be used for monitoring treatment if used at least four (4) weeks following completion of therapy. For these purposes, the system utilizes an Infrared Spectrophotometer for the measurement of the ratio of $^{13}CO_2$ to $^{12}CO_2$ in breath samples.

For administration by health care professionals.
To be administered under a physician's supervision.

Warnings and Precautions:

1. For in vitro diagnostic use only. The Pranactin®-Citric drug solution is taken orally as part of the diagnostic procedure.
2. Phenylketonurics: Contains Phenylalanine (one of the protein components of Aspartame), 84 mg per dosage unit. (For reference, 12 ounces of typical diet cola soft drinks contain approximately 80 mg of Phenylalanine.)
3. A negative result does not rule out the possibility of *Helicobacter pylori* infection. False negative results do occur with this procedure. If clinical signs are suggestive of *H. pylori* infection, retest with a new sample or an alternative method.
4. Antimicrobials, proton pump inhibitors, and bismuth preparations are known to suppress *H. pylori*. Ingestion of these within two (2) weeks prior to performing the BreathTek UBT may give false negative results.
5. A false positive test may occur due to urease associated with other gastric spiral organisms observed in humans such as *Helicobacter heilmannii*.
6. Premature POST-DOSE breath collection time can lead to a false negative diagnosis for a patient with a marginally positive BreathTek UBT result.
7. A false positive test could occur in patients who have achlorhydria.
8. If particulate matter is visible in the reconstituted Pranactin-Citric solution after thorough mixing, the solution should not be used.

Limitations:

1. The BreathTek UBT should not be used until four (4) weeks or more after the end of treatment for the eradication of *H. pylori* as earlier post-treatment assessment may give false negative results.
2. The performance characteristics for persons under the age of eighteen (18) have not been established for this test.
3. The specimen integrity of breath samples and reference gases stored in breath bags under ambient conditions has not been determined beyond seven (7) days.
4. A correlation between the number of *H. pylori* organisms in the stomach and the BreathTek UBT result has not been established.
5. The predicate device (Meretek UBT®) was standardized in asymptomatic healthy volunteers and subsequently validated in clinical trials limited to patients with documented duodenal ulcer disease.

Presentations in IBD

MMX Mesalamine Gains Efficacy With Extended Induction of Remission

Mesalamine with Multimatrix System (MMX) technology is a recently approved high-dose (1.2 g/tablet) oral formulation (Lialda, Shire), which exclusively distributes 5-aminosalicylic acid (5-ASA) throughout the colon. In addition to a pH-dependent delayed-release enteric coating, an included excipient slows the release of 5-ASA even further, allowing for once-daily administration. Two phase III studies, SPD476-301 and SPD476-302, found that MMX mesalamine was effective in the induction of remission in patients with active mild-to-moderate ulcerative colitis. Recent analysis pooled both of these study populations, showing that the 8-week remission rate was 37.2% and 35.1% in patients receiving 2.4 g/day and 4.8 g/day MMX mesalamine, compared with 17.5% in patients receiving placebo (P<.001). Among patients who did not achieve remission, an open-label extension study of an additional 8 weeks of MMX administration was conducted. In that extension study, an additional 59.5% of patients achieved remission by the end of week 8, suggesting that extended treatment with high-dose MMX mesalamine may be an effective alternative to step-up therapy in these patients. Time to symptom resolution was calculated from the point at which treatment in the open-label extension was initiated until the first day of rectal bleeding cessation and normalization of stool frequency. The investigators reported that the median time to symptom resolution, after completion of the initial 8 weeks, was 15 days after enrollment in the extension study.

Comparing Mesalamine Release Profiles

Wray and colleagues compared the pharmacokinetic and pharmacodynamic profiles of a single dose of MMX mesalamine with a single dose of pH-dependent delayed-release mesalamine. The pharmacology of each of these mesalamine formulations was evaluated in an open-label, two-way cross-over study of 8 healthy male subjects. The participants ranged in age from 18 to 65 years and were randomized to receive either 1 MMX mesalamine tablet (1.2 g/tablet) or 3 pH-dependent delayed-release mesalamine tablets (400 mg/tablet). Each tablet was radiolabeled with 153Sm (1.5 MBq/tablet or 0.5 MBq/tablet, respectively). After hospital admittance, participants began fasting 8 hours prior to dosing and continued until 4 hours following dosing. In conjunction with the mesalamine dosage, participants also were administered 20 radio-opaque beads. Evaluations were performed over the subsequent 96 hours, after which the subjects were discharged and asked to continue stool collection until all radio-opaque beads were recovered.

Each 5-ASA formulation displayed a similar pharmacokinetic profile. The time to maximal concentration was 7.0 ± 3.0 hours and 8.8 ± 3.2 hours for MMX mesalamine and pH-dependent delayed-release mesalamine, respectively. Additionally, similar maximum concentrations and clearance (calculated as area under the curve) of 5-ASA were achieved over the 96-hour period by each formulation. 5-ASA released by MMX mesalamine reached a maximal concentration of 711 ± 540 ng/mL, and an area-under-the-curve of 4,069 ± 3,028 ng/hr/mL, whereas 5-ASA released by the pH-dependent delayed-release formulation reached a maximal concentration of 790 ± 626 ng/mL and an area under the curve of 4,444 ± 2,610 ng/hr/mL.

Although initial tablet disintegration occurred earlier for MMX mesalamine compared with pH-dependent delayed-release mesalamine (4.75 ± 1.31 hours versus 6.16 ± 1.80 hours), total disintegration of MMX mesalamine took a much longer time to complete (17.37 ± 8.63 hours versus 7.27 ± 2.13 hours, respectively). After administration of both formulations, the gastrointestinal transit time was completed in approximately 70 hours.

From these data, the authors concluded that MMX mesalamine steadily released 5-ASA throughout the left side of the colon, whereas the pH-dependent delayed-release mesalamine formulation released the majority of 5-ASA throughout the ascending colon.

Granulated Mesalamine Maintains Remission in Patients With Ulcerative Colitis

A phase III trial, led by Dr. Glenn Gordon, showed that once-daily granulated mesalamine (Apriso, Salix) 1.5 g effectively maintains remission in patients with ulcerative colitis that were in documented remission. Patients received 4 doses of 375 mg of granulated mesalamine daily for 6 months or placebo on a randomized basis. The study's endpoint was the proportion of relapse-free patients

after 6 months of treatment, and those who reported a flare or who required initiation of medication to treat ulcerative colitis were considered treatment failures. The researchers found that a significantly greater percentage of patients receiving mesalamine maintained long-term remission than patients receiving placebo (79% vs 58%; *P*<.001). After 6 months, patients receiving mesalamine had a favorable change from baseline in physician-rated disease activity compared with placebo (78% vs 64%; *P*=.005). Additionally, patients receiving mesalamine had a higher probability of remaining free from relapse compared with placebo (77% vs 56%; *P*<.001). The percentage of patients per adverse event was similar across study groups (64%), with most events considered mild or moderate. Only 11% of patients receiving mesalamine experienced a flare of ulcerative colitis, compared to 27% receiving placebo.

Vitamin D Levels Associated With Quality of Life in Patients With IBD

Researchers from the Medical College of Wisconsin investigated whether patients with inflammatory bowel disease (IBD) deficient in vitamin D experience a lower quality of life or higher disease activity regardless of other risk factors and medical interventions. The retrospective analysis consisted of 504 patients with IBD who were assessed using validated questionnaires to measure disease activity and quality of life. The prevalence and seasonality of deficiency in vitamin D were taken into account, as was its relationship to IBD-related medications, hospitalizations, and surgeries. Nadir levels of vitamin D were recorded. It was discovered that nearly 50% of patients experienced deficient levels of vitamin D, with 11% experiencing severe deficiency. However, this deficiency was not significantly associated with IBD-related hospitalization or surgery. Among patients with Crohn's disease and ulcerative colitis, vitamin D was independently associated with increased disease activity scores in comparison to patients with normal levels of vitamin D. Patients with Crohn's disease, but not ulcerative colitis, had worse quality of life in the absence of sufficient vitamin D, as compared to those with normal levels. The researchers concluded that patients with IBD should have their levels of vitamin D assessed regularly, and when low, aggressive correction is warranted.

Infliximab Alone or Plus Azathioprine Associated With Positive Outcomes in Crohn's Disease

The Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease (SONIC) showed that patients with Crohn's disease who are naive to immunomodulating agents are more likely to achieve mucosal healing when treated with infliximab (Remicade, Centocor) than with azathioprine. Moreover, such patients are more likely to achieve corticosteroid-free clinical remission. A total of 508 patients were treated with infliximab 5 mg/kg plus placebo, infliximab 5 mg/kg plus azathioprine 2.5 mg/kg, or azathioprine 2.5 mg/kg plus placebo, and those on either infliximab-containing arm of the study achieved better outcomes than those on the azathioprine-monotherapy arm. The primary endpoint of SONIC was corticosteroid-free clinical remission at 26 weeks. Infliximab plus azathioprine was associated with a remission rate of 56.8% (*P*<.001), infliximab monotherapy with a remission rate of 44.4% (*P*=.009), and azathioprine with a remission rate of 30.6%. It was observed that patients with high levels of C-reactive protein and/or endoscopic evidence of ulcers had better outcomes with infliximab-containing regimens. Among these patients, corticosteroid-free clinical remission survival was doubled at 26 weeks with infliximab monotherapy versus azathioprine monotherapy (56.9% vs 28%; *P*<.001), and 68.8% of these patients were corticosteroid-free survivors at 26 weeks on the combination therapy (*P*<.001). There was no statistically significant difference for such patients between infliximab monotherapy or combination therapy. Finally, 44% and 30% of patients receiving infliximab combination therapy (*P*<.001) and monotherapy (*P*=.0223) achieved mucosal healing, respectively, whereas only 17% of patients receiving azathioprine monotherapy did so. The authors concluded that immunomodulator-naive patients who receive azathioprine plus infliximab achieve better outcomes as compared to either agent alone.

Certolizumab Pegol Associated With Improvement in Mucosa in Patients With Crohn's Disease

A prospective, international open-label trial investigated the efficacy of certolizumab pegol (CZP; Cimzia, UCB) in resolving mucosal lesions in patients with Crohn's disease. CZP is a pegylated antagonist of TNFα. Entry criteria included patients with clinically moderate-to-severe Crohn's disease (by Crohn's Disease Activity Index [CDAI]) and severe endoscopic disease (≥2 segments with endoscopic ulcerative lesions and a Crohn's Disease Endoscopic Index of Severity [CDEIS] score of ≥8). CZP was administered at a dose of 400 mg subcutaneously at weeks 0, 2, 4, and every 4 weeks thereafter. The primary endpoint was change from baseline to week 10 in CDEIS. The intention-to-treat population included

89 patients (mean age, 30.2 years; mean disease duration, 7.9 years). At week 10, mean reduction from baseline in CDEIS score was 6.5 points (95% confidence interval, -7.6–-5.3; *P*<.0001). CDEIS remission and response rates were 55.1% and 74.4%, respectively. It was noted that there was a poor correlation between clinical (CDAI) and endoscopic (CDEIS) findings, but at week 10, 46.1% of patients achieved CDAI remission. The most commonly observed adverse events were headache (18%), arthralgia (11.2%), nausea (9%), and anal fissure (7.9%). The investigators concluded that CZP is efficacious in providing both endoscopic and clinical improvement. Long-term follow-up will elucidate the clinical relevance of mucosal healing and its effect on disease modification.

Adalimumab Maintenance Decreases Hospitalizations in Moderate-to-Severe Crohn's Disease

Adalimumab (Humira, Abbott) is a fully human monoclonal antibody against tumor necrosis factor (TNF), indicated for the treatment of adults with moderate-to-severe Crohn's disease. It was investigated in a phase III trial, the Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM), to evaluate how patients naive to TNF antagonists respond to maintenance therapy (approximately half the patient population was TNF antagonist–naive). All entering patients received open-label induction adalimumab 80 mg, followed by adalimumab 40 mg at week 2. At week 4, patients were stratified by response and randomized to a maintenance regimen of adalimumab 40 mg every other week or weekly or placebo. Crohn's disease–related hospitalization rates among patients receiving adalimumab versus placebo were 1.7% and 7.9% at month 3, 5.2% and 11.3% at month 6, and 6.8% and 13.7% at month 12, respectively. All-cause hospitalization rates among patients receiving adalimumab versus placebo were 3.6% and 10.4% at month 3, 8.9% and 15.4% at month 6, and 12.7% and 20.3% at month 12. Log-rank test showed significant differences in both kinds of hospitalization favoring adalimumab versus placebo. In addition, disease duration of less than 3 years was associated with Crohn's disease–related hospitalization at a rate of 3.2% for those receiving adalimumab versus 11.8% for those receiving placebo. In comparison, disease duration longer than 3 years was associated with Crohn's disease–related hospitalization at a rate of 7.9% for those receiving adalimumab versus 14.8% for those receiving placebo. Overall, CHARM demonstrated that adalimumab significantly decreased the risk of hospitalization versus placebo among patients who were TNF antagonist–naive.

Presentations in GERD

TAK-390MR Demonstrates Higher Healing Rates Than Lansoprazole Among Patients With More Severe Erosive Esophagitis

Two phase III trials demonstrated that the proton pump inhibitor TAK-390MR (Takeda) leads to higher esophageal healing rates than lansoprazole among patients with more severe grades of erosive esophagitis (EE). TAK-390MR comprises two separate releases of dexlansoprazole, an enantiomer of lansoprazole, for extended acid suppression. The trials assessed overall EE healing after 8 weeks of therapy with TAK-390MR in 4,092 patients, who received 60 mg or 90 mg of the drug or 30 mg of lansoprazole on a randomized basis. A retrospective analysis showed that the difference in healing rates between 60 mg and 90 mg of TAK-390MR and 30 mg of lansoprazole increased with the severity of EE. Patients who had grade D EE, the most severe grade, achieved the greatest therapeutic gains (60 mg, 12%; 90 mg, 20%). There was no significant difference in adverse events among the groups, with diarrhea occurring in 3% of patients receiving both doses of TAK-390MR and in 2% of patients receiving lansoprazole.

In related findings, Dr. David Johnson and colleagues observed that once-daily esomeprazole is not inferior to twice-daily lansoprazole in a double-blind, randomized crossover study. Patients with well-controlled typical uncomplicated GERD can achieve similar normalization of quality of life with once-daily esomeprazole as with twice-daily lansoprazole, with comparable pH control.

Pantoprazole Efficacious and Tolerable in Infants With GERD

Gastroesophageal reflux disease (GERD) is common in infants and is thought to predispose them to poor weight gain and respiratory disorders. In order to redress the paucity of data available for infants under 1 year of age, Dr. Gail Comer and coworkers investigated the effect of 4 weeks of therapy with the proton pump inhibitor pantoprazole in infants 1–11 months of age. All infants with symptoms of GERD in the trial received 2 weeks of standardized conservative treatment. Those who remained symptomatic (n=128) entered a 4-week, open-label phase with a daily dose of 1.2 mg/kg of pantoprazole. Those infants who achieved 80% or better compliance after 4 weeks were entered into a 4-week double-blind treatment-withdrawal phase of the study. The primary endpoint was withdrawal rate from the double-blind phase due to lack of efficacy. The randomization consisted of placebo versus the same dose of pantoprazole as in the open-label phase of the study. Site visits every 2 weeks up to week 8, telephone interviews in between, and daily electronic symptom diaries were used to assess the infants' GERD symptoms. Mean weekly GERD symptom scores based on the daily diary assessments were compared with baseline scores. The intention-to-treat population for the withdrawal phase comprised 106 infants, with a mean age of 5.1 months. At the trial's completion, there was no significant difference in rates of withdrawal due to efficacy between the active-treatment and placebo groups. But Dr. Comer and coworkers noted that significant reductions in weekly GERD symptom scores were observed in all patients during the open-label phase ($P<.001$), with greater reductions in patients older than 6 months ($P<.005$) and those with higher baseline symptom scores ($P<.0001$). The greatest difference in symptom scores between the groups occurred at week 5, with slightly worse scores for the placebo group ($P=.09$), mainly due to a decrease in episodes of arching back with pantoprazole. Overall, up to 70% healing at 4 weeks along with durable response was observed, meaning that prolonged treatment over 4 weeks is not necessary in infants.

Preoperative Evaluation May Find Eosinophilic Esophagitis in Presumed GERD Patients

Studies have shown that patients diagnosed with refractory GERD in some cases actually have eosiniphilic esophagitis (EoE). A series of case studies was reported based on patients seen at the University of North Carolina presumed to have refractory GERD, who underwent Nissen fundoplication and were found to have EoE. Using a database of information on patients with esophageal eosinophilia from any cause from 2000 to 2007, the researchers identified patients diagnosed with EoE after prior Nissen fundoplication in addition to patients with high levels of esophageal eosinophilia and a prior Nissen. EoE was defined as more than 15 eosinophils per high-powered field, with at least one typical symptom (eg, dysphagia, heartburn, or feeding intolerance) and other causes of esophageal eosinophilia excluded. A total of 8 patients were identified who underwent a prior Nissen fundoplication and had high levels of esophageal

eosinophilia. Of these, 4 met the criteria for diagnosis of EoE in this study (2 males; age range, 8–56 years). These patients' symptoms (dysphagia in 2, food impaction in 1, heartburn in 3, and failure to thrive in 1) and esophageal eosinophilia persisted after surgery. In contrast, 4 patients diagnosed with "refractory GERD" who were treated with Nissen fundoplication were subsequently diagnosed with EoE. Therefore, a proportion of patients who undergo surgery for incomplete resolution of GERD symptoms appear to be undiagnosed cases of EoE. As a result, the researchers consider it prudent to obtain proximal and distant biopsies in such patients prior to antireflux surgery.

Validation of a Simple Scoring System for Diagnosis of GERD or Related Conditions

Dr. Andrew Roorda and associates reported on the need for a novel scoring system as a diagnostic aid to distinguish GERD from nonerosive esophageal reflux disease (NERD) or reflux-like dyspepsia (RLD) because symptoms commonly overlap. Based on symptoms alone, it can be difficult to make an accurate diagnosis. The researchers prospectively evaluated and validated a multifactorial scoring system for use in patients with epigastric pain and heartburn. A total of 63 patients (29 males) whose symptoms were partially relieved by therapy with a proton pump inhibitor were initially evaluated for symptoms. The patients subsequently underwent endoscopy; distal biopsies to evaluate the esophagus, stomach, and duodenum; and monitoring of intestinal motility and 24-hour ambulatory pH monitoring to assess esophageal function and pathologic acid exposure. Using a total of nine variables, a total score was calculated and compared to a prior cohort of 110 patients. Among the 63 patients in the validation cohort, endoscopy identified erosive or complicated GERD in 22 (35%). Of the remainder, 32 (51%) had abnormal pH and motility, leading to classification as NERD. The remaining 9 patients had normal functional studies, leading to classification as RLD. Overall, using this scoring system, a score higher than 4 excludes RLD, whereas 4 or less excludes GERD; a score higher than 10 excludes NERD.

Manometric Placement of Bravo Capsule Associated With Less Discrepant Day-to-Day Measurement of Esophageal Acid

The wireless pH monitoring system (Bravo Capsule) is a well-tolerated method of collecting 48 hours' worth of data in patients suspected of having GERD. However, there is a significant day-to-day discrepancy in measurements, thought to be due to sedation used in the endoscopic placement of the device. A study of 310 patients evaluated transnasal placement of the capsule based on motility measurements of the lower esophageal sphincter to determine if this method affects the discrepancy in measurements, and, if so, what variability can be attributed to the status of the lower esophageal sphincter. Patients were scored and grouped as: both days abnormal, both days normal, and discrepancy between first and second day. The characteristics of the lower esophageal sphincter were recorded, and in those patients with a discrepancy, the response of the lower esophageal sphincter to a test meal was evaluated by comparison of preprandial and postprandial acid exposure ratios. A total of 60 patients (19%) had a discrepancy in score between the 2 days, with 127 having a normal score and 123 an abnormal score on both days. Of the 60, 27 had an abnormal score on the first day and 33 on the second. Patients with abnormal scores on both days tended to have more defective lower esophageal sphincter characteristics compared with those who had an abnormal score on only 1 of the days. Among the 28 discrepant patients who received a test meal, 10 had an abnormal acid exposure ratio before and after the meal on the normal day. The researchers concluded that manometric placement of Bravo Capsule results in less discrepant pH recording across two 24-hour periods in comparison to endoscopic placement. Furthermore, in patients with abnormal pH on both days, defective lower esophageal sphincter is more prevalent than in those with abnormal pH on a single day. The variability across days may be attributable to impairment of the gastroesophageal barrier in patients with early reflux disease.

BRIEF SUMMARY: Consult the Full Prescribing Information for complete product information.

PENTASA® (mesalamine) Rx only
Controlled-Release Capsules 250 mg and 500 mg

INDICATIONS AND USAGE
PENTASA is indicated for the induction of remission and for the treatment of patients with mildly to moderately active ulcerative colitis.

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PENTASA is contraindicated in patients who have demonstrated hypersensitivity to mesalamine, any other components of this medication, or salicylates.

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General
Caution should be exercised if PENTASA is administered to patients with impaired hepatic function.
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 cannot be ascertained, 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. If a rechallenge is performed later in order to validate the hypersensitivity, it should be carried out under close medical supervision at reduced dose and only if clearly needed.

Renal
Caution should be exercised if PENTASA is administered to patients with impaired renal function. Single reports of nephrotic syndrome and interstitial nephritis associated with mesalamine therapy have been described in the foreign literature. There have been rare reports of interstitial nephritis in patients receiving PENTASA. In animal studies, 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. Patients with preexisting renal disease, increased BUN or serum creatinine, or proteinuria should be carefully monitored, especially during the initial phase of treatment. Mesalamine-induced nephrotoxicity should be suspected in patients developing renal dysfunction during treatment.

Drug Interactions
There are no data on interactions between PENTASA and other drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility
In a 104-week dietary carcinogenicity study of mesalamine, CD-1 mice were treated with doses up to 2500 mg/kg/day and it was not tumorigenic. For a 50 kg person of average height (1.46 m^2 body surface area), this represents 2.5 times the recommended human dose on a body surface area basis (2960 mg/m^2/day). 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 represents 1.5 times the recommended human dose on a body surface area basis.
No evidence of mutagenicity was observed in an in vitro Ames test and 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 (0.8 times the recommended human dose based on body surface area).
Semen abnormalities and infertility in men, which have been reported in association with sulfasalazine, have not been seen with PENTASA capsules during controlled clinical trials.

Pregnancy
Category B. Reproduction studies have been performed in rats at doses up to 1000 mg/kg/day (5900 mg/M^2) and rabbits at doses of 800 mg/kg/day (6856 mg/M^2) and have revealed no evidence of teratogenic effects 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, PENTASA should be used during pregnancy only if clearly needed.
Mesalamine is known to cross the placental barrier.

Nursing Mothers
Minute quantities of mesalamine were distributed to breast milk and amniotic fluid of pregnant women following sulfasalazine therapy. When treated with sulfasalazine at a dose equivalent to 1.25 g/day of mesalamine, 0.02 µg/mL to 0.08 µg/mL and trace amounts of mesalamine were measured in amniotic fluid and breast milk, respectively. N-acetylmesalamine, in quantities of 0.07 µg/mL to 0.77 µg/mL and 1.13 µg/mL to 3.44 µg/mL, was identified in the same fluids, respectively.
Caution should be exercised when PENTASA is administered to a nursing woman.
No controlled studies with PENTASA during breast-feeding have been carried out. Hypersensitivity reactions like diarrhea in the infant cannot be excluded.

Pediatric Use
Safety and efficacy of PENTASA in pediatric patients have not been established.

ADVERSE REACTIONS
In combined domestic and foreign clinical trials, more than 2100 patients with ulcerative colitis or Crohn's disease received PENTASA therapy. Generally, PENTASA therapy was well tolerated. The most common events (ie, greater than or equal to 1%) were diarrhea (3.4%), headache (2.0%), nausea (1.8%), abdominal pain (1.7%), dyspepsia (1.6%), vomiting (1.5%), and rash (1.0%).
In two domestic placebo-controlled trials involving over 600 ulcerative colitis patients, adverse events were fewer in PENTASA-treated patients than in the placebo group (PENTASA 14% vs placebo 18%) and were not dose-related. Events occurring at 1% or more are shown in the table below. Of these, only nausea and vomiting were more frequent in the PENTASA group. Withdrawal from therapy due to adverse events was more common on placebo than PENTASA (7% vs 4%).

Table 1. Adverse Events Occurring in More Than 1% of Either Placebo or PENTASA Patients in Domestic Placebo-controlled Ulcerative Colitis Trials. (PENTASA Comparison to Placebo)

Event	PENTASA n=451	Placebo n=173
Diarrhea	16 (3.5%)	13 (7.5%)
Headache	10 (2.2%)	6 (3.5%)
Nausea	14 (3.1%)	---
Abdominal Pain	5 (1.1%)	7 (4.0%)
Melena (Bloody Diarrhea)	4 (0.9%)	6 (3.5%)
Rash	6 (1.3%)	2 (1.2%)
Anorexia	5 (1.1%)	2 (1.2%)
Fever	4 (0.9%)	2 (1.2%)
Rectal Urgency	1 (0.2%)	4 (2.3%)
Nausea and Vomiting	5 (1.1%)	---
Worsening of Ulcerative Colitis	2 (0.4%)	2 (1.2%)
Acne	1 (0.2%)	2 (1.2%)

Clinical laboratory measurements showed no significant abnormal trends for any test, including measurement of hematological, liver, and kidney function.
The following adverse events, presented by body system, were reported infrequently (ie, less than 1%) during domestic ulcerative colitis and Crohn's disease trials. In many cases, the relationship to PENTASA has not been established.
Gastrointestinal: abdominal distention, anorexia, constipation, duodenal ulcer, dysphagia, eructation, esophageal ulcer, fecal incontinence, GGTP increase, GI bleeding, increased alkaline phosphatase, LDH increase, mouth ulcer, oral moniliases, pancreatitis, rectal bleeding, SGOT increase, SGPT increase, stool abnormalities (color or texture change), thirst
Dermatological: acne, alopecia, dry skin, eczema, erythema nodosum, nail disorder, photosensitivity, pruritus, sweating, urticaria
Nervous System: depression, dizziness, insomnia, somnolence, paresthesia
Cardiovascular: palpitations, pericarditis, vasodilation
Other: albuminuria, amenorrhea, amylase increase, arthralgia, asthenia, breast pain, conjunctivitis, ecchymosis, edema, fever, hematuria, hypomenorrhea, Kawasaki-like syndrome, leg cramps, lichen planus, lipase increase, malaise, menorrhagia, metrorrhagia, myalgia, pulmonary infiltrates, thrombocythemia, thrombocytopenia, urinary frequency
One week after completion of an 8-week ulcerative colitis study, a 72-year-old male, with no previous history of pulmonary problems, developed dyspnea. The patient was subsequently diagnosed with interstitial pulmonary fibrosis without eosinophilia by one physician and bronchiolitis obliterans with organizing pneumonitis by a second physician. A causal relationship between this event and mesalamine therapy has not been established.
Published case reports and/or spontaneous postmarketing surveillance have described infrequent instances of pericarditis, fatal myocarditis, chest pain and T-wave abnormalities, hypersensitivity pneumonitis, pancreatitis, nephrotic syndrome, interstitial nephritis, hepatitis, aplastic anemia, pancytopenia, leukopenia, agranulocytosis, or anemia while receiving mesalamine therapy. Anemia can be a part of the clinical presentation of inflammatory bowel disease. Allergic reactions, which could involve eosinophilia, can be seen in connection with PENTASA therapy.

Postmarketing Reports
The following events have been identified during post-approval use of the PENTASA brand of mesalamine in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of seriousness, frequency of reporting, or potential causal connection to mesalamine:
Gastrointestinal: Reports of hepatotoxicity, including elevated liver enzymes (SGOT/AST, SGPT/ALT, GGT, LDH, alkaline phosphatase, bilirubin), hepatitis, jaundice, cholestatic jaundice, cirrhosis, and possible hepatocellular damage including liver necrosis and liver failure. Some of these cases were fatal. One case of Kawasaki-like syndrome which included hepatic function changes was also reported.
Other: Postmarketing reports of pneumonitis, granulocytopenia, systemic lupus erythematosis, acute renal failure, chronic renal failure and angioedema have been received in patients taking PENTASA.

OVERDOSAGE
Single oral doses of mesalamine up to 5 g/kg in pigs or a single intravenous dose of mesalamine at 920 mg/kg in rats were not lethal.
There is no clinical experience with PENTASA overdosage. PENTASA is an aminosalicylate, and symptoms of salicylate toxicity may be possible, such as: tinnitus, vertigo, headache, confusion, drowsiness, sweating, hyperventilation, vomiting, and diarrhea. Severe intoxication with salicylates can lead to disruption of electrolyte balance and blood-pH, hyperthermia, and dehydration.
Treatment of Overdosage. Since PENTASA is an aminosalicylate, conventional therapy for salicylate toxicity may be beneficial in the event of acute overdosage. 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 and the symptomatic treatment of mildly to moderately active ulcerative colitis is 1g (4 PENTASA 250 mg capsules or 2 PENTASA 500 mg capsules) 4 times a day for a total daily dosage of 4g. Treatment duration in controlled trials was up to 8 weeks.
Store at 25°C (77°F) excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Manufactured for **Shire US Inc.** 725 Chesterbrook Blvd., Wayne, PA 19087, USA
Licensed U.S. Patent Nos. B1 4,496,553 and 4,980,173 189 0107 009
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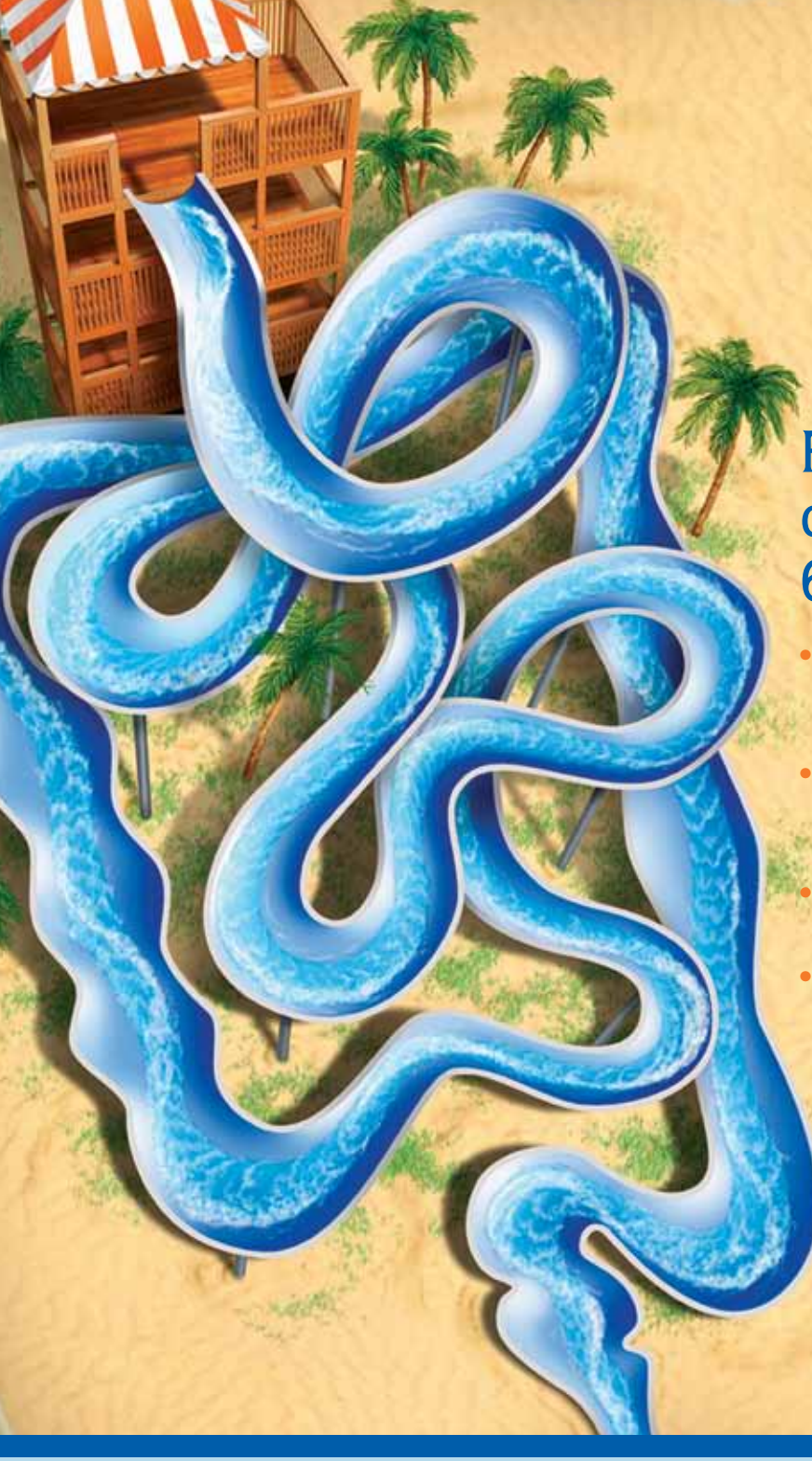

RELIABLE DELIVERY
PENTASA®
SINCE 1993

Reliably delivering for over 15 years and 6 million prescriptions[1]

- Moisture-activated PENTASA begins delivery of 4 grams of mesalamine at the duodenum[2,3]
- PENTASA 4 grams per day reduced symptoms and improved patients' quality of life[4]
- PENTASA reliably delivers 5-ASA throughout the small and large intestine
- PENTASA is indicated for the induction of remission and for the treatment of patients with mildly to moderately active ulcerative colitis

500-mg capsules

PENTASA®

(mesalamine) 250 mg 500 mg

controlled-release capsules

Delivers 4 grams top to bottom

Important Safety Information

- PENTASA is generally well tolerated. In worldwide clinical trials (N>2100), the most common adverse events were diarrhea (3.4%), headache (2.0%), nausea (1.8%), abdominal pain (1.7%), dyspepsia (1.6%), vomiting (1.5%), and rash (1.0%). As with other mesalamine products, serious adverse events may occur. PENTASA is contraindicated in patients with a hypersensitivity to salicylates. Caution should be used in patients with impaired hepatic or renal function. Patients with pre-existing renal disease, increased BUN or serum creatinine, or proteinuria should be monitored during PENTASA therapy.

References: 1. IMS National Prescription Data. December 1, 2007. **2.** Nugent SG, Kumar D, Rampton DS, Evans DF. Intestinal luminal pH in inflammatory bowel disease: possible determinants and implications for therapy with aminosalicylates and other drugs. *Gut.* 2001;48:571-577. **3.** Sinha A, Ball DJ, Connor AL, Nightingale J, Wilding IR. Intestinal performance of two mesalamine formulations in patients with active ulcerative colitis as assessed by gamma scintigraphy. *Pract Gastroenterol.* 2003;27:56-69. **4.** Robinson M, Hanauer S, Hoop R, Zbrozek A, Wilkinson C. Mesalamine capsules enhance the quality of life for patients with ulcerative colitis. *Aliment Pharmacol Ther.* 1994;8:27-34.

Please see brief summary of Full Prescribing Information on the adjacent page.

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