GASTROENTEROLOGY & HEPATOLOGY™
The Independent Peer-Reviewed Journal

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THE GASTRO & HEP REPORT

Presentation summaries in:

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

- The 2009 American College of Gastroenterology Annual Scientific Meeting
  October 23–28, 2009
  San Diego, California
- The 60th Annual Meeting of the American Association for the Study of Liver Diseases
  October 30–November 3, 2009
  Boston, Massachusetts
- The 2009 Advances in IBD/Crohn's & Colitis Foundation's Clinical & Research Conference
  December 3–6, 2009
  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

At 1200 mg, the highest 5-ASA dose per tablet[1]

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.

Visit Lialda.com

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

LIA-00884 06/09

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.

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Included in EMBASE

Presentations in Gastroesophageal Reflux Disease

Dexlansoprazole MR Improves Nighttime Heartburn and Sleep Quality in Patients With Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) is frequently associated with nocturnal heartburn and sleep disturbances, which can have a negative effect on quality of life and can increase patients' risk for esophagitis. Fass and colleagues performed a randomized, double-blind, placebo-controlled study to evaluate the efficacy of dexlansoprazole MR (Kapidex, Takeda) in treating nighttime symptoms of GERD. The study enrolled 305 patients 18–66 years of age with symptomatic GERD and no esophageal erosions, as determined by endoscopy. The researchers found that patients receiving dexlansoprazole MR experienced a greater rate of heartburn-free nights than those receiving placebo: 73% versus 36%, respectively ($P<.001$). The relief of nocturnal heartburn and GERD-related sleep disturbances occurred in 48% and 70% of drug-treated patients, respectively, compared to 20% and 48% of placebo patients ($P<.001$). Patients receiving the active drug also reported significantly greater improvements in sleep quality and work productivity.

Abnormal Bravo pH Capsule Monitoring Test Associated With Higher Gastroesophageal Reflux Disease-Q Scores in Patients With Gastroesophageal Reflux Disease off Proton Pump Inhibitor Therapy

Lacy and colleagues conducted 48-hour wireless Bravo capsule monitoring in 204 GERD patients to compare results with the GERD-Q questionnaire. The investigators compared pH data and symptom-associated probability (SAP) for day 1, day 2, and total study time (48 hours). For 53% of the patients, the pH study was completed while the patients were taking proton pump inhibitor (PPI) therapy. Capsule monitoring revealed abnormal acid exposure in 17% of patients on PPIs and 52% of patients off PPI therapy. In patients who were studied off PPIs, the GERD-Q was associated with increased odds of an abnormal pH study and SAP, but the same was not true for patients studied while on PPIs. More frequent use of extra medications to treat GERD symptoms was associated with an abnormal pH study. The investigators concluded that higher GERD-Q scores were predictive of an abnormal pH study in patients evaluated while off PPI therapy.

Electron Microscopy Superior to Light Microscopy for Diagnosing Gastroesophageal Reflux Disease in Patients With Refractory Heartburn

The diagnosis of GERD can be challenging in patients who have ongoing heartburn despite the use of PPIs. Light microscopy (LM), which shows histologic changes in biopsies, is a suboptimal diagnosis method. Electron microscopy (EM) shows the dilation of intercellular space distance in the epithelium, but its sensitivity and specificity are unknown. Craft and associates set out to measure the effectiveness of this method by comparing the sensitivity and specificity of EM and LM on biopsies of patients with heartburn and normal endoscopy and pH-multichannel intraluminal impedance (MII) testing. The investigators found that, using rigorous criteria to diagnose GERD (including esophagitis on endoscopy or abnormal pH-MII), the sensitivity and specificity of EM was 83% and 88%, respectively, whereas the sensitivity and specificity of LM was 67% and 44%, respectively. Using less rigorous criteria to diagnose GERD (including a positive symptom index) yielded a 58% sensitivity and 100% specificity for EM. For LM, the sensitivity and specificity using these criteria were 67% and 50%, respectively. The investigators concluded that EM is superior to LM for excluding GERD in patients with refractory heartburn and that it provides good sensitivity, particularly in patients diagnosed using rigorous criteria.

Preliminary Results Suggest that Morning and Bedtime Dosing of Immediate-Release Omeprazole/Sodium Bicarbonate Are Equally Effective at Resolving Severe Erosive Reflux Esophagitis

Francis and colleagues are conducting a study to compare the effectiveness of morning and bedtime dosing of immediate-release omeprazole/sodium bicarbonate (IR-OME; Zegerid, Santarus) in achieving endoscopic resolution. By study end, the investigators plan to enroll 100 patients with esophagitis, randomized to receive

either morning or bedtime dosing of IR-OME. In the study, esophagogastroduodenoscopy is performed at baseline and at 8 weeks, and pH testing is offered to all subjects at 8 weeks. To date, the study has recruited 58 patients, 46 of whom have completed the study. Of the 21 patients randomized to morning dosing, 15 (71%) were healed at 8 weeks, and the 6 patients who did not achieve healing experienced improvements in severity. Of the 25 patients randomized to bedtime dosing of IR-OME, 19 (76%) healed, 4 improved, 1 had the same severity grade, and 1 worsened in severity. Too few pH studies were performed to detect differences in reflux patterns between morning and bedtime dosing schedules. The investigators found that these preliminary results suggest that both morning and bedtime dosing of IR-OME are effective in resolving severe erosive reflux esophagitis at 8 weeks.

High Rates of Persistently Abnormal Esophageal Acid Exposure Found Using pH-Multichannel Intraluminal Impedance Testing

In order to assess the outcomes of pH-MII testing in clinical practice, Madanick and colleagues reviewed data from 393 pH-MII studies performed between February 2006 and October 2008 in 375 patients visiting a motility laboratory at a large tertiary care center. The researchers found that 11% of patients were 1 year old or younger, 18% were between the ages of 1 and 17 years, and 71% were 18 years or older. Among all the studies in patients who were being treated with acid-suppressive therapy, 46% showed abnormal acid exposures, 13% showed significant nonacid reflux only (based on a high number of reflux events without abnormal acid exposure), 7% showed hypersensitivity (defined as normal acid exposures and normal reflux but a symptom index of ≥50% for the primary symptom), 33% were negative (showing no abnormal acid exposure, a normal number of reflux events, and a symptom index of ≤50%), and 2% of studies were not interpretable. The investigators concluded that a markedly higher proportion of studies showed abnormal acid exposure among patients receiving acid-suppressive therapy than has previously been reported in controlled studies.

Presentations in Endoscopy

Computed Tomography Enterography Is More Sensitive Than Capsule Endoscopy in the Diagnosis of Endoscopy-Negative Small-Bowel Tumors

Capsule endoscopy (CE) is a widely used imaging technology to evaluate the small bowel of patients with initial negative endoscopies, but small-bowel tumors can be difficult to detect, given their submucosal location. Hakim and associates compared the sensitivities of CE and computed tomography enterography (CTE) in detecting small-bowel tumors in 103 patients with newly diagnosed, endoscopy-negative small-bowel tumors. Of these patients, 41 had undergone CE, CTE, or both. The sensitivity of CE was found to be 29.6% in patients undergoing CE alone, whereas the sensitivity of CTE was 92.7% in patients receiving only that test. In patients undergoing both CE and CTE, the sensitivity of CTE and CE was 94.1% and 35.3%, respectively. Because only 17 patients underwent both CE and CTE, a head-to-head comparison of these 2 methods showed a strong trend in favor of CTE, but did not reach statistical significance.

Solid Pancreatic Lesions Larger Than 20 mm With Suspicious Cytology Have High Likelihood of Malignancy

Wagh and colleagues performed a database review to evaluate outcomes in patients with pancreatic lesions that were found to have suspicious or indeterminate cytology upon endoscopic ultrasound–guided fine-needle aspiration (EUS-FNA). The researchers reviewed records from 2002 to 2007 and categorized outcomes for 12 months following EUS-FNA. Among the 70 patients classified as having masses with suspicious or indeterminate cytology, 63% were women, and the mean age was 62 years. The diagnosis was adenocarcinoma in 47%, benign in 35%, and "other neoplasms" (including intraductal papillary mucinous neoplasms, neuroendocrine tumors, lymphomas, Schwannomas, pseudopapillary tumors, and mucinous cystadenomas) in 18% of patients. The mean size of the lesions was 29.4 mm, and 90% of adenocarcinomas were more than 20 mm in size, whereas 67% of benign cases were less than 20 mm. Most of the solid lesions with indeterminate cytology were adenocarcinomas. The researchers concluded that solid pancreatic lesions greater than 20 mm with suspicious cytology have a very high likelihood of malignancy.

High-Definition Colonoscopy Imaging Induces a Learning Effect in Clinical Practice

High-definition (HD) white-light colonoscopies may enable better detection of subtle mucosal changes and adenomas than standard-definition (SD) white-light colonoscopies. In this retrospective review, Buchner and associates compared adenoma detection with HD and SD colonoscopy in their practice between September 2006 and August 2007. They randomly placed HD scopes in 3 of 6 rooms and randomly assigned endoscopists and patients to HD or SD rooms throughout the study period. In all, 2,011 patients participated in the study; 1,188 were assigned to SD and 823 to HD. Adenomas were detected more frequently in the HD group than in the SD group (28.55% vs 23.40%; P=.01). Over time, detection rates increased in both HD and SD groups, suggesting a learning effect associated with better detection through HD colonoscopy.

Prophylactic 5F Pancreatic Duct Stents Are Easier and Faster to Place than 3F Stents in High-Risk Patients

Zolotarevsky and colleagues set out to compare 3 Fr × 6 cm (3F) and 5 Fr × 5 cm (5F) stents in terms of ease of placement, time and number of wires needed for placement, and spontaneous passage (SP) rates. Seventy-eight high-risk patients were randomized to receive 3F or 5F stents, and a total of 77 stents were placed. SP failure rates were similar between the 2 groups (10.5% for 5F stents and 10% for 3F stents). The study was inadequately powered to differentiate SP rates. However, the data collected confirmed that 5F stent placement was easier, as "difficult" or "very difficult" placement was reported more frequently for 3F stents. Fast placement (<5 minutes) was reported more frequently with 5F stents, and the average number of wires required for placement was lower in the 5F group. Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis occurred at similar rates for the 2 groups: 10.5% in the 5F group and 17.5% in the 3F group (P=.59). The investigators recommend the use of

5F stents for this population, as 5F stents are easier and faster to place and require fewer wires than 3F stents.

Split-Dose Polyethylene Glycol Electrolyte Provides Better Bowel Preparation Than Standard Dosing Before Colonoscopy

Split-dose administration of polyethylene glycol electrolyte (PEG-E) solution provides an alternative to single-dose administration. Lim and colleagues assessed the efficacy and tolerability of this approach in a group of inpatients undergoing colonoscopy at a tertiary care center. To date, 43 patients have been enrolled in the study, 21 of whom were randomly assigned to split-dose administration (2 liters at 5 PM the night before the procedure, and 2 liters at 5 AM on the day of the procedure) and 22 to single-dose administration (4 liters at 5 PM the night before the procedure). Adherence was similar for both groups. The group receiving split-dose administration reported less abdominal pain, better tolerability, and a higher level of willingness to repeat the procedure. There was a trend toward greater overall satisfaction with split-dose administration and better rectosigmoid cleansing, and this group had statistically significant better cleansing in the right and mid-colon. Using the Ottawa Preparation Quality Scale, split dosing performed better than standard dosing in this study.

Gastroenterologist-directed Sedation Similar to Anesthesiologist-directed Sedation in Endoscopic Retrograde Cholangiopancreatography Pancreatitis Outcomes

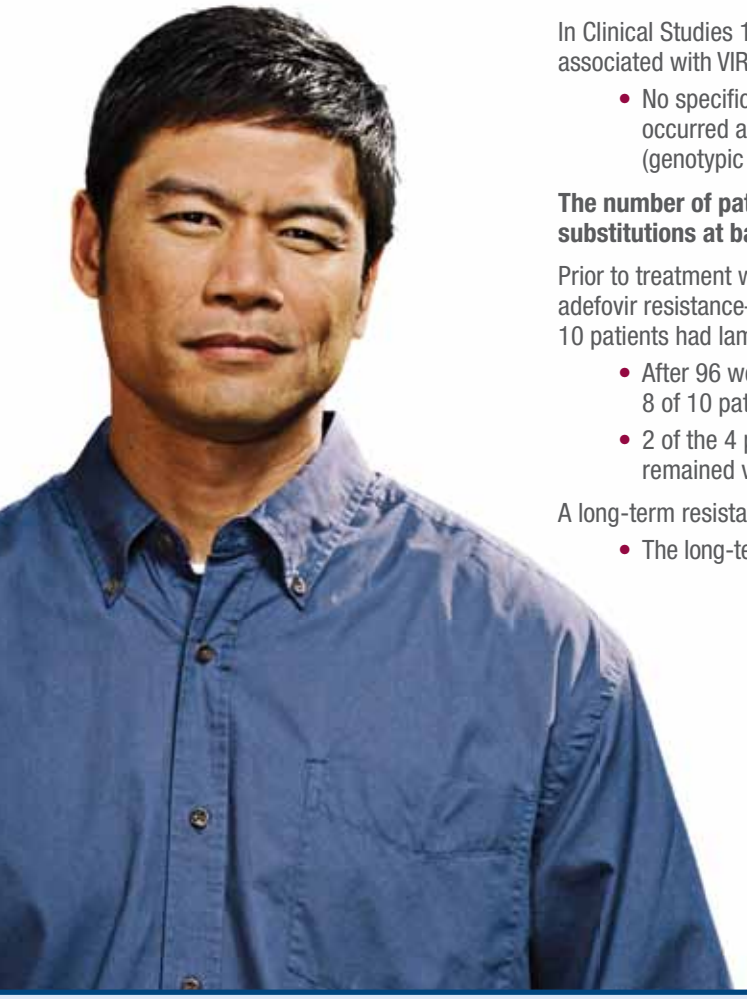
Because there is limited information on the cannulation success and complication rates for anesthesiologist-directed sedation (ADS) versus gastroenterologist-directed sedation (GDS) for ERCP, Mehta and associates performed a review of all ERCPs completed by senior endoscopists at a tertiary referral center over a 2-year period. During the first year of study, all ERCPs involved the use of GDS, whereas during the second year, all procedures used ADS. In all, 373 patients were included in the analysis, 183 patients who received GDS and 190 patients who received ADS. Overall cannulation success rates were similar between the 2 groups. The GDS group required more precut papillotomies to achieve cannulation, but this did not lead to a difference in postprocedure complication rates.

Meta-Analysis Finds Good Accuracy for Endoscopic Ultrasound in Differentiating Mucosal Versus Submucosal Superficial Lesions

Singh and colleagues performed a systematic review and meta-analysis to assess the sensitivity, specificity, and likelihood ratios of endoscopic ultrasound (EUS) in differentiating mucosal from submucosal esophageal carcinomas (EC). The authors pooled the results of 10 studies, which enrolled a total of 702 patients with EUS-based staging of EC. The pooled sensitivity and specificity of EUS in staging mucosal lesions were 0.88 and 0.83, respectively. For submucosal lesions, the sensitivity and specificity were 0.83 and 0.88. The area under the curve was 0.93 for both mucosal and submucosal lesions, suggesting good accuracy for EUS. However, the studies had a *P* value of X2 heterogeneity, indicating significant heterogeneity among studies. The investigators concluded that a variety of factors, including the location and type of lesion, method and frequency of EUS probe, and experience of the endosonographer, can all affect the diagnostic accuracy of EUS.

In adult patients with chronic hepatitis B and compensated liver disease in clinical trials

The confidence of 0% HBV resistance at 48 weeks (1 year) and 96 weeks (2 years)[1]



In Clinical Studies 102 and 103, no patients treated with VIREAD developed mutations associated with VIREAD resistance at 2 years[1]

- No specific amino acid substitutions in the HBV reverse transcriptase domain occurred at a sufficient frequency to be associated with resistance to VIREAD (genotypic or phenotypic analyses)[1]

The number of patients with lamivudine or adefovir resistance–associated substitutions at baseline was too small to establish efficacy in this subgroup.[1]

Prior to treatment with VIREAD (Studies 102, 103*, and 106†), 13 patients had adefovir resistance–associated substitutions (rtA181T/V and/or rtN236T) and 10 patients had lamivudine resistance–associated substitution (rtM204I/V)[1]

- After 96 weeks of VIREAD, 11 of 13 patients with adefovir-resistant HBV and 8 of 10 patients with lamivudine-resistant HBV achieved viral suppression[1]
- 2 of the 4 patients harboring both the rtA181T/V and rtN236T substitutions remained viremic following 24 weeks of VIREAD[1]

A long-term resistance surveillance program is ongoing for up to 8 years[2,3]

- The long-term resistance profile of VIREAD beyond 2 years is not known at this time

*In Studies 102 (HBeAg–) and 103 (HBeAg+), 641 adult patients with chronic hepatitis B who were primarily treatment-naïve entered a 48-week, randomized, double-blind, active-controlled treatment period comparing VIREAD 300 mg to adefovir dipivoxil 10 mg. 585 patients then rolled over with no interruption in treatment to open-label VIREAD for analysis through Week 96. At Week 72 or thereafter, all patients with HBV DNA ≥400 copies/mL were genotyped and phenotyped and provided the option to add emtricitabine. Cumulative VIREAD genotypic resistance analysis of paired pretreatment and on-treatment isolates was performed on patients remaining viremic with HBV DNA >400 copies/mL at the last evaluable visit after 96 weeks of treatment.[1-3]

†Ongoing Phase 2 study in adefovir–treatment-experienced patients (previously treated for 24-96 weeks with adefovir and had HBV DNA levels ≥1000 copies/mL at screening).[1]

My Liver.  *My Fight. My VIREAD.*

Important Safety Information for VIREAD

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 primarily on data from treatment of nucleoside–treatment-naïve subjects and a smaller number of subjects who had previously received lamivudine or adefovir. Subjects were adults with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease
- The numbers of subjects in clinical trials who had lamivudine- or adefovir-associated substitutions 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 continued Important Safety Information and brief summary of full Prescribing Information for VIREAD on the following pages.

Viread® 300mg tablets
tenofovir disoproxil fumarate

Important Safety Information for VIREAD (continued)

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, including those who have previously experienced renal events while receiving HEPSERA® (adefovir dipivoxil). Avoid administering VIREAD with concurrent or recent use of nephrotoxic drugs
- Coadministration with other products:
  - — Do not use with other tenofovir-containing products (eg, ATRIPLA® [efavirenz/emtricitabine/tenofovir disoproxil fumarate] and TRUVADA® [emtricitabine/tenofovir disoproxil fumarate])
  - — Do not administer 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 (eg, 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

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

GRADE 3/4 LABORATORY ABNORMALITIES REPORTED IN ≥1% OF SUBJECTS IN STUDIES 102 AND 103 (0-48 WEEKS)

VIREAD-treated subjects (n=426): 19% any ≥Grade 3 laboratory abnormality; 2% elevated creatine kinase (M: >990 U/L; F: >845 U/L); 4% elevated serum amylase (>175 U/L); 3% glycosuria (≥3+); 4% elevated AST (M: >180 U/L; F: >170 U/L); 10% elevated ALT (M: >215 U/L; F: >170 U/L). Grade 3/4 laboratory abnormalities were similar in nature and frequency in subjects continuing treatment for up to 96 weeks in these studies.

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 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.*

References: 1. VIREAD Prescribing Information. Foster City, CA: Gilead Sciences, Inc.; October 2009. **2.** Study 102. Data of file. Gilead Sciences, Inc. **3.** Study 103. Data on file. Gilead Sciences, Inc.

*Please see brief summary of full Prescribing Information for VIREAD, including **BOXED WARNINGS**, on the following pages.*

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 primarily on data from treatment of nucleoside-treatment-naïve subjects and a smaller number of subjects who had previously received lamivudine or adefovir. Subjects were adults with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease.
- The numbers of subjects in clinical trials who had lamivudine- or adefovir-associated substitutions 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 subjects 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]			
	≥50	30–49	10–29	Hemodialysis Patients
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, including VIREAD, 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, including patients who have previously experienced renal events while receiving HEPSERA. 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 subjects 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 subjects receiving VIREAD + lamivudine + efavirenz (-2.2% ± 3.9) compared with subjects 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 subjects vs. 21% of the stavudine-treated subjects 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 subjects in the VIREAD group and 6 subjects 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 subjects with chronic hepatitis B (0102 and 0103), more subjects treated with VIREAD during the 48-week double-blind period experienced nausea: 9% with VIREAD versus 2% with HEPSERA. Other treatment-emergent adverse reactions reported in >5% of subjects treated with VIREAD included: abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain, and skin rash. No significant change in the tolerability profile (frequency, nature, or severity of adverse reactions) was observed in subjects continuing treatment with VIREAD for up to 96 weeks in these studies.

Table 2 Grade 3/4 Laboratory Abnormalities Reported in ≥1% of VIREAD-Treated Chronic Hepatitis B Subjects in Studies 0102 and 0103 (0-48 Weeks)

	VIREAD (N=426)	HEPSERA (N=215)
Any ≥ Grade 3 Laboratory Abnormality	19%	13%
Creatine Kinase (M: >990U/L; F: >845 U/L)	2%	3%
Serum Amylase (>175 U/L)	4%	1%
Glycosuria (≥3+)	3%	<1%
AST (M: >180 U/L ; F: >170 U/L)	4%	4%
ALT (M: >215 U/L; F: >170 U/L)	10%	6%

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 subject had evidence of decompensation. ALT flares typically resolved within 4 to 8 weeks without changes in study medication. Grade 3/4 laboratory abnormalities were similar in nature and frequency in subjects continuing treatment for up to 96 weeks in these studies. **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, including angioedema, 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 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 (tenofovir disoproxil fumarate) 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:

- The use of VIREAD has not been shown to reduce the risk of transmission of HBV to others through sexual contact or blood contamination. Patients should be advised to continue to practice safer sex and to use latex or polyurethane condoms to lower the chance of sexual contact with any blood fluids such as semen, vaginal secretions or blood. Patients should be advised never to re-use or share needles.
- 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 and ATRIPLA 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.

REFERENCES: 1. VIREAD® (tenofovir disoproxil fumarate) Prescribing Information. Foster City, CA: Gilead Sciences, Inc.; October 2009.

GILEAD

Presentations in Hepatology

Tenofovir Disoproxil Fumarate Effective in Producing Continuous Viral Suppression in Patients With Chronic Hepatitis B

Marcellin and associates presented preliminary 3-year data from an ongoing trial of tenofovir disoproxil fumarate (TDF; Viread, Gilead Sciences) in patients with hepatitis B e antigen (HBeAg)-negative chronic hepatitis B (CHB). In the initial study, patients were randomized to receive once-daily TDF at 300 mg/day or adefovir dipivoxil (ADV; Hepsera, Gilead Sciences) at 10 mg/day. After 48 weeks, patients with a biopsy at week 48 were switched to open-label TDF for up to an additional 7 years with the option to add emtricitabine as a fixed-dose combination therapy. To date, 328 patients have completed week 144 of the study. In a long-term intent-to-treat (ITT) analysis, 88% of the patients had low levels of hepatitis B virus (HBV; DNA of less than 400 c/mL). In an on-treatment analysis, 99.1% of patients had low levels of HBV DNA, 3 patients had high levels, and 1 additional patient discontinued with high levels of HBV DNA. The overall mean alanine aminotransferase (ALT) was 33 U/L. TDF was well tolerated, with potent, continuous viral suppressions and no mutations associated with TDF resistance at 3 years.

In a study using the same methodology, Heathcote and colleagues presented 3-year data for a trial of TDF in patients with HBeAg-positive CHB. In this trial, 214 patients completed week 144. Using a long-term evaluation analysis (ITT), the researchers found that 78% of patients had low levels of HBV DNA. In an on-treatment analysis, 95% of the patients who had received TDF for 3 years and 91% of those who had received ADV for 1 year followed by 2 years of TDF had low levels of HBV DNA. Overall, 14 patients had high levels of HBV DNA and 3 patients had high levels at their last available time point prior to discontinuation. The overall mean ALT was 38.5 U/L. No patients discontinued due to adverse events, and there were no deaths during the study. The investigators concluded that these preliminary results indicate that TDF was well tolerated and produced potent and continuous viral suppression.

Extended Entecavir Treatment Produces Significant Viral Load Reduction and Alanine Aminotransferase Normalization in Chronic Hepatitis B Patients

In a retrospective cross-sectional study, Baqai and associates examined the long-term effects of entecavir (Baraclude, Bristol-Myers Squibb) in patients with CHB. The patient population included 109 men and 44 women who had been treated with entecavir for at least 12 months. At the start of therapy, the mean ALT was 12 U/L. Of the 85 patients with an elevated ALT, 82% had a biochemical response to therapy at 12 months. In patients who had baseline HBV DNA levels of less than 8 log, the rates of virologic response were 78%, 92%, and 98% at 12, 24, and 36 months of therapy, respectively. In patients with baseline HBV DNA of greater than 8 log, the response rates were 69%, 75%, and 86%, respectively. In subgroup analyses, the researchers found that the response to entecavir treatment was significantly better in treatment-naive patients than in those previously exposed to lamuvidine and ADV. In addition, responses were better in patients with HBeAg-negative precore mutations and low baseline HBV DNA.

PROVE3 Study Finds Benefit of Sustained Virologic Response With Telaprevir-based Regimen in Hepatitis C Genotype 1-infected Patients Who Failed Prior Treatment

PROVE3 is a randomized phase II study assessing the efficacy and safety of telaprevir (VX-950, Vertex/Johnson & Johnson) plus peginterferon alfa-2a (P; Pegasys, Genentech) with or without ribavirin (R) in hepatitis C virus (HCV) genotype 1 patients who failed previous PR treatment. Patients were randomized to receive 1 of 4 protocols: telaprevir/PR for 24 weeks followed by PR for 24 weeks; telaprevir/P for 24 weeks followed by PR for 24 weeks; telaprevir/P for 24 weeks or placebo/PR for 24 weeks followed by PR for 24 weeks; or PR for 48 weeks. Overall, the sustained virologic response (SVR) rates in groups receiving telaprevir treatment were

significantly higher than in those not receiving it. All patients who completed a telaprevir regimen and achieved SVR maintained virologic response 48 weeks after the end of treatment, except for 1 patient who was lost to follow-up. The safety profile in this population was similar to that observed in treatment-naive patients.

Researchers Optimize Predictive Model of Individual Chance for Sustained Virologic Response in Patients With Chronic Hepatitis C Treated With Pegylated Interferon Alfa-2a and Ribavirin

Martens and colleagues developed a predictive model of SVR in hepatitis C treatment with peginterferon alfa-2a and ribavirin based upon study data. Recently, Mauss and associates updated this model to represent real-world conditions. They performed stepwise multivariate logistic analyses on data from 5,018 patients collected through the Association of German Gastroenterologists. They confirmed the overall validity of Martens' model, but they modified it to provide validity in a nontrial setting. The researchers derived a new model yielding improved areas under receiver operation characteristic (ROC) compared with the Martens model. As with the older model, the updated version includes HCV genotype, HCV-RNA, age, total cholesterol, ALT, and gamma-glutamyl transpeptidase. In addition, it includes serum glucose and thrombocytes as independent predictors of response to treatment. Unlike the older model, liver fibrosis was dropped from this model, as a result of a low number of liver biopsies in the patient population.

Acute Rejection Is the Key Predictor of Graft Loss and Severe Hepatitis C Virus Disease in Hepatitis C Virus–HIV Co-infected Liver Transplant Patients

Terrault and associates performed an analysis comparing 1- and 3-year survival rates and rates of severe HCV disease in liver transplant patients co-infected with HCV and HIV versus those infected with HCV alone. They followed 81 HCV-HIV patients and 213 HCV controls for a median of 1.5 and 1.4 years, respectively. Both groups of patients had similar gender characteristics, Model for End-Stage Liver Disease scores at the time of transplant, rates of hepatocellular carcinoma, rates of dual kidney-liver transplant, and rates of HCV-positive donors. HCV-HIV co-infected patients had lower median age, lower donor age, lower body mass index (BMI) at enrollment, higher rates of treated acute infection, and higher rates of HCV therapy than HCV-only infected patients. One- and 3-year graft survival rates were 71% and 59%, respectively, in HCV-HIV patients, and 86% and 67%, respectively, in HCV patients. Although patient and graft survival rates were lower in co-infected patients, the key predictor of graft loss and severe HCV disease was treated acute rejection. The investigators concluded that better markers of immune activation-suppression are needed in the HCV-HIV population, and that dual kidney-liver transplants, low BMI, and the use of HCV-positive donors increase the risk of poor outcomes.

Hepatitis C Virus SPRINT-1 Trial Finds Response-guided Therapy May Be Powerful Tool to Individualize Boceprevir Combination Treatment

In the SPRINT-1 trial, Kwo and colleagues investigated HCV patient response to a 4-week lead-in of pegylated interferon alfa-2b (PegIntron, Schering-Plough) plus ribavirin prior to the introduction of boceprevir (Schering-Plough) for 24 or 44 weeks. The patients studied all had genotype-1 HCV and included African Americans (15%), cirrhotics (7%), and those with a high viral load (90%). Sixty-four percent of patients had undetectable HCV-RNA levels after 4 weeks of triple therapy following the lead-in, and 82% had a high rate of SVR following a shortened 28-week treatment duration, with similar SVR rates in long and

Table 1. SVR After 28 and 48 Weeks of Boceprevir Combination Treatment in the SPRINT-1 Trial

	28-Week Treatment			48-Week Treatment		
	Patient Distribution			Patient Distribution		
Time to First Negative (wk)	n	%	SVR	N	%	SVR
≤8	66	64%	82% (54/66)	66	64%	94% (62/66)
>8 – ≤16	19	18%	21% (4/19)	19	18%	79% (15/19)
>16 – never	18	17%	0% (0/18)	18	17%	0% (0/18)

SVR=sustained virologic response.

short treatment arms (Table 1). The investigators concluded that only a small percentage of treatment-naive genotype-1 patients will require therapy for more than 28 weeks and that measuring responses at week 8 may be a useful way to predict an individual's need for longer treatment duration. The SPRINT-2 trial will prospectively confirm the benefits of this paradigm.

Canadian POWeR Program Examines Determinants of Virologic Relapse in Hepatitis C Patients

Cooper and associates reported on the POWeR Program, an open-label observational study that followed 1,950 HCV patients between 2002 and 2007. All patients received at least 1 dose of pegylated interferon alfa-2b and ribavirin. The investigators compared end-of-treatment responses by genotype and found that the responses were 51% in genotype-1 patients, 86% in genotype-2 patients, and 77% in genotype-3 patients. The rates of SVR were 39%, 73%, and 65% for genotype-1, genotype-2, and genotype-3, respectively. The relapse rate was significantly higher among genotype-1 patients (25%) than in genotype-2 and genotype-3 patients (16%; $P<.0001$). For patients with liver biopsy specimens, relapse rates in genotype-1 patients were significantly higher among those patients with advanced fibrosis or cirrhosis compared with those who had minimal or mild fibrosis. The investigators concluded that baseline viral load and weight were not independently associated with higher relapse rates, but advanced fibrosis and cirrhosis significantly increased relapse rates in genotype-1 patients.

Vigorous Exercise Associated With Lower Nonalcoholic Fatty Liver Disease Severity

Federal guidelines recommend 150 or more minutes of moderate exercise or 75 or more minutes of vigorous exercise per week. Kistler and colleagues performed a study to determine the relationship between exercise levels and the histologic severity of nonalcoholic fatty liver disease (NAFLD). They followed 609 adult patients with NAFLD, 56% of whom were classified as sedentary, 19% of whom met the moderate exercise targets, and 26% of whom met vigorous targets. When the researchers compared disease severity among the exercise groups, they found that sedentary patients and moderate exercisers had similar severity levels, whereas subjects meeting vigorous targets had significantly reduced odds of having steatohepatitis, with an odds ratio of 0.58. For subjects who doubled the vigorous exercise target (performing 150 or more minutes of vigorous exercise per week), the odds ratio was 0.39.

Presentations in Inflammatory Bowel Disease

Mesalamine Persistence Levels Are Low, But MMX Mesalamine Shows Highest Persistency Rates Among Formulations

Kane and colleagues performed an analysis of persistency rates among 19,398 patients identified as continuing mesalamine therapy for longer than 3 months according to refill records in a pharmacy database. Patients who refilled their prescription within a time frame of up to double the duration of their prescription were defined as "continuing," whereas those who refilled their prescription after this time frame were considered to "restart" therapy. Among those who were persistent at 3 months, the rate of persistency at 12 and 18 months was highest in patients receiving MMX mesalamine (Lialda, Shire) compared with those receiving delayed-release mesalamine (Asacol, Procter & Gamble), controlled-release mesalamine (Pentasa, Shire), olsalazine (Dipentum, UCB), or balsalazide (Colazal, Salix) (Table 2). The researchers suggested that higher persistency with MMX mesalamine may be explained by once-daily dosing, a lower pill burden, and higher levels of patient satisfaction.

In a related study, Kane and colleagues reviewed the refill records of 44,191 patients starting a new course of therapy with MMX mesalamine, delayed-release mesalamine, controlled-release mesalamine, olsalazine, or balsalazide. They found that a higher proportion of patients receiving MMX mesalamine were persistent at 3 months and 18 months (60% and 13%, respectively) compared with those receiving delayed-release mesalamine (41% and 5%), controlled-release mesalamine (41% and 6%), balsalazide (43% and 6%), or olsalazine (35% and 6%). In general, children were more persistent than adults, though the most persistent subgroup was patients 41–55 years of age receiving MMX mesalamine. Overall, persistence rates were low, varied by prescriber, and decreased over time. The researchers concluded that further intervention strategies might be needed to improve persistence and maximize mesalamine treatment benefits.

QDIEM Study Shows Once-Daily Dosing of Delayed-Release Oral Mesalamine to Be As Effective As Twice-Daily Dosing for Maintenance of Remission in Ulcerative Colitis

The QDIEM study compared the effectiveness of once-daily dosing of delayed-release mesalamine at maintaining remission in patients with ulcerative colitis (UC). A total of 1,023 patients were randomized to receive once- or twice-daily dosing schedules of delayed-release mesalamine, and all received the same total daily dose of mesalamine as they received prior to study entry (range,

Table 2. Persistency at 12 and 18 Months of Various Mesalamine Therapies

	12-month persistency (continuing)	12-month persistency (continuing + restart)	18-month persistency (continuing)	18-month persistency (continuing + restart)
MMX mesalamine (n=3,687)	34%	47%	22%	36%
Delayed-release mesalamine (n=10,727)	22%	34%	13%	25%
Controlled-release mesalamine 500 mg (n=2,331)	23%	35%	14%	25%
Controlled-release mesalamine 250 mg (n=555)	22%	33%	11%	22%
Olsalazine (n=126)	29%	36%	16%	27%
Balsalazide (n=1,972)	23%	35%	13%	24%

1.6–2.4 g/day). In all, 70% of patients received 2.4 g/day, 28% received 1.6 g/day, and 2% received 2.0 g/day. The primary objective of noninferiority was met with 90.5% and 91.8% of patients receiving once- and twice-daily dosing, respectively. The time to relapse and incidence of serious adverse events was similar between the 2 dosing schedules. The investigators concluded that once-daily dosing was as effective as twice-daily dosing for the maintenance of remission in patients with UC.

PRECiSE 3 Study Finds Good Remission Rates for Certolizumab Pegol in Crohn's Disease

PRECiSE 3 is a 3-year follow-up study assessing the sustainability of remission maintenance of certolizumab pegol (Cimzia, UCB) following the 6-month PRECiSE 2 study. One hundred and forty-one patients who were in remission following 26 weeks of therapy in PRECiSE 2 were included in this analysis. Patients received 400 mg of certolizumab pegol every 4 weeks and were evaluated at 1.5, 2.5, and 3.5 years. Using an observed case analysis, remission rates were 56%, 38%, and 31% at 1.5, 2.5, and 3.5 years, respectively. Using last observation carried forward analyses, the rates were 83%, 75%, and 82%, respectively. Among patients in remission at the start of the follow-up study, 61%, 41%, and 36% of patients were in remission at 1, 2, and 3 years, respectively. The researchers concluded that certolizumab pegol demonstrated long-term remission without dose escalation in patients who initially responded to therapy and that no new safety concerns were observed during the follow-up period.

Expert Panel Evaluates Appropriateness of Concomitant Immunomodulators With Anti-Tumor Necrosis Factor □ Agents for the Treatment of Crohn's Disease

Melmed and associates aimed to develop a consensus on the use of immunomodulators with anti-tumor necrosis factor (TNF) □ therapy in Crohn's disease (CD) patients. They constructed 134 theoretical scenarios and presented them to the BRIDGe Group, a panel of 13 gastroenterologists experienced in the treatment of inflammatory bowel disease (IBD). Panelists confidentially rated the appropriateness of using concomitant immunomodulators for each scenario. In all, the concomitant use of immunomodulators was rated as "appropriate" for 63 scenarios, "uncertain" for 60 scenarios, and "inappropriate" for 11 scenarios. Immunomodulator use was generally considered to be more appropriate in women, in patients with more extensive disease, shorter duration of disease, perianal disease involvement, a history of prior surgery, and in those older than 26 years of age. An "uncertain" rating was more likely in patients previously failing immunomodulator therapy and in those in anti-TNF □–induced remission. A rating of "inappropriate" was most often assigned for scenarios involving young men and in some scenarios involving uncomplicated disease. Ratings were not influenced by smoking status or the particular anti-TNF □ agent used. The panelists had a high level of agreement on ratings, disagreeing on ratings of only 6 of the 134 scenarios.

Long-term Maintenance With Mesalamine Granules in Patients Previously Treated With Corticosteroids Is Associated With a Low Incidence of Ulcerative Colitis–related Adverse Events

Mesalamine granules (Apriso, Salix) combine delayed- and extended-release mechanisms to allow for prolonged distribution of mesalamine throughout the colon with once-daily dosing. In 2 earlier studies, a higher proportion of patients treated with mesalamine granules who had previously been treated with steroids remained in remission compared with placebo-treated patients who also had a history of steroid use (77% vs 55%; $P<.004$). In this study, Lichtenstein and colleagues followed these patients in an open-label extension study. Seventy-four subjects treated with mesalamine granules continued open-label therapy and were followed for up to 30 months. During the double-blind study period, mesalamine granules reduced the risk of treatment-related adverse events of UC and UC-related symptoms over 6 months (hazard ratio, 0.508), and this low probability of UC recurrence was sustained during the open-label period. The rate of adverse events leading to premature withdrawal was similar for placebo and drug-treated patients during the double-blind period, and declined during the open-label phase.

Mucosal Healing Is Correlated With Modified Pouchitis Disease Activity Index Scores and Pouchitis Disease Activity Index Endoscopy Scores, But Not Pouchitis Disease Activity Index Symptom Scores in Patients With Pouchitis

Consensus is lacking on the utility of mucosal healing as an endpoint in clinical trials of IBD. Wang and colleagues performed a study to assess the correlation between endoscopic mucosal healing and inflammation scores on pouch endoscopy and symptom scores in patients with pouchitis. The researchers analyzed medical records of 43 consecutive patients with ileal pouch-anal anastomosis

in a pouchitis clinical database. Seventy percent of the patients were men, and the mean age was 49±13 years, with a mean duration of IBD of 18±11 years. When ulcers of the pouch on endoscopy were re-evaluated, the ulcer score was positively correlated with the modified pouchitis disease activity index (PDAI) endoscopy score in patients evaluated before antibiotic treatment and at the first and second post-treatment pouchoscopy. There was a positive correlation between mucosal ulceration scores and modified PDAI scores, and the correlation between ulceration score and PDAI symptom scores fell into a wide range. The investigators concluded that mucosal healing or ulcer scores may provide additional information for the diagnosis and prognosis of pouchitis.

SONIC Extension Study Finds Addition of Azathioprine to Infliximab Therapy Useful in Maintaining Remission in Crohn's Disease Patients

In the SONIC study, 508 immunomodulator-naive patients were randomized to receive azathioprine 2.5 mg capsules and placebo infusions (AZA+PBO), placebo capsules and infliximab 5 mg/kg infusions (PBO+IFX), or azathioprine and infliximab for 30 weeks (AZA+IFX), with the option of a double-blinded extension through week 50. At week 26, the proportion of patients in steroid-free remission was 56.8% for AZA+IFX, 44.4% with PBO+IFX, and 30.0% with AZA+PBO. Fifty-five percent of the original patients entered the extension study. Of these patients, the proportion in steroid-free remission at week 50 was 72.2% for AZA+IFX, 60.8% for PBO+IFX, and 54.7% for AZA+PBO. The safety profile of the 3 regimens was similar. The investigators concluded that patients treated with infliximab plus azathioprine or infliximab alone are more likely to maintain CD remission than those receiving azathioprine alone.

Adalimumab Sustains Clinical Remission in Patients With Moderate to Severe Crohn's Disease in the ADHERE Extension Study

The CHARM study enrolled 854 CD patients who received open-label induction with adalimumab (Humira, Abbott) at weeks 0 and 2. The patients were then randomized to receive placebo, adalimumab 40 mg every other week, or adalimumab 40 mg every week. Patients who experienced flares at or after week 12 could receive open-label adalimumab every other week, switching to subsequent weekly therapy if appropriate. After the 56-week study ended, patients were eligible to enroll in the ADHERE study. In this extension study, blinded patients received 40 mg adalimumab every other week, and open-label patients continued their study regimen. A total of 467 patients enrolled in the ADHERE study. In a last observation carried forward analysis, 83% of patients were in remission 3 years after enrollment in the CHARM trial. Using a nonresponder imputation analysis, the rate of remission at 3 years was 64%. The investigators concluded that most of the patients in remission at the end of the CHARM trial stayed in remission for an additional 2 years in the ADHERE study.

Presentations in Irritable Bowel Syndrome

Patient-reported Outcome Measures Found to Be Useful in Assessing Irritable Bowel Syndrome-C Symptom Changes in a Phase IIb Study of Linaclotide

Linaclotide (Ironwood Pharmaceuticals/Forest Laboratories) is a minimally absorbed peptide agonist of the intestinal guanylate cyclase type-C receptor. Carson and associates reported on a phase IIb, randomized, double-blind, placebo-controlled study of linaclotide in constipation-predominant irritable bowel syndrome (IBS-C) patients and evaluated the measures used to assess changes in symptom severity used in the trial. Four hundred and twenty adults were randomized to receive placebo or 4 doses of oral linaclotide per day. Patients completed 12 IBS-C patient-reported outcome (PRO) measures at baseline, at 12 weeks of treatment, and at 2 weeks post-treatment. The investigators evaluated the reliability of PRO measures and found excellent test-retest reliability, high sensitivity to change, and good results for discriminant validity tests. Linaclotide significantly improved abdominal pain, discomfort, bloating, and bowel habits, and the PRO measures were found to be reliable, valid, responsive, and useful gauges of change in IBS-C severity.

Rifaximin Improves Symptoms in Patients With Irritable Bowel Syndrome and Small Intestinal Bacterial Overgrowth

Infantalino and associates performed a retrospective study to evaluate the efficacy of rifaximin (Xifaxan, Salix) in patients with small intestinal bacterial overgrowth (SIBO) and IBS, and to determine the significance of the type of gas excreted during lactulose breath testing (LBT) in response to treatment. The researchers reviewed charts of 145 patients with SIBO and IBS who received rifaximin over a 3-year period. Rifaximin improved symptoms in 59% of patients and eradicated SIBO in 12%. The investigators found that a greater percentage of patients experienced improvement on higher doses and longer durations of therapy with rifaximin. The presence of hydrogen gas detected by the baseline LBT was significantly associated with SIBO eradication (P=.03) and symptom improvement (P=.03) with rifaximin therapy.

"Constipation Minus Diarrhea" Score Found to Be Useful in Assessing Constipation Symptom Outcomes

The tendency for patients to exaggerate or minimize IBS symptoms is a problem in evaluating treatment success. Kunkel and colleagues set out to validate a new tool combining diarrhea and constipation severity ratings using a visual analogue score (VAS). Eighty-four IBS patients were asked to rate their constipation (C) and diarrhea (D) symptoms on a VAS scale from 0–100. The VAS scores for C, D, and C minus D were compared with true stool events (including frequency and consistency) using the Bristol stool score. Using the C score alone discriminated constipation and nonconstipation groups, but not as effectively as using the C minus D score. The investigators found that using the C minus D score was a better predictor of stool diary-based measures of constipation compared with constipation VAS-measured severity alone.

Use of Proton Pump Inhibitors Does Not Explain Abnormal Hydrogen Breath Testing in Patients With Irritable Bowel Syndrome

SIBO has been associated with IBS, and IBS patients commonly take PPIs for GERD and dyspepsia. In this study, Hong and colleagues examined the relationship between SIBO and PPI use in a large population of patients undergoing hydrogen breath testing (HBT). They performed a chart review of 2,092 patients who underwent glucose or lactulose HBT over a 3-year period at 2 academic medical centers. IBS status was defined according to Rome III criteria, and non-IBS patients included those with a history of diabetes, cirrhosis, collagen vascular disease, gastrointestinal surgery, or thyroid disease. In all, the analysis included 507 IBS patients and 1,619 non-IBS patients who underwent HBT for diarrhea, constipation, or bloating. The researchers found that although PPI use was an independent predictor of positive HBT in non-IBS patients, it was a negative predictor of positive HBT in IBS patients. They concluded that PPI therapy does not explain the increased prevalence of abnormal HBT results in IBS patients.

Table 3. Colonic Transit and Stool Passage With Colesevelam or Placebo

	Placebo (N=12)	Colesevelam (N=12)
Colonic filling at 6 h (%)	64.5±8.17	58.5±8.72
Colonic transit GC 4 h	0.81±0.19	0.42±0.16
Colonic transit GC 24 h*	3.30±0.33	2.68±0.32
Colonic transit GC 48 h	4.47±0.20	4.65±0.13
Ascending colon emptying $t_{1/2}$ (h)	14.9±3.58	18.85±2.88
Stool frequency per day	2.25±0.34	2.14±0.31
Stool consistency by Bristol Stool Form Scale**	4.57±0.35	3.78±0.27
Ease of stool passage (scale 1–7)***	4.39±0.11	4.18±0.14

*P=.18; **P=.12; ***P=.047.

GC=geometric center.

Bile Acid Binding Slows Colonic Transit and Eases Stool Passages in Irritable Bowel Syndrome Patients With Diarrhea

Bile acid malabsorption is found in up to 70% of patients with chronic diarrhea. Odunsi and colleagues measured the effects of the bile acid binder colesevelam hydrochloride (WelChol, Daiichi Sankyo) on gastrointestinal and colonic transit, bowel function, and intestinal and colonic permeability in patients with diarrhea-predominant IBS (IBS-D). The study enrolled 24 female IBS-D patients who were randomized to colesevelam 1.875 g/day or placebo for 14 days. The compliance rate for the study was 100%. There was a tendency for a treatment effect on overall colonic transit at 24 hours (P=.18), with 7 of 12 patients on colesevelam experiencing greater than 0.7 geometric center unit retardation of colonic transit at 24 hours (Table 3). Colesevelam therapy was associated with greater ease of stool passage (P=.047) and firmer stool consistency (P=.12). The researchers concluded that bile acid binding with colesevelam deserves further study in IBS-D, as it showed a tendency for improvements in transit time and ease of stool passage in this population.

GASTROENTEROLOGY & HEPATOLOGY™

Author Guidelines 2010

Introduction

Gastroenterology & Hepatology (G&H) is a peer-reviewed journal addressing the interrelated fields of gastroenterology and hepatology, including content on endoscopy, inflammatory bowel disease, gastroesophageal reflux disease, and other pertinent topics. Dr. Gary R. Lichtenstein is the Editor-in-Chief. The Associate Editors of the journal are Drs. Stephen Hanauer, Eugene Schiff, Joel Richter, and John Baillie.

Scope of Manuscripts

G&H will consider the following types of articles for publication:

Reviews: Reviews are overview articles that summarize and synthesize the literature to date on various topics in a scholarly and clinically relevant fashion. Reviews may focus on one or a number of disease states. Suitable topics include diagnosis and staging; treatment (all modalities); outcomes; quality of life; pain management and palliative care; epidemiology; cost-effectiveness.

Original Reports: Original reports present methodologically sound original data on topics of interest to the clinician.

Letters to the Editor: All letters will be considered for publication.

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Diagnostic and Treatment Algorithms: Original algorithms intended to aid diagnosis and treatment will be considered for publication.

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General Information: The manuscript should be e-mailed to cl@clinicaladvances.com. Please use "Manuscript Submission" as the subject of the e-mail and list the file names of all attachments in the body of the e-mail so that we may confirm receipt of all materials.

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Length: Approximate word counts are as follows: Reviews, 3,000–4,000 (please try to limit reference list to 100 items); Original Reports, 3,000; Letters, 500; Clinical Case Studies, up to 2,000. Algorithms should contain a sufficient introduction, a flowchart or series of graphs that fill 5 or more journal pages, and a concise summary. Inclusion of tables and figures with all article types is encouraged. Please include appropriate keywords.

Spacing: One space after commas and periods. Manuscripts should be double spaced.

Abstract and Keywords: All reviews and original reports must contain an abstract approximately one paragraph long and up to 6 keywords.

References: All submissions should be referenced. Please use American Medical Association style. References must be numbered and referred to in the text by numbers. Manuscripts with incorrect reference style may be returned, or publication may be delayed. See the following examples:

1. Davis JT, Allen HD, Powers JD, et al. Population requirements for capitation planning in cardiac surgery. *Arch Pediatr Adolesc Med*. 996;150:257-259.

2. Stryer L. *Biochemistry*. 2nd ed. San Francisco, Calif: WH Freeman Co; 1981:559-596.

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1. Original manuscript: Submit a double-spaced Word file electronically to **cl@clinicaladvances.com**.

2. Contact information for all authors, including name, mailing address, phone, fax, e-mail. Please note corresponding author.

3. Titles and affiliations for all authors

4. Any required permission letters to reprint copyrighted material.

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.

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Shire

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**

At 1200 mg, the highest 5-ASA dose per tablet[1]

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.

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.

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