GASTROENTEROLOGY & HEPATOLOGY™
The Independent Peer-Reviewed Journal

A Special Meeting Review Edition

Fall 2010

THE GASTRO & HEP REPORT

Presentation summaries in:

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

- The 45th Annual Meeting of the European Association for the Study of the Liver
  April 14–18, 2010
  Vienna, Austria
- Digestive Disease Week 2010
  May 1–5, 2010
  New Orleans, Louisiana

Indexed through the National Library of Medicine (PubMed/Medline), PubMed Central (PMC), and EMBASE

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
Pruritus	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

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.

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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Rev. 6/09 LIA-01794

Shire

For patients with active, mild to moderate ulcerative colitis (UC),

There are a number of reasons physicians are choosing Lialda®

- Lialda is indicated for the induction of remission in patients with active, mild to moderate UC. Safety and effectiveness of Lialda beyond 8 weeks have not been established
- Lialda offers flexibility of both 2.4 g and 4.8 g once-daily doses
- Lialda is covered on most commercial managed care plans[1]*

*Reported for commercial plans, including BCBS.

- Over **1 million** prescriptions filled[2]
- Prescribed to over **150,000** patients[3]

Important Safety Information

- 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 allergic to sulfasalazine.
- Patients with pyloric stenosis may have prolonged gastric retention of Lialda, which could delay mesalamine release in the colon.
- 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. 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. Caution should be taken when prescribing Lialda to patients with conditions that predispose them to myocarditis or pericarditis.
- 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. In patients with renal impairment, 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.
- 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.
- 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 adjacent page.

References: 1. Fingertip Formulary. May 24, 2010. **2.** IMS Health, NPA *Plus*™, March 2007–January 2010, TRxs. **3.** Total Patient Tracker (TPT) from SDI; January 2007–December 2009. **4.** Kamm MA, Sandborn WJ, Gassull M, et al. Once-daily, high-concentration MMX mesalamine in active ulcerative colitis. *Gastroenterology*. 2007;132:66-75.

1200 mg of 5-ASA, once daily[4]

Lialda® with MMX®
(mesalamine) 1.2g
delayed release tablets

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GASTROENTEROLOGY & HEPATOLOGY™

THE GASTRO & HEP REPORT

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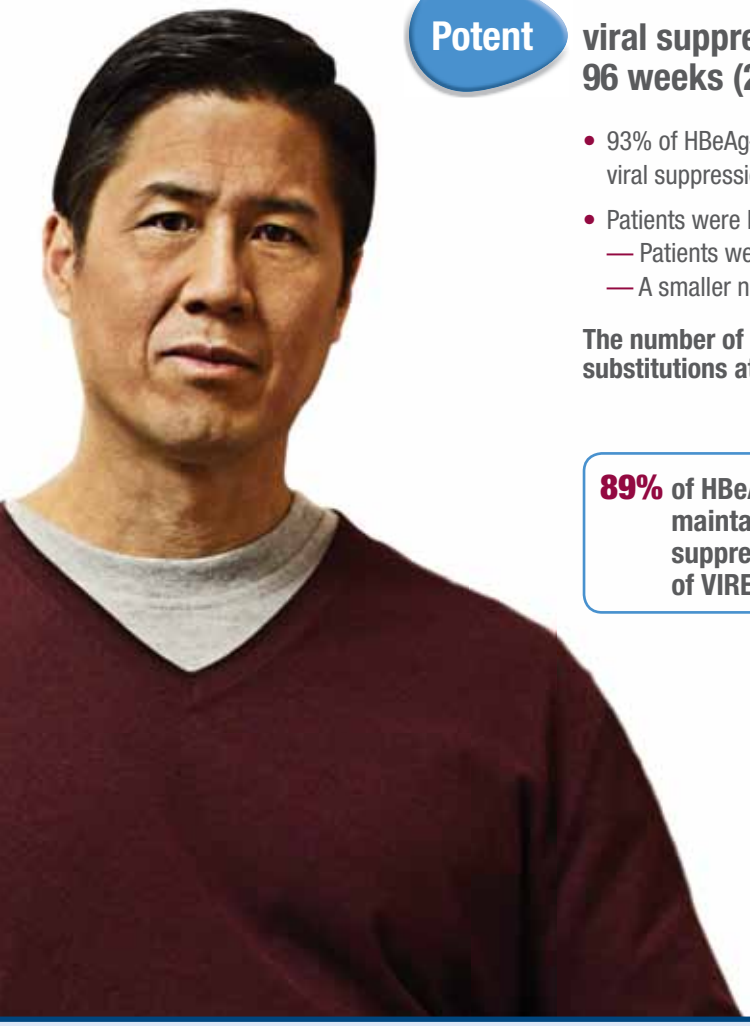
In adult patients with chronic hepatitis B and compensated liver disease in clinical trials

The power of viral suppression



Potent viral suppression at 48 weeks (1 year) maintained through 96 weeks (2 years) in Studies 102 and 103[1*]

- 93% of HBeAg– patients (n=250) and 76% of HBeAg+ patients (n=176) achieved viral suppression (HBV DNA <400 copies/mL) at 1 year with VIREAD[1]
- Patients were HBeAg– and HBeAg+ adults with compensated liver disease[1]
  - Patients were primarily nucleoside–treatment-naïve
  - A smaller number of patients had previously received lamivudine or adefovir

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

89% of HBeAg– patients maintained viral suppression with 2 years of VIREAD*(n=235)[1]

81% of HBeAg+ patients maintained viral suppression with 2 years of VIREAD*(n=154)[1]

*In Studies 102 (HBeAg–) and 103 (HBeAg+), 641 adult patients with chronic hepatitis B entered a 48-week, randomized, double-blind, active-controlled treatment period comparing VIREAD 300 mg to adefovir 10 mg with a primary endpoint of complete response, as defined by HBV DNA <400 copies/mL + histological response. 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.[1-3]

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® 300 mg 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.

TRUVADA, EMTRIVA, HEPSERA, and VIREAD are registered trademarks of Gilead Sciences, Inc. ATRIPLA is a trademark of Bristol-Myers Squibb & Gilead Sciences, LLC. All other trademarks referenced herein are the property of their respective owners.

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

GILEAD

Presentations in Hepatology

Tenofovir for Treatment of Chronic Hepatitis B in Patients With Suboptimal Response to Adefovir

Manns and colleagues presented results of a pooled analysis evaluating the efficacy of tenofovir disoproxil fumarate (TDF; Viread, Gilead) in patients with suboptimal response to adefovir dipivoxil (ADV; Hepsera, Gilead). The analysis included patients enrolled across 3 clinical trials: Study 102 (in hepatitis B e antigen [HBeAg]-negative patients), Study 103 (in HBeAg-positive patients), and Study 106 (in ADV-refractory chronic hepatitis B patients). The current analysis focused on patients with a suboptimal response to ADV, defined as 48 weeks of ADV exposure prior to enrolling in Studies 102 and 103 with a hepatitis B virus (HBV) DNA level of at least 69 IU/mL (≥400 copies/mL) or with 24–96 weeks of ADV exposure in Study 106 with an HBV DNA level of at least 172 IU/mL (≥1,000 copies/mL). Of the 160 patients evaluated, 65% were HBeAg-positive; 54% were white, and 34% were Asian; the mean HBV DNA level was 7.66 $\log_{10}$ copies/mL; and the mean alanine aminotransferase (ALT) was 122.4 U/L. Mean prior ADV duration was 53 weeks; 23% of patients had received prior lamivudine (LAM). Resistance to ADV and LAM was detected in 7.5% and 4.4% of patients, respectively. At Week 96 after starting TDF, viral suppression was attained by 75% of patients without ADV or LAM resistance, 10 of 12 (83%) patients with ADV resistance, and 6 of 7 patients (86%) with LAM resistance, in a missing/switch=failure analysis. Mean ALT at Week 96 in these subgroups was 39 U/L, 31 U/L, and 25 U/L, respectively. The overall median HBV DNA level was 29 IU/mL (169 copies/mL). HBeAg loss occurred in 10% of patients by Year 1 and 15% by Year 2. HBeAg seroconversion occurred in 7% and 10% of patients, respectively. In regard to safety, TDF-related serious adverse events occurred in 2 patients (1.3%) and grade 3/4 laboratory abnormalities were reported in 13.8%. No patients discontinued therapy due to adverse events. Although 34 patients had HBV DNA levels greater than 400 copies/mL (>69 IU/mL) after receiving up to 96 weeks of TDF, no TDF-associated resistance was detected.

Rifaximin Associated With Quality-of-Life Improvements in Patients With Hepatic Encephalopathy

Rifaximin (Xifaxan, Salix) is a broad-spectrum oral antibiotic that is gut-selective and minimally absorbed. The agent has demonstrated efficacy in acute hepatic encephalopathy (HE). The randomized, double-blind, multinational, phase III trial RFHE3001, conducted in 299 patients with cirrhosis and a history of recurrent overt episodic HE, showed that rifaximin reduces the risk of breakthrough overt HE by 58% compared to placebo. In the current analysis, Sanyal and colleagues evaluated the effects of rifaximin and breakthrough HE on patient-reported health-related quality of life in patients enrolled in RFHE3001. Quality of life was assessed using the validated and disease-specific Chronic Liver Disease Questionnaire (CLDQ), in which 6 domains are ranked on a 7-point scale, with higher scores indicating a better quality of life. The investigators found that rifaximin was associated with a significant improvement in the mean time-weighted average (TWA) score for the overall CLDQ (3.7 vs 2.9; P=.0093) and for all individual domains, including fatigue (3.2 vs 2.5; P=.0087). Adverse events occurred in 80% of patients in each arm. The most common adverse events were peripheral edema (15.0% with rifaximin vs 8.2% with placebo), nausea (14.3% vs 13.2%), dizziness (12.9% vs 8.2%), fatigue (12.1% vs 11.3%), and diarrhea (10.7% vs 13.2%). Twenty patients died during the trial, including 9 patients receiving rifaximin and 11 patients receiving placebo. The majority of deaths were attributed to disease progression. The investigators concluded that rifaximin is associated with significant quality-of-life improvements in patients with hepatic cirrhosis and recurrent, overt HE.

Telaprevir, Peginterferon Alfa-2a, and Ribavirin Effective in Patients With Chronic Hepatitis C With Suboptimal Response to Peginterferon/Ribavirin

Muir and colleagues reported results from Study 107, an open-label rollover study evaluating the addition of telaprevir to peginterferon alfa-2a and ribavirin in patients with genotype 1 chronic hepatitis C virus (HCV) who did not attain sustained virologic response (SVR) with peginterferon/ribavirin during a phase II trial of telaprevir. The study included null responders (patients with HCV RNA reductions <1 $\log_{10}$ at Week 4 or <2 $\log_{10}$ at Week 12), partial responders (patients with ≥2 $\log_{10}$ decrease in HCV RNA at Week 12 but with detectable HCV RNA at Week 24), patients with viral breakthrough, and patients with HCV relapse. The analysis included 117 patients from the PROVE1/2/3 studies. Patients initially received telaprevir 750 mg every 8 hours plus standard-dose peginterferon/ribavirin for 12 weeks, followed by 12 weeks of standard-dose peginterferon/ribavirin. The study design was amended to allow an additional 24 weeks

of peginterferon/ribavirin in patients with detectable HCV RNA at Week 4 and/or Week 12 and in null responders. The patient population included patients with genotype 1A (59%) and genotype 1B (33%) HCV; 83% of patients had HCV RNA levels of at least 800,000 IU/mL; 38% had cirrhosis or bridging fibrosis. Viral breakthrough occurred in 25% of prior null responders, 10% of prior partial responders, 13% of patients with prior viral breakthrough, and no patients with prior relapse. Relapse rates in the same subgroups were 23%, 22%, 0%, and 4%. The discontinuation rate due to adverse events was 9%, including 4% due to rash and 2% due to anemia. Rates of grade 3 rash and anemia were 5% each.

Venous Ammonia Concentrations Predict Breakthrough HE in Patients With HE Receiving Rifaximin

In another analysis of RFHE3001, Sanyal and colleagues investigated the relationship between venous ammonia concentrations, breakthrough HE, and rifaximin treatment. Blood ammonia has been proposed as a useful marker of the severity of overt HE, as elevated ammonia levels are associated with the pathogenesis of overt HE and the development of central nervous system effects. In the current study, the investigators measured venous ammonia concentrations at baseline and on Days 24, 84, and 168 of treatment with rifaximin or placebo. Rifaximin was associated with significant reductions in venous ammonia concentrations versus placebo (5.7 vs 0.3 mg/dL; *P*=.0391). Breakthrough HE, defined as an increase in Conn score to at least 2, or an increase in Conn score to 1 and asterixis grade increase by 1 unit in patients with a baseline Conn score of 0.2, occurred in 35% of patients. Venous ammonia concentrations were significantly higher in patients with breakthrough HE versus those remaining in remission (mean TWA, 102.4 vs 85.4 mmol/L; *P*=.0079). A significant positive correlation was found between mean venous ammonia TWA and breakthrough HE (Spearman correlation coefficient, 0.22; *P*=.0005). Moreover, venous ammonia concentrations appeared to be a good predictor of breakthrough HE, as determined by a receiver operating characteristics curve analysis (0.64; 95% confidence interval [CI], 0.57–0.72). Given the significant independent association between venous ammonia concentrations and breakthrough HE, the investigators suggested that the Conn score is a reliable clinical indicator of breakthrough HE.

TDF-associated Resistance Mutations in Patients With Persistent Viremia

Snow-Lampart and colleagues investigated the development of TDF-associated resistance mutations in patients from Studies 102 and 103 with detectable viremia after up to 144 weeks of TDF. Studies 102 and 103 allowed patients with detectable viremia at Week 52 to add emtricitabine (FTC) 200 mg to open-label TDF 300 mg. Overall, 51 of 641 patients (8%) met this criterion; 34 of these patients (67%) elected to add FTC, whereas 17 (33%) patients remained on single-agent TDF. The addition of FTC did not appear to increase the virologic response rate. At Week 144, HBV DNA levels less than 400 copies/mL were observed in 65% of patients receiving FTC and TDF and 71% of patients receiving TDF monotherapy. Population sequencing analyses were conducted on samples from all 17 patients with detectable viremia at Week 144. Conserved site changes were observed in 1 patient each at the following sites: rtR51K, rtG152E, rtA181T±rtL180M±rtM204V, rtR192H, and rtN236T±rtR274Q. Nonadherence was reported by 8 patients (47%). Clonal analysis performed in 5 patients with persistent viremia (all HBeAg-positive) revealed no evidence of viral breakthrough. One patient was found to be nonadherent. In the 4 treatment-adherent patients, the median baseline HBV DNA level was 9.84 $\log_{10}$ copies/mL and the median HBV DNA reduction from baseline was 6.1 $\log_{10}$ copies/mL. Clonal analysis revealed 17 distinct conserved site changes. The only change observed in more than 1 patient was rtF183L, which was observed in 2 patients. The presence of rtF183L did not affect phenotypic susceptibility to TDF in vitro. The investigators concluded that in patients remaining adherent to TDF, persistent viremia was rare, occurring in only 0.6% of patients, and was associated with no demonstrable virologic resistance to TDF.

Long-Term Entecavir Treatment Associated With Histologic Improvement in Asian Patients With Chronic Hepatitis B

Long-term entecavir (Baraclude, Bristol-Myers Squibb) therapy induces durable virologic suppression and histologic benefit, including reversal of fibrosis or cirrhosis, in both HBeAg-positive and -negative chronic hepatitis B. Tong and colleagues evaluated long-term histologic outcomes following entecavir therapy in a nucleoside-naive Asian patient population. The investigators analyzed patients who completed the clinical trials ETV-022 or -027 and subsequently received entecavir 1.0 mg daily in the rollover study ETV-901. The group included 31 patients with baseline and follow-up biopsies, including 24 patients with HBeAg-positive disease. At baseline, the mean HBV DNA level was 9.5 $\log_{10}$ copies/mL; mean ALT was 127 U/L; mean Knodell necroinflammatory score was 7.5, and mean Ishak fibrosis score was 2.2. After a median entecavir treatment duration of 283 weeks, histologic improvement was observed in 100% of patients, representing an increase from the 71% histologic improvement rate observed at Week 48. The mean reductions from baseline in Knodell

necroinflammatory score at Week 48 and at long-term follow-up were 3.4 and 6.2, respectively. The proportion of patients with improvements in Ishak fibrosis score was 29% and 87%, respectively, and the mean change in Ishak fibrosis score from baseline was -0.2 and -1.5, respectively. The proportion of patients with HBV DNA levels less than 300 copies/mL was 68% at Week 48 and 100% at long-term follow-up; ALT of no more than 1 times the upper limit of normal was observed in 61% and 77% of patients, respectively. No new safety issues were reported.

Efficacy of FTC/TDF Administered With or Without Hepatitis B Immune Globulin in Patients Undergoing Orthotopic Liver Transplantation

The randomized trial Study 107 is evaluating fixed-dose FTC/TDF with or without hepatitis B immune globulin (HBIG) for the prevention of hepatitis B recurrence in patients undergoing orthotopic liver transplantation (OLT). The trial enrolled 40 patients with chronic hepatitis B who had undergone OLT, received at least 12 weeks of post-transplant prophylaxis, including HBIG, and had no evidence of chronic recurrence after transplant. Patients had not received TDF or FTC/TDF after transplant. Other eligibility criteria included creatinine clearance of at least 40 mL/min, adequate organ function, and no co-infection with hepatitis C, hepatitis D, or HIV. All patients received FTC/TDF and HBIG for 24 weeks and then were randomly assigned to continue FTC/TDF plus HBIG (19 patients) or switch to FTC/TDF alone (18 patients) for an additional 72 weeks, for a total treatment period of 2 years. In a safety analysis, no FTC/TDF-related serious or grade 3/4 adverse events were reported. Grade 2–4 adverse events considered to be related to FTC/TDF included 1 case of a moderate increase in creatinine level/decrease in creatinine clearance and 1 case of moderate ulcerative colitis. Three patients did not receive the full 24 weeks of therapy: 1 patient discontinued due to an increase in ALT/aspartate aminotransferase, 1 patient discontinued due to worsening colitis, and 1 patient died from a stroke. Serum creatinine and creatinine clearance remained stable; 4 of 24 patients with a baseline creatinine clearance of 50–80 mL/min (17%) had creatinine clearance of less than 50 mL/min. No patient had detectable HBV DNA levels (≥169 copies/mL) or hepatitis B surface antigen (HBsAg) positivity.

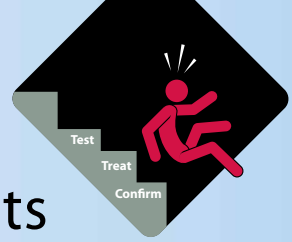
Efficacy of Rifaximin in Patients With Minimal HE

It has been suggested that the minimal absorption associated with rifaximin may make the agent more conducive for long-term use than other antibiotics, which are more readily absorbed and associated with significant side effects. Grande and colleagues conducted a double-blind crossover trial evaluating the use of rifaximin in patients with liver cirrhosis and minimal HE. A total of 17 patients were randomly assigned to rifaximin administered at 1,200 mg/day (2 200-mg tablets given every 8 hours), or placebo, for 4 weeks. After a 4-week washout period, patients received the alternative treatment (rifaximin or placebo) for the next 4 weeks. In this interim analysis, rifaximin was associated with a significant improvement in the area under the curve of glutamine oral challenge compared to placebo (-52.3±53 mg/mL/hr vs -5.62±10.56 mg/mL/hr; P=.045) in the first phase of the study but not the second phase of the study. However, rifaximin was associated with an improvement over placebo in the Psychometric Hepatic Encephalopathy Score in the second phase of the study (2±1.75 vs -1±1.15; P=.05).

Kinetics of HBsAg Loss With TDF and Factors Associated With HBsAg Loss

Gane and colleagues presented an analysis of the kinetics of HBsAg decay in HBeAg-positive patients from Study 103. Among patients attaining HBsAg loss with TDF, HBsAg levels declined rapidly in the first 48 weeks of treatment, with median reductions of 1.01, 2.41, and 4.85 $\log_{10}$ IU/mL, respectively, at Weeks 12, 24, and 48. Median HBsAg reductions at the same time points in patients not attaining HBsAg loss were 0.17, 0.20, and 0.28 $\log_{10}$ IU/mL, respectively. The investigators identified several demographic factors and disease characteristics that were significantly associated with HBsAg loss. At baseline, median HBsAg level was significantly higher in patients with HBsAg loss than those not attaining HBsAg loss (5.11 vs 4.50 $\log_{10}$ IU/mL; P<.001), and patients with HBsAg loss were significantly more likely than other patients to have an HBsAg of at least 4.5 $\log_{10}$ IU/mL (100% vs 48%). HBV genotype was also a significant predictor of HBsAg loss (P<.001). Genotype A/D was present in 12 of 13 evaluated patients with HBsAg loss compared to 82 of 158 patients without HBsAg loss. Baseline median HBV DNA level was also higher in patients with HBsAg loss (P=.003), as was median ALT (P=.043). Finally, there was a trend toward an association between baseline Knodell necroinflammatory score and likelihood of HBsAg loss. Overall, HBsAg loss by Year 3 was observed in 14% of patients with a baseline HBsAg of at least 4.5 $\log_{10}$ IU/mL, 13% of patients with genotype A/D, 16% of patients with an HBV DNA level of at least 9 $\log_{10}$ copies/mL, and 10% of patients with a Knodell necroinflammatory score of at least 9.

Skipping the last step in *H. pylori* eradication could have unfortunate results



Because eradication therapy fails in at least 1 out of 4 patients,[1] follow-up testing after treatment is a necessity.

According to the American College of Gastroenterology (ACG), the ^{13}C urea breath test is the "most reliable non-endoscopic test to document eradication of *H. pylori* infection." The timing and reliability of the fecal antigen test have not been as clearly demonstrated as for the UBT, and serology (antibody testing) cannot distinguish between an active and past infection.[2]

Due to decreasing eradication rates worldwide and increasing antibiotic resistance, testing for eradication is essential.[2] When endoscopic testing is not necessary, use BreathTek® UBT to confirm eradication.

BreathTek UBT is available as either a laboratory or in-office test, and is reimbursable by Medicare and most insurance providers under the following codes:*

83014 Drug administration

83013 *Helicobacter pylori* breath test analysis for urease activity, non-radioactive isotope

Learn more at www.BreathTekFacts.com, or contact us at 1-888-637-3835.

Learn more at ACG 2010.
Visit us in booth #316.

[1] Vakil N, Fendrick M. How to test for *Helicobacter pylori* in 2006. Cleve Clin J Med. 2005;72(Suppl 2): S8-S13.

[2] Chey and Wong. American College of Gastroenterology Guideline on the Management of *Helicobacter pylori* Infection. Am J Gastroenterol 2007;102:1808-1825.

*This reimbursement information is being provided to help the health care professional understand and comply with billing and reimbursement requirements that may apply to products. Use of codes identified here does not guarantee coverage or payment at any specific level.

0510A-0387B August 2010

Brief Summary

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

The BreathTek UBT Kit is for administration by a health care professional, as prescribed by a physician.

Warnings and Precautions:
1. For in vitro diagnostic use only. The Pranactin®-Citric drug solution is taken orally as part of the diagnostic procedure.
2. Phenylketonurics: Contains Phenylalanine (one of the protein components of Aspartame), 84 mg per dosage unit. (For reference, 12 ounces of typical diet cola soft drinks contain approximately 80 mg of Phenylalanine.)
3. Blood glucose: Use with caution in diabetic patients. Pranactin-Citric contains Aspartame.
4. A negative result does not rule out the possibility of *H. pylori* infection. False negative results do occur with this procedure. If clinical signs are suggestive of *H. pylori* infection, retest with a new sample or an alternative method.
5. Antimicrobials, proton pump inhibitors, and bismuth preparations are known to suppress *H. pylori*. Ingestion of these within 2 weeks prior to performing the BreathTek UBT may give false negative results.
6. A false positive test may occur due to urease associated with other gastric spiral organisms observed in humans such as *Helicobacter heilmannii*.
7. Premature POST-DOSE breath collection time can lead to a false negative diagnosis for a patient with a marginally positive BreathTek UBT result.
8. A false positive test could occur in patients who have achlorhydria.
9. If particulate matter is visible in the reconstituted Pranactin-Citric solution after thorough mixing, the solution should not be used.
10. Hypersensitivity: Patients who are hypersensitive to mannitol, citric acid or Aspartame should avoid taking the solution as this drug solution contains these ingredients.
11. Risk of aspiration: Use with caution in patients with difficulty swallowing or who may be at high risk of aspiration due to medical or physical conditions.
12. Pregnancy: No information is available on use of the drug solution during pregnancy.

Postmarketing Experience:
The following adverse events have been identified during postapproval use of BreathTek UBT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to establish a causal relationship to drug exposure: rash, burning sensation in the stomach, tingling in the skin, vomiting and diarrhea.

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

0510L-0360B August 2010

Otsuka
Medical Device Division of Otsuka America Pharmaceutical, Inc.

Urea Breath Test for H. pylori
BreathTek®
DEFINITIVE EVIDENCE

Presentations in GERD

Benefit of Dexlansoprazole or Lansoprazole Maintained After Discontinuation

To evaluate the incidence of acid or symptom rebound following discontinuation of dexlansoprazole MR (DEX; Dexilant, Takeda) or lansoprazole (LAN), an analysis was undertaken evaluating outcomes in patients with *Helicobacter pylori*–negative erosive esophagitis (EE) enrolled in clinical trials who attained healing after 4 or 8 weeks of DEX (60 or 90 mg) or LAN 30 mg once daily who were then randomly assigned to placebo for maintenance trials. Mean gastrin values in these patients did not change substantially from baseline to Months 1 and 3 postplacebo randomization, suggesting that gastrin normalizes within 1 month of proton pump inhibitor (PPI) withdrawal. Mean heartburn severity was significantly lower 1 month after starting placebo than at baseline. Moreover, heartburn severity was similar whether patients attained healing at Week 4 or 8 with DEX or LAN, suggesting no association between longer exposure or more effective therapy and rebound. In patients with 2 months of follow-up data, mean heartburn severity was significantly lower during the first 2 months of placebo than at baseline (median decrease, 0.54 and 0.58 points; both $P<.001$), indicating that the benefit of DEX or LAN is maintained up to 2 months after discontinuation of therapy.

Long-Term Safety of Laparoscopic Antireflux Surgery Versus Esomeprazole in Patients With Gastroesophageal Reflux Disease

LOTUS was a multicenter, randomized trial comparing laparoscopic antireflux surgery (LARS) versus esomeprazole in patients with gastroesophageal reflux disease (GERD). The study was conducted in 11 European countries over 5 years. A total of 554 patients were randomly assigned to LARS (288 patients, 248 of whom actually underwent the procedure) or esomeprazole 20 mg daily (or 40 mg if necessary; 266 patients). No clinically relevant differences in the extent of serious adverse events between arms were reported. Over a 5-year follow-up period, there were 5 cases of death/myocardial infarction (MI) in esomeprazole-treated patients and 4 cases among LARS-treated patients; these all occurred in the first 2 years of the study, and no additional cases of death/MI were reported in the subsequent 3 years of the study. Laboratory analyses revealed no clinically relevant changes during the follow-up period. The pattern of bone metabolism biomarkers (alkaline phosphatase, calcium, vitamin D) was also stable and did not differ between the arms. Elevated gastrin and chromogranin A levels were observed in patients receiving esomeprazole, as would be expected after acid suppression. However, these changes appeared to plateau at 5 years.

DEX Associated With Quality of Life, Symptom Improvements in GERD

A study evaluated the effects of DEX on quality of life and symptom severity in patients with symptomatic nonerosive GERD. In the initial 4-week study, 313 patients (mean age, 49.4 years; 69.3% women) initially received DEX 60 mg, 90 mg, or placebo once daily. In the subsequent multicenter, open-label, 12-month safety study, patients were randomly assigned to DEX 60 mg or 90 mg once daily. Patients initially treated with DEX experienced significant improvements from baseline to Week 4 in the Patient Assessment of Upper Gastrointestinal Disorders–Quality-of-Life scores and significant reductions in symptom severity. These improvements were maintained at each visit during the 12-month study. Patients who had initially received placebo achieved comparable quality-of-life improvements and reductions in symptom severity after the first month of the 12-month study. Similar trends were noted for the subscales evaluated.

Differences in Nighttime Acid Exposure in EE Versus Nonerosive Reflux Disease

A computer-based study compared differences in nighttime esophageal acid exposure associated with EE and nonerosive reflux disease (NERD). The study, which analyzed the topographic distribution of intraesophageal pH, was conducted in 22 patients with NERD (mean age, 45 years; 72% male) and 38 patients with EE (mean age, 41.8 years; 68% male). The time in bed did not differ between the groups. The investigators found several significant differences in acid exposure in the 2 groups. NERD was associated with significantly fewer acid reflux events than EE (20.0 vs 25.9 events), shorter reflux time with a pH less than 4 (24.7 vs 30.1 minutes), a lower proportion of total time with a pH less than 4 (4.0% vs 5.4%; $P<.05$), and fewer reports of symptoms during the night (15.8% vs 9.1%; $P<.05$). Overall, the topographic intraesophageal pH distribution did not differ substantially between NERD and EE for all pH brackets except pH 1–0 (pH 4–3: 55% vs 54%; pH 3–2: 32.9% vs 27%;

pH 2–1: 11% vs 13.2%, respectively; *P*>.05). Thus, the differences in nighttime acid exposure between EE and NERD were attributed to duration, rather than intensity, of exposure.

Activity of Novel Metabotropic Glutamate Receptor 5 Negative Allosteric Modulator ADX10059 in GERD

The novel metabotropic glutamate receptor 5 negative allosteric modulator ADX10059 has been shown to reduce reflux and esophageal acid exposure in both healthy individuals and patients with GERD. Zerbib and colleagues presented results from a double-blind, placebo-controlled, multicenter trial evaluating the effects of single-agent ADX10059 on symptom control in patients with GERD. The study enrolled 103 patients with responses to prior PPIs. After undergoing a 2-week baseline PPI washout period, patients were randomly assigned to receive ADX10059 120 mg (50 patients) or placebo (53 patients) twice daily for 2 weeks. The mean age of enrolled patients was 52 years, mean body mass index (BMI) was 26.7 kg/m^2, and 52% were male. ADX10059 was significantly superior to placebo in regard to the change in the mean number of GERD symptom-free days from baseline to Week 2 (0.46 to 2.5 vs 0.72 to 1.71; *P*=.045) and the change in the mean number of heartburn-free days (0.98 to 2.93 vs 1.28 to 2.11; *P*=.037). ADX10059 also appeared to reduce heartburn and regurgitation severity and the number of days with postprandial GERD. Compared to placebo, ADX10059 was also associated with greater reductions in antacid use (*P*=.017) and improvements in total Patient Assessment of Upper Gastrointestinal Symptom Severity Index (PAGI SYM) score (*P*=.048), PAGI SYM heartburn/regurgitation subscale (*P*=.007), and sleep disturbance (*P*=.022). Patient-reported medication efficacy was also significantly greater with ADX10059 versus placebo (*P*=.047). The 3 most common adverse events included dizziness (16%), vertigo (12%), and upper abdominal pain (10%); 66% of adverse events were mild, and no severe adverse events were observed.

Association Between BMI and Acid Exposure in Patients With Extraesophageal Reflux Disease

Although an association between obesity and the development of GERD has been observed, the relationship between BMI and esophageal acid exposure in patients with extraesophageal reflux disease has not been defined. To investigate this issue, Aslam and colleagues conducted a 48-hour off-treatment pH monitoring study of 365 patients with extraesophageal symptoms (80%) or typical GERD (20%). The median age of enrolled patients was 53 years; 73% were female; and the median BMI was 28 kg/m^2 (interquartile ratio, 24–32 kg/m^2). The investigators found a significant association between increasing BMI and greater esophageal acid exposure (*P*=.004), whether BMI was evaluated as a continuous variable or as a categorical variable, with normal BMI defined as 19 to less than 25 kg/m^2, overweight as 25 to less than 30 kg/m^2, and obese as more than 30 kg/m^2. The greatest increase in acid exposure was noted between BMI of 25–30 kg/m^2. BMI had a minimal effect above 30 kg/m^2. Overall, these findings suggest a significant, nonlinear relationship between BMI and acid exposure.

Addition of Esophageal Intraluminal Impedance Recording to Esophageal pH Monitoring Increases Diagnostic Yield

Esophageal intraluminal impedance recording can be useful for characterizing the components of GERD and for discerning weak or nonacidic GERD, which would be missed by standard esophageal pH monitoring. The current study quantified the diagnostic gain contributed by pH-impedance recording in 220 patients who were undergoing evaluations for typical GERD symptoms (133 patients), respiratory symptoms (44 patients), oropharyngeal symptoms (24 patients), and chest pain (11 patients). GERD, defined as acid exposure of more than 5.8%, was diagnosed in 40.9% of patients. Weakly acidic or nonacidic reflux, defined as having at least 75 GERD events within 24 hours but with less than 5.8% acid exposure, was diagnosed in 12.7% of patients. The study investigated the correlation between symptoms and reflux, defined as symptom association probability (SAP). A SAP of at least 95% indicated an association between symptoms and reflux. Overall, 12.7% of patients had a SAP of less than 95% for acidic GERD and a lack of quantitative GERD, a condition defined as hypersensitive esophagus to acid reflux. Another 9.1% of patients were diagnosed with hypersensitive esophagus to weak/nonacidic reflux, indicating a lack of quantitative GERD and a SAP of less than 95% for weak/nonacidic GERD. The remaining 27.3% included patients with normal pH impedance outcomes. No significant differences were noted between these subgroups in regard to age, gender, indication, or response to PPI therapy. The coupling of impedance to pH monitoring identified 28 cases of weak/nonacidic GERD and 20 cases of hypersensitive esophagus to weak or nonacid reflux, resulting in an overall diagnostic gain of 21%. The investigators added that the diagnostic gain attained with impedance occurred regardless of symptoms.

When symptoms of **Crohn's disease** remain uncontrolled

Stop losing time continuing with conventional therapy

Act earlier

to break the cycle of relapse and remission

NOW MORE THAN EVER, IT'S TIME TO CONSIDER A DIFFERENT APPROACH

Centocor Ortho Biotech Inc.

Presentations in IBD

Switch to Adalimumab Not Advised in Patients With Crohn's Disease Controlled by Maintenance Infliximab

Both adalimumab (Humira, Abbott) and infliximab (Remicade, Centocor) can be used for maintenance of remission in patients with Crohn's disease. However, whereas infliximab is administered intravenously, adalimumab is administered subcutaneously at home and, thus, may be preferred by patients. In a prospective, randomized study, Van Assche and colleagues evaluated the feasibility of switching to adalimumab in patients with Crohn's disease who were maintaining a Crohn's disease activity index (CDAI) of less than 200 on infliximab maintenance therapy administered every 6–8 weeks. A total of 73 patients were randomly assigned to switch to adalimumab administered at 80 mg followed by 40 mg every other week (36 patients) or to remain on infliximab (37 patients). More than half of the patients receiving adalimumab (between 50% and 71% at various time points) preferred adalimumab over infliximab; 17–25% preferred infliximab. However, 8 patients in the adalimumab arm (22%) had to switch to infliximab due to treatment intolerance (5 patients) or due to complete loss of response (3 patients). Conversely, no infliximab-treated patients had to switch to adalimumab (P=.002). Crossovers due to treatment intolerance occurred after a median of 15 weeks, while those attributed to loss of response occurred after a median of 6.3 weeks. All 8 patients successfully restarted infliximab therapy. Compared to infliximab, adalimumab was also associated with a higher composite rate of dose adjustments for loss of response and treatment discontinuation due to complete loss of response or intolerance (39% vs 14%; P=.02). Adverse event rates were similar, though there were more injection site reactions to adalimumab than infusion reactions to infliximab (19% vs 0%; P<.005). Overall, these results led the investigators to prematurely end enrollment in the study.

MMX Mesalamine Associated With Health-Related Quality-of-Life Improvements in Patients With Ulcerative Colitis

Kane and colleagues presented results on the effect of MMX mesalamine (Lialda, Shire) on health-related quality of life in patients with mild-to-moderate ulcerative colitis. In this 2-phase, multicenter, open-label study, a total of 132 patients received MMX mesalamine administered 2.4–4.8 g once daily. A baseline analysis showed that ulcerative colitis has a substantial negative effect on health-related quality of life, with patients demonstrating significantly lower scores in most domains of the SF-12v2 scale than a general-population sample matched for age and gender. Ulcerative colitis appeared to have the greatest effect on general health, physical role, and social functioning, followed by physical functioning, bodily pain, vitality, and emotional role. Only the mental health domain was not significantly lower. In an analysis of 107 patients, 8 weeks of MMX mesalamine was associated with significant improvements in all but 1 domain of the SF-12v2 scale (P<.01 for each). Moreover, significant improvements were observed from baseline to Week 8 in the mean physical health summary score (46.4 vs 49.8; P<.001) and the mental health summary score (48.2 vs 51.1; P<.01). Improvements in rectal bleeding severity and bowel movement frequency were both associated with significantly greater health-related quality-of-life improvements.

Predictive Factors in Patients With Crohn's Disease Receiving Certolizumab Pegol

The open-label WELCOME trial evaluated the efficacy of certolizumab pegol (Cimzia, UCB) in patients with previous response to infliximab who had a loss of response or who developed hypersensitivity. In the open-label phase, patients with a CDAI score between 220 and 450 received induction therapy with certolizumab pegol 400 mg administered subcutaneously at Weeks 0, 2, and 4. In the double-blind phase of the trial, patients who had attained response by Week 6 were randomly assigned to maintenance therapy with certolizumab pegol every 2 or 4 weeks or to placebo. In the current post-hoc analysis, Sandborn and colleagues investigated predictors of response (a decrease of ≤100 CDAI) and remission (a CDAI score ≤150) in these patients. In a multivariate analysis, factors significantly predictive of remission at Week 26 included disease localization in the colon, no resection performed, and baseline CDAI score of less than 298. Among patients not receiving corticosteroids at baseline, those with a baseline CDAI score of less than 298 were more than 4 times more likely than other patients to achieve remission. No baseline factors were significantly predictive of clinical response at Week 26. It was noted, however, that interactions between several variables were associated with predictive value for clinical response. These included baseline anti-infliximab antibodies or smoking status by C-reactive protein level and the reason for previous infliximab failure by resection.

Association Between Infliximab Trough Levels and Mucosal Healing in Crohn's Disease

The relationship between infliximab trough levels and outcomes in patients with inflammatory bowel disease has not been well defined. To better understand the significance of infliximab pharmacokinetics, Van Moerkercke and colleagues conducted a retrospective study evaluating the association between infliximab trough levels and mucosal healing in 210 patients receiving infliximab for the treatment of Crohn's disease. Endoscopic data were available before and after infliximab initiation. Serum samples were available at baseline, 2–6 weeks after the first infusion, and at the time of endoscopy. Infliximab trough levels were measured using an enzyme-linked immunosorbent assay developed in-house, in which diluted serum samples were applied to plates coated with tumor necrosis factor (TNF)-alfa. The investigators found that infliximab treatment was associated with complete mucosal healing (no detectable lesions) in 39% of patients, partial healing (clear endoscopic improvement but ulcerations remaining) in 22% of patients, and no healing in 39% of patients. Median infliximab trough levels were significantly higher in patients with any degree of mucosal healing than in patients with no healing (5.00 vs 0.95 µg/mL; *P*=.006). This relationship appeared to be dose-dependent (*P*=.013); the median infliximab trough level was 5.77 µg/mL in patients with complete healing, 3.89 µg/mL in patients with partial healing, and 0.95 µg/mL in patients with no mucosal healing. The investigators suggested that the trough level assay could be useful for optimizing infliximab therapy. If low trough levels are detected in patients without mucosal healing, a dose increase or shorter dosing interval may be warranted. On the other hand, if patients without mucosal healing are found to have high infliximab trough levels, the agent should be switched.

Adalimumab Associated With Deep Remission in Patients With Moderate-to-Severe Ileocolonic Crohn's Disease

The randomized, placebo-controlled EXTEND trial evaluated the efficacy of adalimumab in 135 patients with moderate-to-severe ileocolonic Crohn's disease (CDAI 220–450) and baseline mucosal ulceration. In the study, all patients received open-label adalimumab 160-/80-mg induction therapy at Weeks 0/2; at Week 4, 129 patients were randomly assigned to maintenance therapy with adalimumab 40 mg every other week or placebo. Starting at Week 8, patients with flares or nonresponse could switch to open-label adalimumab. In the current analysis, Colombel and colleagues evaluated the ability of adalimumab to induce deep remission, defined as clinical remission (CDAI <150) and mucosal healing, in the 123 patients with ulceration at screening. At Treatment Week 12, adalimumab was associated with a higher deep remission rate than placebo (16.1% vs 9.8%), though this difference was nonsignificant in the unadjusted analysis. In a post-hoc sensitivity analysis of the overall intention-to-treat population of 129 patients, the likelihood of attaining deep remission was 3.4-fold higher in patients receiving adalimumab versus placebo (*P*<.05) after adjusting for confounding factors (disease duration, prior anti-TNF therapy, baseline immunosuppressant use, corticosteroid use, and C-reactive protein levels). The difference in the deep remission rate between adalimumab and placebo was greater at Week 52 (19.4% vs 0%; *P*<.001). The investigators suggested that the use of open-label adalimumab induction therapy, and the designation of patients switching to open-label therapy as nonresponders, may have resulted in an underestimation of the effect of adalimumab at Week 12.

Rapid Induction of Remission With MMX Mesalamine in Ulcerative Colitis

The phase IV, open-label SIMPLE trial evaluated the efficacy of MMX mesalamine in patients with mild-to-moderate ulcerative colitis. The study, conducted at 52 centers across the United States, comprised 2 phases: a 2-month acute phase, which evaluated the efficacy of MMX mesalamine in patients with active ulcerative colitis, and a 12-month maintenance phase, which evaluated the efficacy of MMX mesalamine in patients with quiescent ulcerative colitis (score of 0 for rectal bleeding and bowel movements). Patients could directly enroll in the maintenance phase or could proceed to the maintenance phase after attaining quiescent ulcerative colitis in the active phase. MMX mesalamine was administered at 2.4–4.8 g once daily in the acute phase and at 2.4 g once daily in the maintenance phase. The primary endpoint of the study was clinical recurrence at 6 months, with recurrence defined as at least 4 bowel movements per day above normal frequency and associated with urgency, abdominal pain, or rectal bleeding. Other endpoints included clinical recurrence at 12 months, compliance, and safety. In the current analysis, Kane and colleagues evaluated the short-term effect of MMX mesalamine on clinical symptoms in the 138 patients with active ulcerative colitis enrolled in the active phase of the trial. Within 1 week of starting MMX mesalamine, approximately 40% of patients reported resolution of rectal bleeding or normalization of stool frequency.

Single-Agent Infliximab Prevents Post-Resection Crohn's Disease Recurrence

In addition to its role in inducing and maintaining remission of Crohn's disease, infliximab has also been shown

to prevent recurrence of Crohn's disease in patients who have undergone intestinal resection. To further assess the ability of infliximab to prevent postoperative recurrence, Yoshida and colleagues conducted a prospective, randomized, open-label trial of single-agent infliximab in Japanese patients with Crohn's disease who had undergone intestinal resection. A total of 27 patients who had undergone surgery within the past 4 weeks and had not received immunomodulators were randomly assigned to infliximab administered at 5 mg/kg every 8 weeks for 12 months (15 patients) or no infliximab (12 patients). The primary endpoint, the proportion of patients maintaining clinical remission (CDAI ≤150) at 12 months, was higher in patients receiving infliximab versus those in the control group (85.7% vs 66.7%). Infliximab was also associated with a significantly higher rate of endoscopic remission at 1 year. During the study period, there were no differences between the 2 groups in the use of concomitant therapies. Moreover, no patients in either group required steroids or thiopurine. One patient discontinued infliximab at 3 months due to severe dyspnea. The investigators concluded that infliximab monotherapy administered on a scheduled basis every 8 weeks prevents postresection recurrence in patients with Crohn's disease.

Treatment Compliance Associated With Recurrence in Patients With Quiescent Ulcerative Colitis Receiving Maintenance MMX Mesalamine

Treatment compliance is an important factor in treatment of Crohn's disease, as poor adherence can result in disease. Whereas standard mesalamine formulations require multiple tablets to be taken multiple times per day, MMX mesalamine allows patients to take fewer pills on a once-daily schedule. This convenience may improve compliance, which is known to be poor with standard mesalamine. In this report, also from the SIMPLE trial, Kane and colleagues evaluated the role of treatment compliance and clinical outcomes in 208 patients with ulcerative colitis receiving maintenance therapy with MMX mesalamine. Compliance was calculated using prescription refill data, and noncompliance was defined as filling fewer than 80% of prescriptions. Recurrence rates among the 207 evaluable patients were 23% at 6 months and 36% at 12 months. The mean compliance was 87%; compliance rates were 79% at Month 6 and 77% at Month 12. Rates of recurrence were significantly higher in noncompliant versus compliant patients at 6 months (36.1% vs 20.6%; nominal P=.0476) and at 12 months (52.5% vs 31.2%; nominal P=.0120). Given this association between compliance and clinical outcomes, the investigators concluded that selecting medications that enhance compliance may increase the likelihood of remission.

Registry Data Reveal Long-Term Safety of Infliximab in Crohn's Disease

The large, observational TREAT registry is evaluating the safety of infliximab and other therapies in patients with Crohn's disease. The cohort includes 6,273 individuals, consisting of 3,401 patients who have received infliximab and 2,872 patients who have received other therapies only. The current analysis reviewed the safety of these therapies after a mean follow-up of 4.8 years, reflecting 16,129 patient-years of infliximab and 11,633 patient-years of other therapies. At registration, patients receiving infliximab were significantly more likely than other patients to have moderate-to-severe Crohn's disease (29.5% vs 10.2%; P<.001) or severe-fulminant Crohn's disease (2.4% vs 0.6%; P<.001). They were also more likely to have been hospitalized in the year prior to enrollment (27.2% vs 18.9%; P<.001) and to be taking prednisone (26.8% vs 15.9%; P<.001) or immunomodulators (48.8% vs 31.6%; P<.001). Of all infliximab infusions administered, 3.1% resulted in infusion reactions and 0.07% resulted in severe infusion reactions. Infliximab was not associated with increased mortality; mortality rates among infliximab-treated and non–infliximab-treated patients were 0.59 and 0.60 deaths per 100 patient-years, respectively. However, prednisone and narcotic use were both associated with an approximate doubling of mortality risk (hazard ratio [HR] for prednisone, 2.11; 95% CI, 1.51–2.95; P<.001; HR for narcotics, 1.95; 95% CI, 1.39–2.74; P<.001). Disease severity was also not significantly associated with mortality risk. The registry data also showed no significant difference in the incidence of malignancies between infliximab-treated and non–infliximab-treated patients (0.44 and 0.56 cases per 100 patient-years, respectively) or in the incidence of lymphoma (0.05 cases per 100 patient-years in both groups). However, infliximab did appear to increase the risk of serious infections. In an unadjusted analysis, the incidence of serious infections was 2.5-fold higher in infliximab-treated patients versus non–infliximab-treated patients (1.69 vs 0.69 cases per 100 patient-years; relative risk, 2.47; 95% CI, 1.55–3.93; P<.001). In an adjusted Cox analysis, infliximab treatment was significantly predictive of serious infection (HR, 1.44; 95% CI, 1.03–2.01; P=.035). Narcotic use increased the risk of serious infection 2.3-fold (P<.001), and prednisone use increased the risk 1.6-fold (P=.003). Predictors of serious infection in a multivariate analysis included narcotic use (HR, 2.33; P<.001), prednisone use (HR, 1.97; P<.001), and infliximab use (HR, 1.48; P=.011). Disease severity was also an independent significant predictor of serious infection. Nonfatal tuberculosis developed in 3 patients receiving infliximab and in 1 patient receiving other therapies.

Presentations in Endoscopy

Radiofrequency Ablation in Barrett Esophagus Associated With Durable Epithelial Reversion

For many patients with dysplastic Barrett esophagus (BE), treatment with radiofrequency ablation (RFA) is associated with complete eradication of dysplasia and intestinal metaplasia, though the durability of eradication has not been well defined. Moreover, the efficacy of RFA in patients without complete eradication at 1 year is not known. The randomized, sham-controlled AIM Dysplasia Trial evaluated RFA plus surveillance versus surveillance alone in patients with dysplastic BE. Following stratification by degree of dysplasia and length of BE (<4 vs 4–8 cm), patients were randomly assigned 2:1 to RFA or sham treatment. Patients in the active treatment arm received step-wise circumferential and focal RFA. All enrolled patients underwent surveillance with biopsy every 3 months for high-grade disease or every 6 months for low-grade disease. Patients in the active arm received continued surveillance, whereas those in the control arm were offered RFA. After 1 year, 65 of 78 patients in the RFA arm (83%) had attained a complete response for intestinal metaplasia (CR-IM). These patients were a median of 66 years old; 85% were male; the mean BE length was 4.7 cm; and 34 patients had high-grade disease. Of the 13 patients with persistent BE at 1 year, the median age was 67; 92% were male; the mean BE length was 6.0 cm; 7 patients (54%) had high-grade disease; and 12 patients (92%) had multifocal dysplasia. The investigators conducted additional follow-up to evaluate the durability of CR-IM and the feasibility of response in patients not attaining CR-IM after 1 year. After a follow-up of 2 years in 62 RFA-treated patients attaining CR-IM at 1 year, CR-IM was maintained in 59 patients (95.2% in a per-protocol analysis/90.8% in an intent-to-treat analysis). In the remaining 3 patients, who had 5–6-cm, multifocal, high-grade disease at baseline, the dysplasia grade had improved at Year 2. In the 13 patients with persistent BE at 1 year, 11 patients (84.6%) achieved CR-IM at 2 years, with an average of 1.2 focal RFA sessions during the second year. Finally, a 3-year follow-up of patients with CR-IM at Year 1 showed durable responses, with maintenance of CR-IM in 13 of 13 evaluable patients.

Use Patterns in a Computed Tomography Colonography Colorectal Cancer Screening Program

Modeling studies have suggested that the introduction of computed tomography colonography (CTC) screening could lead to a reduction in the use of optical colonoscopies. However, this hypothesis has not been evaluated. In 2004, the University of Wisconsin was the first US institution to gain third-party payer coverage of CTC for colorectal cancer screening in average-risk individuals. In the current analysis, Benson and colleagues analyzed the uptake of a CTC screening program and its effect on optical colonoscopies in individuals 50–75 years of age over a 5-year period. The researchers compared screening rates from 2003 (the year before the approval of open-access third party–covered CTC) to 2008 (5 years after the program initiation). Use of CTC screening peaked in the third quarter of 2005 with 307 CTC examinations and declined to 203 examinations in the fourth quarter of 2008. Conversely, use of screening optical colonoscopy increased significantly from 2003 to 2008 from an average of 555 to 995 screenings per quarter ($P<.001$). Over the same time period, the number of total optical colonoscopies performed in this population increased from 1,104 to 1,976 ($P<.001$). The number of therapeutic colonoscopies performed per quarter did not increase significantly from 2003 to 2009 (463 vs 490; $P=.36$). Overall, colorectal cancer screening examinations of any type increased significantly from 2003 to 2008, from 555 to 1,187 examinations per quarter ($P<.001$). In 2009, CTC accounted for only 8.5% of all screenings, indicating that optical colonoscopy remains the primary screening method. The authors concluded that the introduction of the CTC screening program was not associated with a reduction in the use of optical colonoscopy; rather, there was an overall increase of screenings performed during the time period.

Autofluorescence Imaging Versus Zoom–Narrow-Band Imaging for Endoscopic Imaging in BE

Video-autofluorescence imaging (AFI) and magnification narrow-band imaging (zoom-NBI) provide multimodality imaging with a single endoscope, allowing for greater detection of high-grade intraepithelial neoplasia (HGIN) in patients with BE. Whereas zoom-NBI is interpreted based upon the presence of regular versus irregular patterns, AFI is interpreted based upon color changes and, thus, may be easier to interpret. To further evaluate differences between the 2 modalities, Kim and colleagues undertook a study comparing interobserver agreement in images obtained via AFI and zoom-NBI in patients with BE. Images with corresponding biopsies were obtained

from a prospective trial of tandem AFI and zoom-NBI that used a prototype multimodality endoscope capable of switching between the 2 modalities. The current study compared findings determined by 6 endoscopists, including 3 experts and 3 trainees. The participants first underwent an hour-long structured teaching session using 8 AFI/NBI images and then evaluated a set of 36 AFI images (17 with high-grade dysplasia or cancer) and 44 zoom-NBI images (21 with high-grade dysplasia or cancer) obtained from 25 patients. The endoscopists all reported a median image quality score of 3 (good) on a scale of 1–5. Overall, interobserver agreement was good for both AFI (mean kappa value, 0.48) and zoom-NBI (mean kappa value, 0.50). Mean kappa values for prediction of histology were 0.48 and 0.50 for AFI and zoom-NBI, respectively. No differences in interpretation were noted between experts and nonexperts for images obtained with AFI (mean kappa values, 0.48 and 0.44, respectively). However, for images obtained with zoom-NBI, kappa values were lower in experts versus nonexperts (0.39 and 0.63, respectively). Based upon these findings, the researchers suggested that AFI is easier to interpret and has a shorter learning curve. The sensitivity, specificity, and accuracy for detecting HGIN was 79%, 80%, and 80%, respectively, for AFI, and 89%, 68%, and 77%, respectively, for zoom-NBI. The investigators suggested that further improvements are needed to increase the accuracy of detection with both modalities.

Diagnostic Yield Similar With 22-Gauge Versus 25-Gauge Needles During Endoscopic Ultrasound–Guided Fine-Needle Aspiration

Conway and colleagues presented results of a prospective, randomized trial comparing the diagnostic yield of 22-gauge needles, which are preferred by many endosonographers, and 25-gauge needles during endoscopic ultrasound–guided fine-needle aspiration (EUS-FNA). This ongoing study enrolled patients undergoing EUS-FNA of solid lesions between January 2009 and November 2009. All lesions underwent 4 passes—2 with each needle size—using the EchoTip Ultra needle (Cook Medical). Block randomization determined the order of needle use. Cytotechnicians applied 10 cc of suction during each pass. Neither the on-site technician nor the cytopathologist had knowledge of the sampling technique. Of the 75 patients included in this interim analysis, 62% were male, the mean age was 66 years, and 83% were white. Patients assigned to receive the 22-gauge needle first were older than patients in the other group (mean age, 69 vs 62 years; P=.02). Lesions were primarily biopsied from the pancreas (49%) and lymph nodes (23%). The average lesion diameter was 31 mm. Diagnoses included adenocarcinoma (41%), reactive adenopathy (17%), gastrointestinal stromal tumors (8%), and suspicious for cancer (7%); 12% were nondiagnostic. The investigators reported no significant differences in diagnostic yield between the 2 needles in pancreatic masses, lymph nodes, or other lesions. Overall, the diagnostic yield, defined as the acquisition of adequate cells for the pathologist to render a diagnosis, was similar with the 22-gauge and 25-gauge needles (83% and 84%, respectively). Blood was present in 80% and 76% of samples, respectively; clots were present in 61% and 63%, respectively; and high cellularity was noted in 60% and 64% of samples, respectively. No immediate complications or needle failures occurred. The researchers suggested that either needle could be used, as diagnostic yield appears to be independent of needle size.

Capsule Endoscopy and Double-Balloon Enteroscopy Complementary for Detecting Small-Bowel Pathology

In a retrospective chart review of diagnostic procedures, researchers compared the diagnostic yield of capsule endoscopy versus double-balloon enteroscopy in the detection of small-bowel pathology. Outcomes were evaluated in consecutive patients who underwent both procedures, performed by the same endoscopist, between January 2005 and August 2006. The most common indication for double-balloon enteroscopy was obscure overt gastrointestinal bleeding (48%), followed by obscure occult gastrointestinal bleeding (32%), mucosal changes (10%), suspected mass (9%), and a retained capsule (1%). Of the 237 patients evaluated, 50.6% were male and the mean age was 65 years (range, 17–100 years). Abnormalities were detected in 72% of patients with double-balloon enteroscopy, compared to 68% with capsule endoscopy, yielding a nonsignificant trend toward agreement between the 2 tests (kappa value, 0.28; P=.06). Double-balloon enteroscopy revealed small-bowel pathology in 24 of 45 patients (53.3%) with negative results by capsule endoscopy. Seven of these cases involved small intestinal diverticula. Conversely, capsule endoscopy revealed suspected small-bowel pathology in 18 of 37 patients (48.6%) with negative results on double-balloon enteroscopy. The investigators concluded that the 2 techniques appear to be complementary. Whereas double-balloon enteroscopy appears to better detect small-bowel diverticula and normal variants, capsule endoscopy appears to better detect ulcers, masses, and active bleeding. The researchers noted that, although capsule endoscopy may result in some false-positives, double-balloon enteroscopy may identify normal variants in these cases.

Presentations in IBS

2-Week Rifaximin Regimen Associated With Symptom Relief Over 12 Weeks in Nonconstipated Irritable Bowel Syndrome

The randomized, double-blind, placebo-controlled, multicenter phase III trials TARGET 1 and TARGET 2 evaluated the role of rifaximin in nonconstipated irritable bowel syndrome (IBS). A total of 1,260 patients with mild-to-moderate symptoms of nonconstipated IBS were randomly assigned to receive rifaximin 550 mg or placebo 3 times per day for 2 weeks. Patients were followed for the subsequent 10 weeks. The primary endpoint, the proportion of patients with adequate relief of weekly IBS symptoms for at least 2 of the first 4 weeks immediately following the treatment period, was significantly higher with rifaximin versus placebo in TARGET 1, TARGET 2, and the pooled data, in an intent-to-treat analysis (Table 1). Rifaximin was also associated with a significantly higher proportion of patients with IBS symptom relief and adequate relief of bloating. Patients taking rifaximin also had significantly improved daily assessments of IBS symptoms, bloating, abdominal pain, and discomfort compared to those taking placebo. The likelihood of sustained IBS symptom relief over the 3-month study period was also significantly higher with rifaximin versus placebo. The safety profile of rifaximin was similar to that of placebo.

Secondary Causes a Significant Factor in Patients With Presumed IBS With Short Remission After Antibiotic Therapy

The identification of small intestinal bacterial overgrowth (SIBO) by lactulose breath testing (LBT) in patients with IBS prompted the use of antibiotic therapy in IBS. This has led to the recognition of antibiotic-refractory IBS as well as a shift in tertiary care referrals of antibiotic-naive patients. In some cases, patients with abnormal LBT results have had poor responses to antibiotic therapy. To evaluate the role of alternative diagnoses in these patients, Chou and colleagues performed a chart review of patients with IBS and abnormal LBT results who were referred to a tertiary care medical center's gastrointestinal motility program after having poor responses to antibiotics, defined as a response lasting less than 1 month. Of the 65 patients evaluated, alternative explanations for abnormal LBT results and early relapse were identified for 20 patients (30.8%). These included rectocele/prolapse (3 patients), small-bowel obstruction (2 patients), small-bowel diverticular disease (2 patients), intestinal malrotation (1 patient), and volvulus (1 patient). These patients were all referred for surgical treatment. Other factors contributing to SIBO and short remission periods were chronic narcotic use (3 patients), neuropathic causes (1 patient each with Addison disease, scleroderma, colonic inertia, and vagotomy from laryngeal tumor surgery), and inflammatory diseases (1 patient each with ulcerative colitis and nonsteroidal anti-inflammatory drug–induced intestinal ulceration). Unusual causes included mitochondrial myopathy, atrophic gastritis, and vitamin B_{12} deficiency. The researchers concluded that the increasing use of antibiotics in patients with presumed IBS will likely lead to an increase in referrals to tertiary care centers based upon a lack of response to antibiotics.

Spherical Carbon Adsorbent AST-120 Improves Nonconstipating IBS Symptoms

The oral, nonabsorbed, carbon-based adsorbent AST-120 has been safely used in more than 360,000 Japanese patients and has been evaluated in patients with chronic

Table 1. Responders to Adequate Relief of IBS Symptoms and IBS-related Bloating (ITT Population)

Endpoints	TARGET 1 (N=623) (Rifaximin vs placebo)	TARGET 2 (N=637) (Rifaximin vs placebo)	Results of pooled data (N=1,260) (Rifaximin vs placebo)
Adequate relief of IBS symptoms	40.8% vs 31.2% (*P*=.0125)	40.6% vs 32.2% (*P*=.0263)	40.7% vs 31.7% (*P*=.0008)
Adequate relief of IBS-related bloating	39.5% vs 28.7% (*P*=.0045)	41.0% vs 31.9% (*P*=.0167)	40.2% vs 30.3% (*P*=.0002)

IBS=irritable bowel syndrome; ITT=intent-to-treat.

kidney disease, Crohn's disease, and type 2 diabetes. The agent appears to adsorb substances implicated in the pathogenesis of IBS, including bacterial toxins and bile acids. In a randomized, double-blind, placebo-controlled trial, Tack and colleagues evaluated the safety and efficacy of AST-120 in patients with diarrhea-predominant or alternating IBS. After a 2-week run-in period, a total of 115 patients were randomly assigned to AST-120 2 g (56 patients) or placebo (59 patients) administered 3 times per day for 8 weeks. All patients subsequently received placebo for a 2-week washout period, followed by an 8-week phase of open-label AST-120. Patients were considered responders if they had a reduction of at least 50% in days with pain over the previous 2 weeks of treatment compared to the run-in period. Severity of pain and bloating were assessed using 100-mm visual analog scales. Response rates were significantly higher with AST-120 versus placebo at Treatment Week 4 (27% vs 10%; *P*=.029) and increased to 32% versus 25%, respectively, at Week 8, regardless of gender or IBS subtype. Over the course of the 8-week randomized phase, responses were achieved in 21% of patients receiving AST-120 versus 11% of patients receiving placebo. Compared to placebo, AST-120 was also associated with greater mean reductions in bloating severity at Week 2 (13 mm vs 2 mm; *P*=.007) and Week 4 (14 mm vs -1 mm; *P*=.002). Patients receiving AST-120 were also more likely to attain at least a 1-point improvement in stool consistency and a greater improvement in regard to the effects of IBS symptoms on daily activities. These benefits abated during the washout period but resumed upon restarting AST-120 therapy. The agent appeared tolerable; more than 85% of patients in both groups completed the 8-week randomized phase, and adverse event rates were lower with AST-120 versus placebo.

Psychological Distress Associated With Development of Functional Gastrointestinal Disorders in Healthy Individuals

The exact causes of functional gastrointestinal disorders (FGIDs) have not been elucidated, though several etiologic factors have been proposed. Koloski and colleagues conducted a 12-year longitudinal, prospective, population-based cohort study evaluating the role of psychological factors in the development of FGIDs. The study, initiated in 1997, included 1,175 individuals from Penrith, Australia, 591 of whom did not meet Rome II diagnostic criteria for FGIDs. After 12 years, 35% of these participants had developed FGIDs, including functional abdominal bloating (11%), functional heartburn (11%), IBS (6%), and functional dyspepsia (4%). The investigators reported a significant correlation between anxiety levels in 1997 and diagnosis of an FGID in 2009. For every 5-point change in score on the Delusions-Symptom-States Inventory scale, the risk of FGID diagnosis was increased by 59% (odds ratio [OR], 1.59; 95% CI, 1.11–2.26; *P*=.01). This relationship remained after controlling for age, gender, and medication use for gastrointestinal symptoms. FGIDs that correlated with high anxiety at baseline included functional abdominal bloating (OR, 1.62; 95% CI, 1.04–2.52; *P*=.03) and functional dyspepsia (OR, 2.86; 95% CI, 1.62–5.08; *P*≤.001). Only functional dyspepsia remained an independent predictor (OR, 2.64; 95% CI, 1.44–4.84; *P*=.002). The presence of depression at baseline was also a significant independent predictor of functional dyspepsia at follow-up (OR, 2.51; 95% CI, 1.28–4.93; *P*=.007).

Efficacy, Safety of 12-Week Regimen of Once-Daily Oral Linaclotide in Patients With Chronic Constipation

Linaclotide is an orally administered, minimally absorbed, guanylate cyclase type-C receptor agonist. Two double-blind phase III trials (01 and 303) evaluated the efficacy and safety of linaclotide in 1,272 patients with chronic constipation. Patients had met the modified Rome II standardized criteria for chronic constipation, with fewer than 3 complete spontaneous bowel movements (CSBM) per week and no more than 6 SBMs per week during a 2-week baseline period. Patients were randomly assigned to linaclotide administered at 133 µg or 266 µg or placebo once daily for 12 weeks. The primary endpoint, the proportion of CSBM overall responders (≥3 CSBM, with an increase of ≥1 CSBM from baseline, for at least 9 weeks of the 12-week treatment phase), was met at both dose levels of linaclotide in both trials. In Trial 01, CSBM overall response rates were 16.0%, 21.3%, and 6.0%, respectively, for linaclotide 133 µg, 266 µg, and placebo (*P*=.0012 for low-dose linaclotide vs placebo; *P*<.0001 for high-dose linaclotide vs placebo). In Trial 303, CSBM response rates were 21.2%, 19.4%, and 3.3%, respectively (*P*<.0001 for both linaclotide doses vs placebo). Secondary endpoints (change from baseline in CSBMs, SBMs, stool consistency, straining, constipation severity, abdominal discomfort, and bloating) also improved with linaclotide versus placebo. Treatment responses first occurred during Week 1 and were sustained over the 12-week treatment period. The most common adverse event, diarrhea, was more frequent with linaclotide versus placebo in both trials (Trial 01, 17% vs 3%; Trial 303, 13% vs 7%). A few linaclotide and placebo patients discontinued treatment due to diarrhea (Trial 01, 5% and 1%, respectively; Trial 303, 3% and 1%, respectively).

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
Pruritus	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

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.

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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Shire

For patients with active, mild to moderate ulcerative colitis (UC),

There are a number of reasons physicians are choosing Lialda®

- Lialda is indicated for the induction of remission in patients with active, mild to moderate UC. Safety and effectiveness of Lialda beyond 8 weeks have not been established
- Lialda offers flexibility of both 2.4 g and 4.8 g once-daily doses
- Lialda is covered on most commercial managed care plans[1]*

*Reported for commercial plans, including BCBS.

- Over **1 million** prescriptions filled[2]
- Prescribed to over **150,000** patients[3]

Important Safety Information

- 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 allergic to sulfasalazine.
- Patients with pyloric stenosis may have prolonged gastric retention of Lialda, which could delay mesalamine release in the colon.
- 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. 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. Caution should be taken when prescribing Lialda to patients with conditions that predispose them to myocarditis or pericarditis.
- 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. In patients with renal impairment, 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.
- 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.
- 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 adjacent page.

References: 1. Fingertip Formulary. May 24, 2010. **2.** IMS Health, NPA *Plus*™, March 2007–January 2010, TRxs. **3.** Total Patient Tracker (TPT) from SDI; January 2007–December 2009. **4.** Kamm MA, Sandborn WJ, Gassull M, et al. Once-daily, high-concentration MMX mesalamine in active ulcerative colitis. *Gastroenterology*. 2007;132:66-75.

1200 mg of 5-ASA, once daily[4]

Lialda® with MMX®
(mesalamine) 1.2g
delayed release tablets

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