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April 18–22, 2012
Barcelona, Spain

Digestive Disease Week 2012

May 19–22, 2012
San Diego, California

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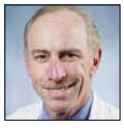

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GASTROENTEROLOGY & HEPATOLOGY

THE GASTRO & HEP REPORT

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Presentations in IBS

Oral Methylnaltrexone Relieves Opioid-Induced Constipation in Patients with Noncancer Pain

Opioid-induced constipation can influence patients' quality of life and pain control. Currently, a subcutaneous, injectable form of methylnaltrexone bromide (Relistor, Salix Pharmaceuticals) is available to treat opioid-induced constipation in patients with advanced illness. To evaluate whether an oral formulation of this drug is also effective for treatment of opioid-induced constipation in patients with chronic noncancer pain, Richard L. Rauck and associates recently conducted a phase III, double-blind, placebo-controlled trial. The results of this trial were presented at the 2012 Digestive Disease Week (DDW) meeting, held May 19–22, 2012 in San Diego, California.

This study enrolled 804 patients who were taking at least 50 mg oral morphine equivalents per day for at least 1 month and had a history of opioid-induced constipation. Patients were randomized to receive oral methylnaltrexone at 1 of 3 doses (150 mg, 300 mg, or 450 mg) or placebo once daily for 4 weeks and then as needed for another 8 weeks.

Over the 12 weeks of the study, the proportion of patients who experienced rescue-free bowel movements (RFBMs) within 4 hours of dosing was significantly higher among patients treated with 300-mg and 450-mg doses of methylnaltrexone compared to placebo. There was also a significant difference in all treatment groups compared to placebo in terms of the proportion of patients who attained a RFBM within 24 hours after the first dose (150 mg, 34%; 300 mg, 41%; 450 mg, 42%; placebo, 23%). Among patients treated with 300-mg and 450-mg doses of methylnaltrexone, a significantly greater proportion of patients achieved at least 3 RFBMs per week with an increase of at least 1 RFBM per week over baseline, compared to placebo (300 mg, 47.8%; 450 mg, 50.5%; placebo, 36.8%). Finally, there was a linear dose response for all 3 methylnaltrexone treatment groups over the first 4 weeks of dosing (P<.0001). The investigators noted that the incidence of adverse events was similar among treatment groups and placebo; abdominal pain, nausea, flatulence, and diarrhea were the most common adverse events reported.

Linaclotide Significantly Improved Abdominal Pain in Patients with IBS Regardless of Baseline Pain Severity

Previously, 2 phase III trials showed that linaclotide (Linzess, Ironwood Pharmaceuticals/Forest Pharmaceuticals) can effectively improve symptoms in patients with irritable bowel syndrome (IBS) with constipation. In these trials, patients were randomized to receive oral linaclotide (290 µg once daily) or placebo. During the 2-week baseline period and the 12-week treatment period, patients used an interactive, voice-response system to rate their highest level of abdominal pain in each 24-hour period; pain was rated on a 10-point scale from 0 (none) to 10 (very severe). Once treatment began, patients rated their relief of abdominal pain over the past week compared to baseline using a balanced 7-point scale.

During the 2012 DDW meeting, Philip S. Schoenfeld and colleagues presented the results of a post–hoc analysis in which they pooled data from these phase III studies and assessed the efficacy of linaclotide when patients were stratified according to their mean baseline abdominal pain score (<5, ≥5 to <7, or ≥7). This analysis found a significant improvement in 12-week abdominal pain scores with linaclotide compared to placebo (P<.0001). Further, improvements in abdominal pain with linaclotide occurred regardless of baseline abdominal pain severity (decreases in pain scores of 29–36% with linaclotide vs 18–20% with placebo; P<.0001). There was a correlation between baseline abdominal pain scores and the absolute improvement in abdominal pain (magnitude of change from baseline; r=0.26; P<.0001), but baseline abdominal pain scores did not correlate with the percent improvement from baseline (r=0.00; P=.92). For patient-reported relief of abdominal pain, linaclotide achieved higher ratings than placebo (2.9 vs 3.5 overall; P<.0001); in addition, significant improvements occurred with linaclotide across the 3 baseline pain level subgroups. Overall, the authors of the study concluded that linaclotide resulted in significant improvement in abdominal pain.

26 Weeks of Linaclotide Treatment Is Effective for Patients with IBS and Constipation

In another analysis of linaclotide, a phase III trial investigated this drug for treatment of IBS and constipation over an extended treatment period. In this randomized, double-blind trial presented at the 2012 DDW meeting, William D. Chey and associates assessed adequate relief and symptom severity over 26 weeks of linaclotide treatment among patients with IBS and constipation.

Patients with IBS and constipation were randomized to receive oral linaclotide (290 µg once daily) or placebo for 26 weeks. On a daily basis, patients rated abdominal pain at its worst during the previous 24 hours (0=none to 10=very severe), and they provided data on spontaneous bowel movement frequency. On a weekly basis, patients

reported adequate relief of IBS symptoms (yes/no) and IBS severity (1=none to 5=very severe). For this analysis, adequate relief responders were defined as patients with adequate relief of IBS symptoms for at least 13 of the 26 weeks of treatment.

The proportion of patients who were adequate relief responders was significantly higher in the linaclotide arm than in the placebo arm (49.1% vs 25.1%; *P*<.0001). Adequate relief responders had a mean decrease in abdominal pain of 52% compared to 18% for nonresponders (*P*<.0001), and they had an increased spontaneous bowel movement frequency of 3.0 per week compared to 0.8 per week for nonresponders (*P*<.0001). Both improvements in abdominal pain and spontaneous bowel movement frequency correlated with adequate relief (r=0.48 and r=0.53, respectively). The investigators concluded that patients with IBS and constipation who were treated with 26 weeks of linaclotide were more likely than placebo-treated patients to achieve adequate relief of symptoms and improvement in IBS severity.

Patients Respond Well to Lubiprostone for the Treatment of Moderate-to-Severe IBS with Constipation

Lubiprostone (Amitiza, Sucampo Pharmaceuticals) is a selective CIC-2 chloride channel activator that is approved for the treatment of IBS with constipation in women. At the 2012 DDW meeting, Taryn R. Joswick and colleagues presented the results of a post–hoc analysis of 2 pivotal, phase III trials in which patients were randomized 2:1 to receive lubiprostone (8 µg twice daily) or placebo for 12 weeks.

In this analysis, the authors investigated the effect of lubiprostone for the treatment of moderate-to-severe IBS with constipation; specifically, this study included patients with at least moderate abdominal pain and fewer than 3 spontaneous bowel movements per week at baseline. In analysis 1, patients were classified as responders if they achieved a 30%-or-greater improvement in mean abdominal pain scores from baseline, at least 1 more spontaneous bowel movement per week than at baseline, and at least 3 spontaneous bowel movements per week for either 6 of 12 treatment weeks or 9 of 12 treatment weeks. In analysis 2, patients with severe or very severe abdominal pain at baseline were assessed for weekly improvements in abdominal pain.

Of the 318 patients in analysis 1, treatment with lubiprostone resulted in significantly greater proportions of 6-of-12 week responders compared to placebo (24.1% vs 9.2%; *P*=.0031); the proportion of 9-of-12 week responders was also significantly higher among lubiprostone-treated patients compared to placebo (12.6% vs 3.4%; *P*=.0109). In analysis 2, patients with severe or very severe abdominal pain at baseline (n=277) showed significant improvements in abdominal pain on a weekly basis with lubiprostone compared to placebo (*P*=.0002). In addition, 35.1% of patients with severe or very severe pain at baseline had overall improvements of 30% or greater with lubiprostone.

Overall, lubiprostone was well tolerated; nausea, headache, and diarrhea were the most commonly reported adverse events. The researchers concluded that patients with severe symptoms at baseline had significant improvement in symptoms when treated twice daily with 8 µg of lubiprostone.

Alterations of Intestinal Microbiota After Probiotic Treatment Are Associated with Symptomatic Improvement in IBS

In a double-blind, placebo-controlled study presented at the 2012 DDW meeting, Kang Nyeong Lee and associates investigated whether changes in intestinal microbiota following treatment with probiotics correlated with changes in IBS symptoms. Patients diagnosed with IBS using the Rome III criteria were randomized to receive a mixture of probiotics (n=25 patients)—including *Bifidobacterium longum*, *Bifidobacterium breve*, *Bifidobacterium lactis*, *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, and *Streptococcus thermophilus*—or placebo (n=24) twice daily for 4 weeks.

Patients in both the probiotic treatment group and the placebo group showed similar improvements in diarrhea and constipation. However, patients treated with probiotics had significantly greater improvements in abdominal pain severity, frequency of pain, and frequency of defecation compared to patients treated with placebo (*P*<.05). In addition, the probiotic treatment group had greater improvements at 4 weeks in abdominal pain, satisfaction with bowel habits, and daily life activities compared to the placebo group (*P*<.05).

In addition to assessing patient symptoms, a quantitative real-time polymerase chain reaction assay was used to analyze DNA in feces both before and after treatment in a subset of patients (18 patients in the probiotic treatment group and 15 patients in the placebo group). There was no difference in fecal microbiota at baseline. Four weeks of treatment with probiotics resulted in significant increases in total numbers of *B. lactis, L. rhamnosus,* and *S. thermophilus*; this change was not seen in patients who received placebo. No changes were seen in the numbers of *B. longum, Bifidobacterium bifidum, L. acidophilus, Clostridium perfringens*, or *Escherichia coli* in either the probiotic group or the placebo group after 4 weeks of treatment. Finally, improvement rates for frequency of abdominal pain were significantly greater among those patients who showed a 10-fold increase in *B. lactis* compared to patients with no change in *B. lactis* numbers (91.9% vs 54.5%; *P*=.03).

Presentations in GERD

Proton Pump Inhibitor Treatment May Benefit Some Patients with Suspected Reflux–Chronic Cough

At the 2012 DDW meeting, Peter J. Kahrilas and colleagues presented the results of a study that sought to determine whether chronic cough responds to proton pump inhibitor (PPI) therapy in patients with evidence of gastroesophageal reflux disease (GERD). To address this question, the authors used systematic searches in PubMed and Embase from 1966 to August 2011 to identify clinical trials reporting PPI therapy and cough response in patients with GERD or laryngopharyngeal reflux (LPR). The search identified 52 potentially relevant clinical trials published in English. Of these trials, 10 were randomized, placebo-controlled studies that included an assessment of whether cough responds to either PPI or histamine receptor antagonist (H_2RA) therapy. Six studies included data on PPI efficacy in patients with confirmed GERD or confirmed LPR, 1 study included data on H_2RA efficacy in patients with confirmed GERD, and 4 studies included data from patients with unconfirmed GERD or unconfirmed LPR.

Five of the 7 studies with sufficient data on patients with confirmed GERD showed a positive therapeutic gain for treatment with PPIs or H_2RAs compared to placebo (range, 12.5–35.8%). Among all 7 studies of patients with confirmed GERD, 2 showed significantly improved cough scores with therapy, 1 study revealed a nonsignificant trend toward improved cough scores, 1 study showed no significant difference in the prevalence of cough response, and 3 studies found no significant improvement in cough scores.

Two studies had sufficient data to calculate therapeutic gain in patients with unconfirmed GERD or LPR (range, 0.0–8.6%); only 1 of these studies showed a positive therapeutic gain for PPI therapy versus placebo. Only 1 study had separate data for patients with unconfirmed GERD, and it showed no significant improvement in cough scores with treatment. Kahrilas and coauthors concluded that they could not rule out the possibility that PPI or H_2RA acid suppression therapy might yield a therapeutic benefit for chronic cough.

Weight Loss Reduces GERD Symptoms

High body mass index (BMI) is known to be associated with GERD symptoms, but whether weight loss can provide symptom relief remains unclear. At the 2012 DDW meeting, Elvind Ness-Jensen and associates presented the results of a study in which they assessed the effect of weight loss on GERD symptoms. This analysis used data from the HUNT Study, a population-based, cohort study conducted in the Norwegian county of Nord-Trøndelag. A total of 29,610 patients were prospectively followed from baseline (HUNT 2, 1995–1997) to follow-up (HUNT 3, 2006–2009). Data on GERD symptoms were collected by questionnaires. A logistic regression analysis was then performed, and the results were stratified according to antireflux medication. The results were adjusted for sex, age, smoking status, alcohol consumption, education, and frequency of physical exercise.

In HUNT 2, a total of 9,299 persons reported GERD symptoms; 2,398 (26%) of these individuals reported no GERD symptoms in HUNT 3. Among study participants who had a BMI reduction of at least 3.5 kg/m^2, the odds ratio (OR) for loss of GERD symptoms was 1.98 (95% confidence interval [CI], 1.45–2.72; P<.001) if the patients were taking antireflux medications less than once weekly and 3.95 (95% CI, 2.03–7.65; P<.001) if they were taking antireflux medication at least weekly.

Severe GERD symptoms were reported in 1,553 persons in HUNT 2, with 284 individuals (18%) reporting no GERD symptoms in HUNT 3. For those persons who had a BMI reduction of at least 3.5 kg/m^2, the OR for loss of GERD symptoms was 0.90 (95% CI, 0.32–2.55; P=.189) for patients who were taking antireflux medications less than once weekly and 3.11 (95% CI, 1.13–8.58; P=.047) if they were taking antireflux medication at least weekly. The investigators concluded that weight loss was associated with loss of GERD symptoms, and reductions in BMI appeared to increase the efficacy of antireflux medications.

Underreporting of Symptoms Has Consequences for Interpretation of Ambulatory Reflux Monitoring

Ambulatory pH and impedance monitoring can be used to determine an association between symptoms and reflux events, but timely documentation of symptoms by patients is essential. At the 2012 DDW meeting, Michael F. Vaezi and associates presented the results of a study that determined the temporal accuracy of patient-reported acid reflux events. The investigators employed a novel, ambulatory, acoustic monitoring system that detects coughs through tracheal and chest wall sounds. This system was used in conjunction with ambulatory pH/impedance monitoring that records acid reflux events and nonacid reflux events. Patient-recorded

symptoms were compared to the time of the cough event as detected by the acoustic recording device. The events were considered to be concordant if they occurred within 1, 2, or 5 minutes of each other. The study enrolled patients with chronic cough who had not received PPI therapy in the previous 10 days.

The audio device detected significantly more cough events than the number of cough events reported by patients (median of 216 events [range, 90–275] vs median of 34 events [range, 22–60], respectively; $P<.001$). According to the 1-minute, 2-minute, and 5-minute concordance windows, patients failed to report 91%, 82%, and 71% of audible coughs, respectively. The investigators noted that there was a higher degree of concordance among the 6 audio-recording listeners than between the audio recording and the patient-reported symptoms ($P<.001$). The pattern of cough frequency detected by the audio-recording listeners was similar to the pattern of coughs reported by the patient, but the listeners reported more cough events. The authors of the study concluded that most cough events were not reported by patients; thus, they cautioned against making clinical decisions based solely on ambulatory reflux monitoring.

Utility of Biopsies for Eosinophilic Esophagitis in Patients with Dysphagia

If patients with dysphagia undergo an endoscopy evaluation that does not reveal an obvious cause for their complaint, then tissue biopsies may be taken and evaluated for eosinophilic esophagitis (EoE). To determine whether this approach is beneficial, Vu Le and colleagues assessed the diagnostic yield of EoE in patients with normal and abnormal endoscopy findings. The results of this study were presented at the 2012 DDW meeting.

The investigators retrospectively identified patients with dysphagia who had endoscopic biopsies taken for pathologic evaluation at the University of Oklahoma Health Sciences Center. The analysis included 547 upper endoscopies in 527 patients (age, 18–90 years). Among the 547 endoscopies, 52% (n=284) were normal, 16% (n=85) showed findings suggestive of EoE (furrowing or longitudinal rings), 13% (n=73) showed signs of esophagitis, 8% (n=45) revealed lower esophageal strictures or Schatzki rings, and 11% (n=60) showed other findings, such as erythema or erosions. The pathology reports found that 55% of biopsies (n=303) showed signs of esophagitis, 38% (n=207) showed normal mucosa, and 7% (n=37) showed signs of EoE. Of the 37 patients with EoE that was identified by pathology, only 23 cases were identified as EoE via endoscopy. The remainder of the pathology-diagnosed EoE cases had normal endoscopies (n=7) or other findings (n=7).

The study authors concluded that biopsies for pathologic evaluation of EoE often correlate with observed endoscopic features that are suggestive of EoE—such as furrowing or longitudinal rings. However, some patients had EoE identified by pathology despite normal endoscopic findings. More studies are needed to investigate the diagnostic yield for EoE in patients with normal endoscopic findings.

Smoking Is an Independent Risk Factor for Barrett Esophagus

Smoking has been associated with esophageal adenocarcinoma, but data are lacking to answer the question of whether smoking is a risk factor for Barrett esophagus. To explore this possibility, Gokulakrishnan Balasubramanian and associates conducted a prospective study that assessed the association between smoking and the risk of Barrett esophagus in patients with GERD. Results of this study were presented at the 2012 DDW meeting.

A total of 1,111 consecutive patients undergoing endoscopy for evaluation of GERD were asked to complete a validated GERD questionnaire. The mean age of the patients was 57.5 years, 82.8% of patients were white, 92.8% were male, and patients' mean BMI was 29.5 kg/m^2. The study included 378 (34%) current smokers and 733 (66%) nonsmokers. A univariate analysis found that the smokers were younger (52.3 years vs 60.3 years; $P<.0001$), had a lower BMI (28.8 kg/m^2 vs 29.9 kg/m^2; $P=.001$), and were less likely to be taking aspirin (36.6% vs 44.1%; $P=.018$). No significant differences in race, gender, family history, GERD symptoms, or treatments (PPIs, H_2 blockers, or statins) were observed between smokers and nonsmokers.

Barrett esophagus was diagnosed in 153 patients (13.8%). Among smokers, the calculated adjusted OR for the presence of confirmed Barrett esophagus (intestinal metaplasia on histology) was 1.56 (95% CI, 1.02–2.38). Thus, smokers had a 50–60% higher risk for Barrett esophagus than nonsmokers. The investigators concluded that smoking is an independent risk factor for Barrett esophagus.

Risk Factors for *Helicobacter pylori* Infection in Latin America

At the 2012 DDW meeting, Carolina Porras and associates presented the results of a study that investigated the prevalence of *Helicobacter pylori* infection and the risk factors associated with this infection among adults in Latin America. For this analysis, the authors used data collected during the initial screening visit of a randomized clinical trial for *H. pylori* eradication. This initial population included 1,852 adults who

were screened for *H. pylori* infection by urea breath testing; study participants were from Santiago, Chile; Túquerres, Colombia; Guanacaste, Costa Rica; Copán, Honduras; Obregón, México; Tapachula, México; and León, Nicaragua. The patients were interviewed and completed the Rome III gastrointestinal symptom history questionnaire. Multivariate analyses were adjusted for sex, age, and study center.

The overall prevalence of *H. pylori* infection was 79.4% (95% CI, 77.5–81.2) regardless of sex, age, or study site. (One exception was Tapachula, Mexico, where the prevalence was only 70.1%). Several childhood demographic and socioeconomic conditions were associated with increasing odds of *H. pylori* infection, including increasing number of siblings ($P<.0001$) and factors such as earth flooring (OR, 1.8), more than 2 persons per bedroom (OR, 1.4), and lack of indoor plumbing (OR, 1.3). Current demographic and socioeconomic conditions that were associated with an increased prevalence of *H. pylori* infection included more than 3 children per household (OR, 1.7) and crowding (OR, 1.8). In contrast, the prevalence of *H. pylori* infection was lower among persons with more than 12 years of schooling (OR, 0.5) and those employed outside the home (OR, 0.7). Smoking, alcohol use history, and chronic dyspeptic symptoms were not associated with *H. pylori* infection. The researchers concluded that there is a high prevalence of *H. pylori* infection in these 6 Latin American countries and that infection was associated with poor socioeconomic conditions.

Effect of Amiloride on Acid-Induced Heartburn in Patients with Nonerosive Esophageal Reflux Disease

Acid-sensing ion channels (ASICs) are esophageal nocicepters that have been proposed to mediate heartburn. To determine if ASICs are involved in heartburn in patients with nonerosive esophageal reflux disease, William J. Bulsiewicz and colleagues performed a randomized, double-blind, crossover study in which patients underwent esophageal perfusion with either amiloride (a diuretic agent known to inhibit ASICs) or placebo prior to acid-induced heartburn. The results of this study were presented at the 2012 DDW meeting.

Inclusion criteria included heartburn symptoms for at least 6 months, moderate heartburn for 3 of the last 7 days, partial or complete response to PPI therapy, absence of erosive/EoE, and a positive modified Berstein test. Twenty-three patients were screened for this study, and 14 patients met the inclusion criteria (7 complete PPI responders and 7 partial PPI responders); 13 of the 14 patients were negative for *H. pylori* infection. Patients were randomized to receive intraesophageal perfusion with amiloride (10 mg total) or placebo for 5 minutes. Patients then underwent perfusion with hydrochloric acid (100 mM concentration) for 15 minutes or until the onset of heartburn. Once heartburn had resolved, patients were perfused with the other treatment (either amiloride or placebo) for 5 minutes, after which they again underwent acid perfusion.

As measured by an increase from baseline on a 10-point visual analog scale, heartburn severity was only slightly lower when patients were pretreated with amiloride versus placebo (2.5±0.33 points vs 2.64±0.45 points, respectively). However, the time to heartburn onset, as measured from the start of acid perfusion, was longer with amiloride than with placebo (2.93±0.3 min vs 2.36±0.29 min, respectively; $P>.05$). The results were comparable regardless of which agent was perfused first. No differences were observed between partial PPI responders compared to complete PPI responders. While amiloride prolonged the time until onset of heartburn, the difference compared to placebo was not statistically significant. The investigators suggested that this finding might be due to suboptimal absorption or contact time of the drug.

Presentations in Hepatology

High SVR Rates in Prior Treatment Failures After Re-Treatment with Boceprevir-Based Therapy

The PROVIDE study enrolled patients from the control arms of phase II and phase III clinical trials of boceprevir (Victrelis, Merck); these patients had all received at least 12 weeks of peginterferon and ribavirin but failed to achieve sustained virologic response (SVR) due to futility, virologic breakthrough, or relapse. During the PROVIDE study, patients received boceprevir (800 mg 3 times daily), peginterferon (1.5 µg/kg/week), and weight-based ribavirin (600–1,400 mg/day) for up to 44 weeks. Interim efficacy and safety data from this study were presented by Jean-Pierre Bronowicki at the 47th Annual Meeting of the European Association for the Study of the Liver (EASL), held April 18–22, 2012 in Barcelona, Spain.

The study enrolled 168 patients; 51% of patients were partial responders, 31% were null responders (<2 $\log_{10}$ decline in hepatitis C virus [HCV] RNA level at Treatment Week 12), and 15% were relapsers. A total of 138 patients were included in this interim analysis.

After the lead-in phase, 78% of prior null responders and 24% of prior partial responders/relapsers had a less-than-1 $\log_{10}$ decline in HCV RNA level; among these patients, SVR rates were 36% in prior null responders and 64% in prior partial responders. Among patients with at least a 1 $\log_{10}$ decline in HCV RNA level, the overall SVR rate was 68%: 55% in prior null responders, 72% in prior partial responders, and 56% in relapsers. The overall SVR rate at the end of the follow-up period was 59% (81 of 138 patients): 40% in prior null responders, 68% in prior partial responders, and 56% in relapsers. A multivariate analysis found that prior nonresponder status, baseline platelet levels, gender, and high viral load were independent predictive factors for SVR.

Serious adverse events were observed in 10% of patients. The most common adverse event was anemia, which occurred in 48% of patients; severe anemia (hemoglobin level <8.5 g/dL) occurred in 11% of patients. Other common adverse events included fatigue (47%), dysgeusia (34%), nausea (30%), and neutropenia (22%).

Ribavirin Dose Reduction Versus Erythropoietin for Anemia Management

The addition of an HCV protease inhibitor to peginterferon and ribavirin therapy can increase the risk for anemia. At the 2012 EASL Annual Meeting, Fred Poordad and colleagues presented the results of a study that sought to determine the efficacy, safety, and tolerability of erythropoietin administration versus ribavirin dose reduction for the treatment of anemia in patients receiving boceprevir, peginterferon, and ribavirin.

Treatment-naïve patients with chronic, genotype 1 HCV infection were enrolled in this study. Participants were at least 18 years of age, showed no evidence of hepatocellular carcinoma or co-infection, and had normal baseline hemoglobin levels (12–15 g/dL for female patients; 13–15 g/dL for male patients). Patients received 4 weeks of lead-in therapy with peginterferon (1.5 µg/kg/week) and ribavirin (600–1,400 mg/day) followed by boceprevir (800 mg 3 times daily) plus peginterferon and ribavirin for a total treatment duration of either 28 or 48 weeks.

Hemoglobin levels at or below 10 g/dL after the 4-week lead-in period occurred in 73% (500/687) of patients; these patients were randomly assigned to either a 200–400-mg/day reduction in ribavirin dose (n=249) or 40,000 IU/week erythropoietin (n=251). If hemoglobin levels dropped to 8.5 g/dL or lower, secondary intervention was allowed. If hemoglobin levels dropped to 7.5 g/dL or lower, the patient was discontinued from the study.

Comparison of the ribavirin dose-reduction arm and the erythropoietin arm revealed no differences in end-of-treatment virologic response rates (82% in both groups), relapse rates (10% in both groups), or SVR rates (71% in both groups). Statistical analyses revealed that the probability of achieving SVR was similar for patients managed with ribavirin dose reduction and those given erythropoietin (P=.769), and SVR was not associated with the degree of hemoglobin decline among patients who developed anemia. Finally, the rates of serious adverse events and study discontinuations were similar for patients who were managed with ribavirin dose reduction and those who received erythropoietin.

100% SVR in *IL-28B* CC Patients Treated with 12 Weeks of Telaprevir, Peginterferon, and Ribavirin

In the ADVANCE trial, 90% of patients with genotype 1 HCV infection and the interleukin (IL)-28B CC genotype achieved SVR when treated with telaprevir (Incivek, Vertex), peginterferon, and ribavirin. To investigate SVR rates in patients with *IL-28B* genotype CC versus non-CC, Jean-Pierre Bronowicki and associates performed a retrospective analysis of data from the PROVE2 study; their results were presented at the 2012 EASL Annual Meeting.

Samples from treatment-naïve patients with genotype 1 HCV infection were analyzed for the presence of the *IL-28B* CC genotype at polymorphic site rs12979860. Of the 156 patients who consented to genetic testing, data were available for 141 patients. In terms of *IL-28B* genotype, 43 patients (30%) had genotype CC, 83 patients (59%) had genotype CT, and 15 patients (11%) had genotype TT.

All of the patients with *IL-28B* genotype CC who received telaprevir, peginterferon α-2a, and ribavirin for 12 weeks achieved SVR (n=12). SVR was also achieved in the majority of patients with *IL-28B* genotype CC who received other treatment regimens: 94% (15/16) of patients who were treated with telaprevir, peginterferon α-2a, and ribavirin for 12 weeks followed by peginterferon α-2a and ribavirin for an additional 12 weeks; 75% (3/4) of patients treated with telaprevir and peginterferon α-2a for 12 weeks; and 64% (7/11) of patients in the control group.

Burden of Illness in Treatment-Naïve HCV-Infected Patients in the United States

At the 2012 EASL Annual Meeting, Antoine El Khoury and colleagues presented the results of a study that examined work productivity, daily activities, healthcare resource use, economic costs, and health-related quality of life among treatment-naïve, HCV-infected patients in the United States. The analysis was restricted to patients who reported physician-diagnosed HCV infection, no HIV/AIDS or hepatitis B virus (HBV) co-infection, and no prior or current treatment for HCV infection (n=306). The HCV-infected group was compared to an unmatched control group (n=73,586) and to a matched control group (n=306).

The Work Productivity and Activity Impairment questionnaire was used to assess impairment in work and nonwork activities. This questionnaire revealed that activity impairment was significantly greater in untreated HCV-infected patients (42.2%) than in matched controls (27.3%; *P*<.001). Impairment at work was assessed among employed HCV-infected patients (n=121) and matched controls (n=141). There was no significant difference in absenteeism (the percentage of work time missed due to the patient's health in the past 7 days) between untreated HCV-infected patients and matched controls (5.0% vs 2.8%; *P*=.089); however, untreated HCV-infected patients had increased rates of presenteeism (the percentage of impairment at work due to the patient's health in the past 7 days; 23.2% vs 13.1%; *P*<.001) and overall work impairment (combination of absenteeism and presenteeism; 26.2% vs 14.9%; *P*<.001).

In terms of healthcare resource utilization, untreated HCV patients had significantly more physician visits annually than matched controls (12.2 vs 8.2; *P*<.001), as well as more emergency room visits (0.76 vs 0.54; *P*=.023); however, there was no significant difference in hospitalizations (0.42 vs 0.25; *P*=.071). Associated direct costs were all higher among untreated HCV-infected patients. Additionally, health-related quality of life in untreated HCV-infected patients was poorer than in matched controls as shown by a lower mean Mental Component Summary score (43.7 vs 48.6; *P*<.001), a lower mean Physical Component Summary score (40.2 vs 44.9; *P*<.001), and a lower Health Utility score (0.65 vs 0.73; *P*<.001).

Rifaximin Salvage Therapy Is the Most Cost-Effective Strategy for Management of Chronic Hepatic Encephalopathy

Navin Paul and associates conducted a decision-analysis study to determine which treatment strategy is most cost-effective for treatment of hepatic encephalopathy (HE): rifaximin (Xifaxan, Salix Pharmaceuticals), lactulose, or a hybrid strategy involving both drugs. Results of this analysis were presented at the 2012 DDW meeting.

The investigators employed Markov modeling to test the cost-effectiveness of rifaximin monotherapy, lactulose monotherapy, combination therapy with both rifaximin and lactulose, and rifaximin salvage therapy (initiation of therapy with lactulose followed by crossover to rifaximin in cases of inadequate response or intolerance). This model analyzed the effects of these therapies for a cohort of 50-year-old patients with overt HE.

A systematic literature review identified randomized, controlled trials of patients with HE; all studies had at least 4 weeks of follow-up. Data from these studies were used to calculate probability estimates, which were then varied over a wide range in a sensitivity analysis. The model utilized a third-party payer's perspective and included cost estimates from Medicare and Red Book for a patient with cirrhosis and HE. The primary outcome was discounted cost per life-year (LY) gained.

Rifaximin salvage therapy was the overall dominant strategy in a limited 6-month model. During the first year, 1.3 hospitalizations were projected for the lactulose arm, and 0.8 hospitalizations were projected for the rifaximin arm. When the analysis was extended to a lifetime horizon, rifaximin salvage therapy was the most effective strategy (2.5 LY), and lactulose monotherapy was the least effective strategy (2.1 discounted LY).

In terms of cost, rifaximin monotherapy was the most expensive strategy ($65,800). Lactulose monotherapy was the least expensive strategy ($61,300), but this lower long-term cost reflected a higher mortality rate in this treatment group. When balancing both costs and effectiveness, rifaximin monotherapy and rifaximin salvage therapy were found to be the most relevant options. Of these 2 options, the investigators concluded that rifaximin

salvage therapy should be the dominant and preferred approach for treating patients with chronic HE, as it is both more effective and less expensive.

Efficacy of 5 Years of Tenofovir Disoproxil Fumarate in Chronic HBV-Infected Patients with High Viral Loads

Successful treatment of HBV infection in patients with high baseline viral loads remains a significant clinical challenge. At the 2012 DDW meeting, Stuart C. Gordon and coauthors presented the results of a phase III, randomized study that assessed the long-term efficacy of tenofovir disoproxil fumarate (TDF) in this population. All patients were initially randomized to receive 300 mg TDF or 10 mg adefovir dipivoxil (ADV; Hepsera, Gilead). At Week 48, eligible patients initiated open-label TDF for up to an additional 7 years.

Patients were classified according to baseline viral load: 129 patients had high viral loads (HBV DNA ≥9 $\log_{10}$ copies/mL) and 512 patients had non–high viral loads (HBV DNA <9 $\log_{10}$ copies/mL). Most of the patients in both groups were male (74%), but patients with high baseline viral loads were younger than patients with non–high viral loads (31 years vs 43 years, respectively). Among patients with high baseline viral loads, 34.9% had alanine aminotransferase (ALT) levels more than twice the upper limit of normal (ULN), 91.5% were hepatitis B e antigen (HBeAg)-positive at baseline, and only 10% had antibodies to HBeAg at baseline. In contrast, 53% of non–high viral load patients had ALT levels more than twice the ULN, 29% were HBeAg-positive at baseline, and 73% had antibodies to HBeAg at baseline.

At Week 240 on treatment, 69.5% of high viral load patients and 83.5% of non–high viral load patients had achieved ALT normalization. Among patients who were HBeAg-positive at baseline, hepatitis B surface antigen (HBsAg) loss occurred in 19.3% and 4.3% of high viral load patients and non–high viral load patients, respectively (P<.001); HBsAg seroconversion occurred in 13.6% and 4.3%, respectively (P=.011).

Regression of histologic cirrhosis was observed in both the high viral load and non–high viral load groups. Neither group had persistent viremia at Week 240. The majority of patients (96%) achieved HBV DNA levels below 400 copies/mL by Week 240 regardless of their baseline viral load; however, patients with non–high baseline viral loads achieved more rapid viral decline. Among high viral load patients who experienced virologic breakthrough, 2 patients had a conserved site change that did not reduce sensitivity to TDF, 3 patients had a polymorphic site change, and 6 patients had no change.

Outcomes of Oral Antiviral Treatment for Chronic HBV Infection in Routine Clinical Practice

The approved oral antiviral agents that are commonly prescribed for the treatment of chronic HBV infection include lamivudine (LAM), ADV, entecavir (ETV; Baraclude, Bristol-Myers Squibb), and TDF. At the 2012 DDW meeting, Mindie H. Nguyen and associates presented the results of a study in which they examined outcomes when these agents were used in a routine clinical care setting. The study included 957 consecutive patients treated with LAM, ADV, ETV, or TDF for at least 6 months. The endpoints of the study were complete viral suppression (HBV DNA level <40–60 IU/mL) and ALT normalization (ALT level ≤40 U/L) at 6 and 12 months of treatment.

Among treatment-naïve patients, complete viral suppression at 6 months was achieved in 38% of patients treated with LAM, 44% of patients treated with ADV, 63% of patients treated with ETV, and 63% of patients treated with TDF. At 12 months, complete viral suppression rates were 37% with LAM, 50% with ADV, 73% with ETV, and 79% with TDF. The ETV and TDF treatment groups also had similar rates of ALT normalization at 6 months (91% vs 88%, respectively) and 12 months (94% vs 93%, respectively). Baseline clinical characteristics were similar among treatment-naïve patients who received ETV (n=373) and those who received TDF (n=107).

Among treatment-experienced patients who were switched to ETV (n=165) or TDF (n=67), those who were switched to ETV had a higher mean HBV DNA level at the time of the switch (3.82 $\log_{10}$ IU/mL vs 2.33 $\log_{10}$ IU/mL, respectively; P<.001); patients switched to ETV also had a higher median ALT level at the time of the switch (35 U/L vs 29 U/L, respectively; P=.07). Among treatment-experienced patients, the ETV and TDF treatment groups had similar rates of complete viral suppression at both 6 months (75% vs 79%, respectively) and 12 months (82% vs 89%, respectively); they also had similar rates of ALT normalization at both 6 months (94% vs 90%, respectively) and 12 months (91% vs 94%, respectively). Patients treated with ETV or TDF showed no evidence of viral breakthrough or viral resistance. Overall, the authors concluded that ETV and TDF were associated with more favorable patient outcomes (compared to LAM and ADV) in both treatment-naïve and treatment-experienced patients.

Incivek Insert 1 FPO

INCIVEK™
(telaprevir) Tablets
Brief Summary of Prescribing Information. See package insert for full prescribing information.

INDICATIONS AND USAGE

Chronic Hepatitis C

INCIVEK™ (telaprevir), in combination with peginterferon alfa and ribavirin, is indicated for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including cirrhosis, who are treatment-naïve or who have previously been treated with interferon-based treatment, including prior null responders, partial responders, and relapsers.

The following points should be considered when initiating treatment with INCIVEK:

- INCIVEK must not be administered as monotherapy and must only be prescribed with both peginterferon alfa and ribavirin.
- A high proportion of previous null responders (particularly those with cirrhosis) did not achieve a Sustained Virologic Response (SVR) and had telaprevir resistance-associated substitutions emerge on treatment with INCIVEK combination treatment.
- INCIVEK efficacy has not been established for patients who have previously failed therapy with a treatment regimen that includes INCIVEK or other HCV NS3/4A protease inhibitors.

CONTRAINDICATIONS

Contraindications to peginterferon alfa and ribavirin also apply to INCIVEK combination treatment.

INCIVEK combination treatment is contraindicated in:

- women who are or may become pregnant. Ribavirin may cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug treatment, the patient should be apprised of the potential hazard to a fetus.
- men whose female partners are pregnant.

INCIVEK is contraindicated when combined with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index). INCIVEK is contraindicated when combined with drugs that strongly induce CYP3A and thus may lead to lower exposure and loss of efficacy of INCIVEK. Contraindicated drugs are listed below.

Drug Class	Drugs within Class that are Contraindicated with INCIVEK	Clinical Comments
Alpha 1-adrenoreceptor antagonist	Alfuzosin	Potential for hypotension or cardiac arrhythmia
Antimycobacterials	Rifampin	Rifampin significantly reduces telaprevir plasma concentrations.
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Potential for acute ergot toxicity characterized by peripheral vasospasm or ischemia
GI motility agent	Cisapride	Potential for cardiac arrhythmias
Herbal products	St. John's wort (*Hypericum perforatum*)	Plasma concentrations of telaprevir can be reduced by concomitant use of the herbal preparation St. John's wort.
HMG CoA reductase inhibitors	Lovastatin, simvastatin	Potential for myopathy including rhabdomyolysis
Neuroleptic	Pimozide	Potential for serious and/or life-threatening adverse reactions such as cardiac arrhythmias
PDE5 inhibitor	Sildenafil (Revatio®) or tadalafil (Adcirca®) [for treatment of pulmonary arterial hypertension][a]	Potential for PDE5 inhibitor-associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope
Sedatives/hypnotics	Orally administered midazolam[b], triazolam	Prolonged or increased sedation or respiratory depression

[a] See table under *Drug Interactions* for co-administration of sildenafil and tadalafil when dosed for erectile dysfunction.
[b] See table under *Drug Interactions* for parenterally administered midazolam.

WARNINGS AND PRECAUTIONS

Pregnancy: Use with Ribavirin and Peginterferon Alfa. Ribavirin may cause birth defects and/or death of the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy.

Because INCIVEK must be used in combination with peginterferon alfa and ribavirin, the contraindications and warnings applicable to those drugs are applicable to combination therapy. Female patients of childbearing potential and their male partners as well as male patients and their female partners must use 2 effective contraceptive methods during treatment and for 6 months after all treatment has ended. Female patients should have monthly pregnancy tests during treatment and during the 6-month period after stopping treatment. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients as significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Refer also to the prescribing information for ribavirin.

Female Patients-Hormonal contraceptives may be continued but may not be reliable during INCIVEK dosing and for up to two weeks following cessation of INCIVEK. During this time, female patients of childbearing potential should use two effective non-hormonal methods of contraception. Examples may include barrier methods or intrauterine devices (IUDs). Two weeks after completion of INCIVEK treatment, hormonal contraceptives are again appropriate as one of the two required effective methods of birth control; however, specific prescribing information recommendations should be followed for the contraceptives.

Serious Skin Reactions. Serious skin reactions, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) and Stevens-Johnson Syndrome (SJS) were reported in less than 1% of subjects who received INCIVEK combination treatment compared to none who received peginterferon alfa and ribavirin alone. These serious skin reactions required hospitalization, and all patients recovered. The presenting signs of DRESS may include rash, fever, facial edema, and evidence of internal organ involvement (e.g., hepatitis, nephritis). Eosinophilia may or may not be present. The presenting signs of SJS may include fever, target lesions, and mucosal erosions or ulcerations (e.g., conjunctivae, lips).

If a serious skin reaction occurs, all components of INCIVEK combination treatment must be discontinued immediately and the patient should be promptly referred for urgent medical care.

Rash. Rash developed in 56% of subjects who received INCIVEK combination treatment. Severe rash (e.g., a generalized rash or rash with vesicles or bullae or ulcerations other than SJS) was reported in 4% of subjects who received INCIVEK combination treatment compared to less than 1% who received peginterferon alfa and ribavirin alone. The severe rash may have a prominent eczematous component.

Patients with mild to moderate rashes should be followed for progression of rash or development of systemic symptoms. If rash progresses and becomes severe or if systemic symptoms develop, INCIVEK should be discontinued. Peginterferon alfa and ribavirin may be continued. If improvement is not observed within 7 days of INCIVEK discontinuation, sequential or simultaneous interruption or discontinuation of ribavirin and/or peginterferon alfa should be considered. If medically indicated, earlier interruption or discontinuation of ribavirin and peginterferon alfa should be considered. Patients should be monitored until the rash has resolved. INCIVEK must not be reduced or restarted if discontinued due to rash. Treatment of rash with oral antihistamines and/or topical corticosteroids may provide symptomatic relief but effectiveness of these measures has not been established. Treatment of rash with systemic corticosteroids is not recommended.

Anemia. Anemia has been reported with peginterferon alfa and ribavirin therapy. The addition of INCIVEK to peginterferon alfa and ribavirin is associated with an additional decrease in hemoglobin concentrations. Hemoglobin values less than or equal to 10 g per dL were observed in 36% of subjects who received INCIVEK combination treatment compared to 17% of subjects who received peginterferon alfa and ribavirin. Hemoglobin values less than 8.5 g per dL were observed in 14% of subjects who received INCIVEK combination treatment compared to 5% of subjects receiving peginterferon alfa and ribavirin.

In subjects receiving INCIVEK combination treatment, 4% discontinued INCIVEK, 1% discontinued INCIVEK combination treatment, and 32% underwent a ribavirin dose modification (reduction, interruption or discontinuation) due to anemia. In subjects treated with peginterferon alfa and ribavirin alone, there were two discontinuations and 12% underwent ribavirin dose modification due to anemia.

Hemoglobin should be monitored prior to and at least at weeks 2, 4, 8 and 12 during INCIVEK combination treatment and as clinically appropriate. For the management of anemia, ribavirin dose reductions should be used (refer to the prescribing information for ribavirin for its dose reduction guidelines). If ribavirin dose reductions are inadequate, discontinuation of INCIVEK should be considered. If ribavirin is permanently discontinued for the management of anemia, INCIVEK must also be permanently discontinued. Ribavirin may be restarted per the dosing modification guidelines for ribavirin. The dose of INCIVEK must not be reduced and INCIVEK must not be restarted if discontinued.

Drug Interactions. See the table above for a listing of drugs that are contraindicated for use with INCIVEK due to potentially life-threatening adverse events or potential loss of therapeutic effect to INCIVEK. Refer to the table included under *Drug Interactions* for established and other potentially significant drug-drug interactions.

Laboratory Tests. HCV-RNA levels should be monitored at weeks 4 and 12 and as clinically indicated. Use of a sensitive real-time RT-PCR assay for monitoring HCV-RNA levels during treatment is recommended. The assay should have a lower limit of HCV-RNA quantification equal to or less than 25 IU per mL and a limit of HCV-RNA detection of approximately 10-15 IU per mL. For the purpose of assessing response-guided therapy eligibility, an "undetectable" HCV-RNA (Target Not Detected) result is required; a confirmed "detectable but below limit of quantification" HCV-RNA result should not be considered equivalent to an "undetectable" HCV-RNA result (reported as "Target Not Detected" or "HCV RNA Not Detected").

Hematology evaluations (including white cell differential count) are recommended prior to and at weeks 2, 4, 8 and 12 and as clinically appropriate. Chemistry evaluations (electrolytes, serum creatinine, uric acid, hepatic enzymes, bilirubin, and TSH) are recommended as frequently as the hematology evaluations or as clinically indicated.

Refer to the prescribing information for peginterferon alfa and ribavirin, including pregnancy testing requirements.

General. INCIVEK must not be administered as monotherapy and must only be prescribed with both peginterferon alfa and ribavirin. Therefore, the prescribing information for peginterferon alfa and ribavirin must be consulted before starting treatment with INCIVEK.

There are no clinical data on re-treating patients who have failed an HCV NS3/4A protease inhibitor-based treatment, nor are there data on repeated courses of INCIVEK.

Hepatic Impairment. INCIVEK is not recommended for patients with moderate or severe hepatic impairment (Child-Pugh B or C; score greater than or equal to 7) or patients with decompensated liver disease. Refer to prescribing information for peginterferon alfa and ribavirin which must be co-administered with INCIVEK.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Pregnancy: Use with Ribavirin and Peginterferon alfa
- Serious Skin Reactions/Rash
- Anemia

INCIVEK must be administered with peginterferon alfa and ribavirin. Refer to their respective prescribing information for their associated adverse reactions.

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The safety assessment is based on data from pooled adequate and well-controlled clinical trials including 1797 subjects who received INCIVEK combination treatment and 493 who received peginterferon alfa and ribavirin.

Serious adverse drug reactions occurred in 3% of subjects who received INCIVEK combination treatment compared to none of the subjects treated with peginterferon alfa and ribavirin. The most frequent serious adverse events in subjects treated with INCIVEK combination treatment were skin disorders (rash and/or pruritus) and anemia. Fourteen percent of subjects discontinued INCIVEK due to adverse drug reactions. Rash, anemia, fatigue, pruritus, nausea, and vomiting were the most frequent adverse drug reactions leading to discontinuation of INCIVEK.

INCIVEK was administered in combination with peginterferon alfa and ribavirin. The following table lists adverse drug reactions that occurred in INCIVEK-treated subjects with an incidence at least 5% greater than in subjects receiving peginterferon alfa and ribavirin alone.

Clinical Adverse Drug Reactions Reported with at Least 5% Higher Frequency Among Subjects Receiving INCIVEK

	INCIVEK, peginterferon alfa, and ribavirin Combination Treatment N=1797	Peginterferon alfa and ribavirin N=493
Rash*	56%	34%
Fatigue	56%	50%
Pruritus	47%	28%
Nausea	39%	28%
Anemia*	36%	17%
Diarrhea	26%	17%
Vomiting	13%	8%
Hemorrhoids	12%	3%
Anorectal discomfort	11%	3%
Dysgeusia	10%	3%
Anal pruritus	6%	1%

*Rash and anemia based on SSC (Special Search Category) grouped terms.

Description of Selected Adverse Drug Reactions

Rash. In controlled clinical trials, rash events (all grades) were reported in 56% of subjects who received INCIVEK combination treatment and in 34% of subjects who received peginterferon alfa and ribavirin. Rash most frequently began during the first 4 weeks, but could occur at any time during INCIVEK combination treatment. Improvement of rash occurs after INCIVEK dosing completion or discontinuation; however, rashes may take weeks for complete resolution.

Rash events led to discontinuation of INCIVEK alone in 6% of subjects and discontinuation of INCIVEK combination treatment in 1% of subjects.

Anemia. In controlled clinical trials, the overall incidence and severity of anemia increased with INCIVEK combination treatment compared to peginterferon alfa and ribavirin alone. The incidence of anemia adverse events was 36% with INCIVEK combination treatment compared to 17% with peginterferon alfa and ribavirin alone. A decrease in hemoglobin levels occurred during the first 4 weeks of treatment, with lowest values reached at the end of INCIVEK dosing. Hemoglobin values gradually returned to levels observed with peginterferon alfa and ribavirin after INCIVEK dosing was completed.

Anorectal Signs and Symptoms. In the controlled clinical trials, 29% of subjects treated with INCIVEK combination treatment experienced anorectal adverse events, compared to 7% of those treated with peginterferon alfa and ribavirin alone. The majority of these events (e.g., hemorrhoids, anorectal discomfort, anal pruritus, and rectal burning) were mild to moderate in severity; less than 1% led to treatment discontinuation and all resolved during or after completion of INCIVEK dosing.

Laboratory abnormalities

White Blood Cells: Treatment with peginterferon alfa is associated with decreases in mean values for total white blood cell, absolute neutrophil, and absolute lymphocyte count. More INCIVEK-treated subjects had decreases in lymphocyte counts to 499/mm^3 or less (15% compared to 5%). Decreases in total white cell counts to 1,499/mm^3 or less were comparable (8% compared to 5%). The incidence of decreases in absolute neutrophil counts to 749/mm^3 or less was 15% in subjects treated with peginterferon alfa and ribavirin alone compared to 12% among those treated with INCIVEK combination treatment.

Platelets: Treatment with peginterferon alfa is associated with decreases in mean platelet counts. More patients treated with INCIVEK combination treatment had decreases in mean platelet values of all grades: 47% compared to 36% treated with peginterferon alfa and ribavirin alone. Three percent of INCIVEK combination treatment subjects had decreases to 49,999/mm^3 or less compared to 1% of those treated with peginterferon alfa and ribavirin-treated alone.

Bilirubin: Forty one percent of INCIVEK-treated subjects compared to 28% of peginterferon alfa and ribavirin-treated subjects had all grade elevations in bilirubin levels; 4% and 2% of subjects, respectively, had greater than or equal to 2.6 x ULN elevations. Bilirubin levels increased most steeply during the first 1 to 2 weeks of INCIVEK dosing, stabilized and between Weeks 12 and 16 were at baseline levels.

Uric Acid: During the INCIVEK combination treatment period, 73% of subjects had elevated uric acid levels compared to 29% for those treated with peginterferon alfa and ribavirin alone. Shifts to greater than or equal to 12.1 mg per dL from baseline in uric acid levels were also more frequent among subjects treated with INCIVEK (7%) compared to peginterferon alfa and ribavirin (1%). Less than 1% of subjects had clinical events of gout/gouty arthritis; none were serious and none resulted in treatment discontinuation.

DRUG INTERACTIONS

Potential for INCIVEK to Affect Other Drugs

INCIVEK is an inhibitor of CYP3A. Co-administration of INCIVEK with drugs that are primarily metabolized by CYP3A may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse reactions. INCIVEK is also an inhibitor of P-gp. Co-administration of INCIVEK with drugs that are substrates for P-gp transport may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse reactions. **If dose adjustments of concomitant medications are made during INCIVEK treatment, they should be re-adjusted after administration of INCIVEK is completed.**

Potential for Other Drugs to Affect INCIVEK

INCIVEK is a substrate of CYP3A and P-gp; therefore, drugs that induce CYP3A and/or P-gp may decrease INCIVEK plasma concentrations and reduce the therapeutic effect of INCIVEK. Co-administration of INCIVEK with drugs that inhibit CYP3A and/or P-gp may increase INCIVEK plasma concentrations.

Established and Other Potentially Significant Drug Interactions

The following table provides effect of concentration of INCIVEK or concomitant drug with INCIVEK. These recommendations are based on either drug interaction trials (indicated with *) or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy.

Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Trials or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on concentration of INCIVEK or Concomitant Drug	Clinical Comment
ANTIARRHYTHMICS		
lidocaine (systemic), amiodarone, bepridil, flecainide, propafenone, quinidine	↑ antiarrhythmics	Co-administration with telaprevir has the potential to produce serious and/or life-threatening adverse events and has not been studied. Caution is warranted and clinical monitoring is recommended when co-administered with telaprevir.

Concomitant Drug Class: Drug Name	Effect on concentration of INCIVEK or Concomitant Drug	Clinical Comment
digoxin*	↑ digoxin	Concentrations of digoxin were increased when co-administered with telaprevir. The lowest dose of digoxin should be initially prescribed. The serum digoxin concentrations should be monitored and used for titration of digoxin dose to obtain the desired clinical effect.
ANTIBACTERIALS		
clarithromycin erythromycin telithromycin	↑ telaprevir ↑ antibacterials	Concentrations of both telaprevir and the antibacterial may be increased during co-administration. Caution is warranted and clinical monitoring is recommended when co-administered with telaprevir. QT interval prolongation and Torsade de Pointes have been reported with clarithromycin and erythromycin. QT interval prolongation has been reported with telithromycin.
ANTICOAGULANT		
warfarin	↑ or ↓ warfarin	Concentrations of warfarin may be altered when co-administered with telaprevir. The international normalized ratio (INR) should be monitored when warfarin is co-administered with telaprevir.
ANTICONVULSANTS		
carbamazepine phenobarbital phenytoin	↓ telaprevir ↑ carbamazepine ↑ or ↓ phenytoin ↑ or ↓ phenobarbital	Concentrations of the anticonvulsant may be altered and concentrations of telaprevir may be decreased. Caution should be used when prescribing carbamazepine, phenobarbital, and phenytoin. Telaprevir may be less effective in patients taking these agents concomitantly. Clinical or laboratory monitoring of carbamazepine, phenobarbital, and phenytoin concentrations and dose titration are recommended to achieve the desired clinical response.
ANTIDEPRESSANTS		
escitalopram* trazodone	↔ telaprevir ↓ escitalopram ↑ trazodone	Concentrations of escitalopram were decreased when co-administered with telaprevir. Selective serotonin reuptake inhibitors such as escitalopram have a wide therapeutic index, but doses may need to be adjusted when combined with telaprevir. Concomitant use of trazodone and telaprevir may increase plasma concentrations of trazodone which may lead to adverse events such as nausea, dizziness, hypotension and syncope. If trazodone is used with telaprevir, the combination should be used with caution and a lower dose of trazodone should be considered.
ANTIFUNGALS		
ketoconazole* itraconazole posaconazole voriconazole	↑ ketoconazole ↑ telaprevir ↑ itraconazole ↑ posaconazole ↑ or ↓ voriconazole	Ketoconazole increases the plasma concentrations of telaprevir. Concomitant systemic use of itraconazole or posaconazole with telaprevir may increase plasma concentration of telaprevir. Plasma concentrations of itraconazole, ketoconazole, or posaconazole may be increased in the presence of telaprevir. When co-administration is required, high doses of itraconazole or ketoconazole (greater than 200 mg/day) are not recommended. Caution is warranted and clinical monitoring is recommended for itraconazole, posaconazole and voriconazole. QT interval prolongation and Torsade de Pointes have been reported with voriconazole and posaconazole. QT interval prolongation has been reported with ketoconazole. Due to multiple enzymes involved with voriconazole metabolism, it is difficult to predict the interaction with telaprevir. Voriconazole should not be administered to patients receiving telaprevir unless an assessment of the benefit/risk ratio justifies its use.
ANTI GOUT		
colchicine	↑ colchicine	Patients with renal or hepatic impairment should not be given colchicine with telaprevir, due to the risk of colchicine toxicity. A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function. Treatment of gout flares: co-administration of colchicine in patients on telaprevir: 0.6 mg (1 tablet) for 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Not to be repeated before 3 days. If used for prophylaxis of gout flares: co-administration of colchicine in patients on telaprevir: If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day. If the original regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day. Treatment of familial Mediterranean fever (FMF): co-administration of colchicine in patients on telaprevir: Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
ANTIMYCOBACTERIAL		
rifabutin	↓ telaprevir ↑ rifabutin	Concentrations of telaprevir may be decreased, while rifabutin concentrations may be increased during co-administration. Telaprevir may be less effective due to decreased concentrations. The concomitant use of rifabutin and telaprevir is not recommended.
BENZODIAZEPINES		
alprazolam*	↑ alprazolam	Concomitant use of alprazolam and telaprevir increases exposure to alprazolam. Clinical monitoring is warranted.
parenterally administered midazolam*	↑ midazolam	Concomitant use of parenterally administered midazolam with telaprevir increased exposure to midazolam. Co-administration should be done in a setting which ensures clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dose reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered. Co-administration of oral midazolam with telaprevir is contraindicated.
zolpidem (non-benzodiazepine sedative)*	↓ zolpidem	Exposure to zolpidem was decreased when co-administered with telaprevir. Clinical monitoring and dose titration of zolpidem is recommended to achieve the desired clinical response.
CALCIUM CHANNEL BLOCKERS		
amlodipine* diltiazem felodipine nicardipine nifedipine nisoldipine verapamil	↑ amlodipine ↑ calcium channel blockers	Exposure to amlodipine was increased when co-administered with telaprevir. Caution should be used and dose reduction for amlodipine should be considered. Clinical monitoring is recommended. Concentrations of other calcium channel blockers may be increased when telaprevir is co-administered. Caution is warranted and clinical monitoring of patients is recommended.
CORTICOSTEROIDS		
Systemic prednisone methylprednisolone	↑ prednisone ↑ methylprednisolone	Systemic corticosteroids such as prednisone and methylprednisolone are CYP3A substrates. Since telaprevir is a potent CYP3A inhibitor, plasma concentrations of these corticosteroids can be increased significantly. Co-administration of systemic corticosteroids and telaprevir is not recommended.
Systemic dexamethasone	↓ telaprevir	Systemic dexamethasone induces CYP3A and can thereby decrease telaprevir plasma concentrations. This may result in loss of therapeutic effect of telaprevir. Therefore this combination should be used with caution or alternatives should be considered.
Inhaled/Nasal fluticasone budesonide	↑ fluticasone ↑ budesonide	Concomitant use of inhaled fluticasone or budesonide and telaprevir may increase plasma concentrations of fluticasone or budesonide resulting in significantly reduced serum cortisol concentrations. Co-administration of fluticasone or budesonide and telaprevir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.
ENDOTHELIN RECEPTOR ANTAGONIST		
bosentan	↑ bosentan	Concentrations of bosentan may be increased when co-administered with telaprevir. Caution is warranted and clinical monitoring is recommended.
HIV-ANTIVIRAL AGENTS: HIV-PROTEASE INHIBITORS (PIs)		
atazanavir/ritonavir*	↓ telaprevir ↑ atazanavir	Concomitant administration of telaprevir and atazanavir/ritonavir resulted in reduced steady-state telaprevir exposure, while steady-state atazanavir exposure was increased.
darunavir/ritonavir*	↓ telaprevir ↓ darunavir	Concomitant administration of telaprevir and darunavir/ritonavir resulted in reduced steady-state exposures to telaprevir and darunavir. It is not recommended to co-administer darunavir/ritonavir and telaprevir.
fosamprenavir/ ritonavir*	↓ telaprevir ↓ fosamprenavir	Concomitant administration of telaprevir and fosamprenavir/ritonavir resulted in reduced steady-state exposures to telaprevir and amprenavir. It is not recommended to co-administer fosamprenavir/ ritonavir and telaprevir.
lopinavir/ritonavir*	↓ telaprevir ↔ lopinavir	Concomitant administration of telaprevir and lopinavir/ritonavir resulted in reduced steady-state telaprevir exposure, while the steady-state exposure to lopinavir was not affected. It is not recommended to co-administer lopinavir/ritonavir and telaprevir.
HIV-ANTIVIRAL AGENTS: REVERSE TRANSCRIPTASE INHIBITORS		
efavirenz*	↓ telaprevir ↓ efavirenz	Concomitant administration of telaprevir and efavirenz resulted in reduced steady-state exposures to telaprevir and efavirenz.
tenofovir disoproxil fumarate*	↔ telaprevir ↑ tenofovir	Concomitant administration of telaprevir and tenofovir disoproxil fumarate resulted in increased tenofovir exposure. Increased clinical and laboratory monitoring are warranted. Tenofovir disoproxil fumarate should be discontinued in patients who develop tenofovir-associated toxicities.
HMG-CoA REDUCTASE INHIBITORS		
atorvastatin	↑ atorvastatin	Plasma concentrations of atorvastatin are markedly increased when co-administered with telaprevir. Avoid concomitant administration of telaprevir and atorvastatin.
HORMONAL CONTRACEPTIVES/ESTROGEN		
ethinyl estradiol* norethindrone	↓ ethinyl estradiol ↔ norethindrone	Exposure to ethinyl estradiol was decreased when co-administered with telaprevir. Two effective non-hormonal methods of contraception should be used during treatment with telaprevir. Patients using estrogens as hormone replacement therapy should be clinically monitored for signs of estrogen deficiency.
IMMUNOSUPPRESSANTS		
cyclosporine* sirolimus tacrolimus*	↑ cyclosporine ↑ sirolimus ↑ tacrolimus	Plasma concentrations of cyclosporine and tacrolimus are markedly increased when co-administered with telaprevir. Plasma concentration of sirolimus may be increased when co-administered with telaprevir, though this has not been studied. Significant dose reductions and prolongation of the dosing interval of the immunosuppressant to achieve the desired blood levels should be anticipated. Close monitoring of the immunosuppressant blood levels, and frequent assessments of renal function and immunosuppressant-related side effects are recommended when co-administered with telaprevir. Tacrolimus may prolong the QT interval. The use of telaprevir in organ transplant patients has not been studied.
INHALED BETA AGONIST		
salmeterol	↑ salmeterol	Concentrations of salmeterol may be increased when co-administered with telaprevir. Concurrent administration of salmeterol and telaprevir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
NARCOTIC ANALGESIC		
methadone*	↓ R-methadone	Concentrations of methadone were reduced when co-administered with telaprevir. No adjustment of methadone dose is required when initiating co-administration of telaprevir. However, clinical monitoring is recommended as the dose of methadone during maintenance therapy may need to be adjusted in some patients.
PDE5 INHIBITORS		
sildenafil tadalafil vardenafil	↑ PDE5 inhibitors	Concentrations of PDE5 inhibitors may be increased when co-administered with telaprevir. For the treatment of erectile dysfunction, sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg dose in 72 hours, or tadalafil at a single dose not exceeding 10 mg dose in 72 hours can be used with increased monitoring for PDE5 inhibitor-associated adverse events. QT interval prolongation has been reported with vardenafil. Caution is warranted and clinical monitoring is recommended. Co-administration of sildenafil or tadalafil and telaprevir in the treatment of pulmonary arterial hypertension is contraindicated.

*These interactions have been studied. The direction of the arrow (↑ = *increase,* ↓ = *decrease,* ↔ = *no change*) indicates the direction of the change in PK.

In addition to the drugs included in the table above, the interaction between INCIVEK and the following drug was evaluated in clinical trials and no dose adjustment is needed for either drug: esomeprazole, raltegravir, or buprenorphine.

USE IN SPECIFIC POPULATIONS

Pregnancy

Because INCIVEK must be used in combination with ribavirin and peginterferon alfa, the contraindications and warnings applicable to those drugs are applicable to combination treatment. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients.

INCIVEK/Peginterferon Alfa/Ribavirin Combination Treatment

Pregnancy Category X: Animal studies have shown that ribavirin causes birth defects and/or fetal deaths while peginterferon alfa is abortifacient. See the prescribing information for ribavirin.

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin; and therefore ribavirin is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Interferons have abortifacient effects in animals and should be assumed to have abortifacient potential in humans (see peginterferon alfa prescribing information).

Extreme caution must be taken to avoid pregnancy in female patients and female partners of male patients while taking this combination. Women of childbearing potential and their male partners should not receive ribavirin unless they are using effective contraception (two reliable forms) during treatment with ribavirin and for 6 months after treatment. Systemic hormonal contraceptives may not be as effective in women while taking INCIVEK. Therefore, two alternative effective methods of contraception, including intrauterine devices and barrier methods, should be used in women during treatment with INCIVEK and concomitant ribavirin.

A Ribavirin Pregnancy Registry has been established to monitor maternal-fetal outcomes of pregnancies in female patients and female partners of male patients exposed to ribavirin during treatment and for 6 months following cessation of treatment. Health care providers and patients are encouraged to report such cases by calling 1-800-593-2214.

INCIVEK (telaprevir) Tablets

Pregnancy Category B: Telaprevir treatment alone in mice and rats did not result in harm to the fetus. The highest doses tested produced exposures equal to 1.84- and 0.60-fold the exposures in humans at the recommended clinical dose, respectively. Telaprevir treatment alone had effects on fertility parameters in rats. The no observed adverse effect level (NOAEL) for testicular toxicity was established at exposures 0.17-fold the human exposures at the recommended clinical dose. Potential effects on sperm (e.g., decreased % motile sperm and increased non-motile sperm count) were observed in a rat fertility study at exposures 0.30-fold the human exposures at the recommended clinical dose. Additional effects on fertility include minor increases in percent preimplantation loss, in percent of dams with nonviable embryos and percent of nonviable conceptuses per litter. These effects are likely associated with testicular toxicity in male but contributions of the female cannot be ruled out. There are, however, no adequate and well-controlled trials in pregnant women.

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients—both during treatment and for 6 months after the completion of all treatment. INCIVEK combination treatment should not be started unless a female patient has a negative pregnancy test immediately prior to initiation of treatment. Pregnancy testing should occur monthly during INCIVEK combination treatment and for 6 months after all treatment has ended. Pregnancy testing in non-pregnant female partners is recommended before INCIVEK combination therapy, every month during INCIVEK combination therapy, and for 6 months after ribavirin therapy has ended.

Hormonal contraceptives may be continued but may not be reliable during INCIVEK dosing and for up to two weeks following cessation of INCIVEK. During this time, female patients of childbearing potential should use 2 effective non-hormonal methods of contraception. Examples may include barrier methods or IUDs. Refer also to the prescribing information for ribavirin.

Two weeks after completion of INCIVEK treatment, hormonal contraceptives are again appropriate as one of the 2 required effective methods of birth control; however, specific prescribing information recommendations should be followed for the contraceptives. Refer also to the prescribing information for ribavirin.

Nursing Mothers

It is not known whether telaprevir is excreted in human breast milk. When administered to lactating rats, levels of telaprevir were higher in milk compared to those observed in plasma. Rat offspring exposed to telaprevir in utero showed no effects on body weight at birth. However, when fed via milk from telaprevir-treated dams, body weight gain of pups was lower than pups fed milk from control dams. After weaning, rat pup body weight gain was similar in offspring from telaprevir-treated and control dams. Because of the potential for adverse reactions in nursing infants, nursing must be discontinued prior to initiation of treatment. See also the prescribing information for ribavirin.

Pediatric Use

The safety, efficacy and pharmacokinetic profile of INCIVEK in pediatric patients have not been established.

Geriatric Use

Clinical trials of INCIVEK did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration and monitoring of INCIVEK in geriatric patients reflecting the greater frequency of decreased hepatic function, and of concomitant disease or other drug therapy.

Hepatic Impairment

INCIVEK is not recommended for use in patients with moderate or severe hepatic impairment (Child-Pugh B or C, score greater than or equal to 7) because no pharmacokinetic or safety data are available regarding the use of INCIVEK in HCV-infected patients with moderate or severe hepatic impairment, and appropriate doses have not been established. No dose adjustment of INCIVEK is necessary for patients with mild hepatic impairment (Child-Pugh A, score 5-6). Refer also to the prescribing information for peginterferon alfa and ribavirin which must be co-administered with INCIVEK.

Renal Impairment

No dose adjustment is necessary for INCIVEK in HCV-infected patients with mild, moderate or severe renal impairment. INCIVEK has not been studied in HCV-infected patients with CrCl less than or equal to 50 mL per min.

The pharmacokinetics of telaprevir were assessed after administration of a single dose of 750 mg to HCV-negative subjects with severe renal impairment (CrCl less than 30 mL per min). INCIVEK has not been studied in subjects with end-stage renal disease (ESRD) or on hemodialysis. Refer also to the prescribing information for peginterferon alfa and ribavirin which must be co-administered with INCIVEK.

Co-infection

The safety and efficacy of INCIVEK have not been established in patients co-infected with HCV/HIV or HCV/HBV.

Solid Organ Transplantation

The safety and efficacy of INCIVEK have not been established in solid organ transplant patients.

OVERDOSAGE

The highest documented dose administered is 1875 mg every 8 hours for 4 days in healthy subjects with INCIVEK alone. In that trial, the following common adverse events were reported more frequently with the 1875 mg q8h regimen compared to the 750 mg q8h regimen: nausea, headache, diarrhea, decreased appetite, dysgeusia, and vomiting. No specific antidote is available for overdose with INCIVEK. Treatment of overdose with INCIVEK consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. In the event of an overdose, it is reasonable to employ the standard supportive measures, such as, removing unabsorbed material from the gastrointestinal tract, employing clinical monitoring (including obtaining an electrocardiogram), and instituting supportive therapy if required. It is not known whether telaprevir is dialyzable by peritoneal or hemodialysis.

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Presentations in Endoscopy

Should Colonoscopy Be Repeated When Bleeding Recurs?

In a retrospective review presented at the 2012 DDW meeting, Parit Mekaroonkamol and colleagues sought to assess the usefulness of repeat colonoscopies performed for the same indication (other than colorectal cancer [CRC] screening or polyp surveillance). This study included patients who had undergone more than 1 colonoscopy for the same indication within 3 years. Patients were excluded if they had repeat colonoscopies due to poor preparation or suspected complications from the first colonoscopy, or if the colonoscopies were performed for CRC screening and/or surveillance.

Of the 19,772 colonoscopies performed between 2000 and 2010 at Albert Einstein Medical Center, 139 pairs of colonoscopies met the inclusion criteria. The mean time between procedures was 261 days. Reasons for repeating the colonoscopy included lower gastrointestinal bleeding (88.4%), a change in bowel habits (6.4%), and abdominal pain (5%). A change in management occurred after 27 of the 123 repeat colonoscopies performed for lower gastrointestinal bleeding and after 2 of the 7 repeat colonoscopies performed for abdominal pain (20.86% overall). Among the cases of recurrent lower gastrointestinal bleeding, the repeat colonoscopies identified 8 new hemorrhoid lesions, 7 actively bleeding lesions that required intervention, 7 previously undetected polyps, 3 cases of radiation colitis, 1 rectal ulcer, and 1 previously undetected cancer.

Of all the clinical parameters that were evaluated, only the length of time between colonoscopies was associated with a decreased likelihood that the repeat colonoscopy would lead to a change in clinical management. The OR for a change in management for procedures performed 365–630 days apart was 0.09 (95% CI, 0.01–0.74; *P*=.025), and the OR for a change in management for procedures performed 630–1,095 days apart was 0.26 (95% CI, 0.09–0.72; *P*=.01).

Does Body Mass Index or Procedure Difficulty Affect the Force Applied During Colonoscopy?

Several factors have been shown to affect the application of force during colonoscopy, including the endoscopist, anesthesia, and patient gender. In an observational study presented at the 2012 DDW meeting, Louis Y. Korman and colleagues assessed whether the patient's BMI or the difficulty of the colonoscopy affected axial and longitudinal force patterns. To measure these forces, the investigators attached a handheld Colonoscopy Force Monitor (CFM) to the colonoscope insertion tube; the CFM measured axial and applied forces used by the endoscopist during insertion and withdrawal.

This study included data from 114 colonoscopies; patients included 62 men and 52 women (mean age, 55.6 years). The study included 37 normal-weight patients (BMI ≤24.9 kg/m^2), 50 overweight patients (BMI 25–29.9 kg/m^2), and 24 obese patients (BMI ≥30 kg/m^2).

Analysis of variance found that increased patient BMI did not affect force parameters during colonoscopy. Specifically, BMI did not significantly affect either the average peak push force (21.6 N in normal-weight patients vs 25.1 N in obese patients), nor did BMI significantly affect examination time (18.6 minutes in normal-weight patients vs 20.4 minutes in obese patients).

The procedure difficulty was rated in 77 of the 114 patients: 23 procedures were rated as not difficult, 38 were rated as moderately difficult, and 16 were rated as difficult. While procedure difficulty was found to increase procedure time, it did not affect the force applied during the procedure.

While the endoscopist, patient gender, and anesthesia do affect the amount of force applied during colonoscopy, the authors of this study concluded that patient BMI and procedure difficulty do not have an effect on the force applied during colonoscopy.

A Review of SpyGlass and Non-SpyGlass Techniques in the Management of Pancreaticobiliary Disease

In a retrospective review presented at the 2012 DDW meeting, Gregory Lutzak and associates compared the single-operator SpyGlass Direct Visualization System (Boston Scientific) to other endoscopic techniques for visualization of the pancreaticobiliary tract. The investigators searched billing codes for all cholangioscopy and pancreatoscopy procedures performed in the past 8 years at Virginia Mason Hospital. A total of 205 patients were identified: 163 underwent cholangioscopy, 35 underwent pancreatoscopy, and 7 underwent pancreatic cystoscopy. The mean age of the patients was 63.3 years, and 54% of the patients were female. The primary endpoint of this study was a change in diagnosis or management following endoscopic retrograde pancreatography in combination with cholangioscopy or pancreatoscopy.

Of the 205 procedures included in this analysis, 143 used the SpyGlass system. Among patients who underwent endoscopic retrograde pancratography in combination with cholangioscopy, there were 140 diagnostic procedures (104 using the SpyGlass system), 20 therapeutic procedures (15 using the SpyGlass system), and 3 procedures for percutaneous transhepatic biliary tract drainage (3 using the SpyGlass system). Among the diagnostic cholangioscopy procedures, malignancy was the most common diagnosis (n=48 patients). Changes in patient management following diagnostic cholangioscopy occurred in 75% of procedures that used the SpyGlass system and in 92% of the procedures that used other techniques. For therapeutic cholangioscopy procedures, fragmentation of stones occurred in 80% (12/15) of procedures that used the SpyGlass system versus 75% (3/4) of procedures that used other techniques; complete eradication of stones occurred in 27% (4/15) and 25% (1/4), respectively.

In the pancreatoscopy group, intraductal papillary mucinous neoplasm was the most common finding (n=18). Changes in patient management or diagnosis following pancreatoscopy occurred in 67% (16/24) of cases that used the SpyGlass system and in 55% (6/11) of procedures that used other techniques. No changes in patient management occurred in the pancreatic cystoscopy group (0/7). Overall, the investigators concluded that the SpyGlass system compared positively to other endoscopic tools for visualization of the pancreaticobiliary system.

Advanced Polypectomy and EMR Can Yield a Low Recurrence Rate for Previously Attempted Large Polyps

As presented by Niket Sonpal and associates at the 2012 DDW meeting, advanced polypectomy and endoscopic mucosal resection (EMR) techniques may be a viable alternative to surgery in patients with large or difficult-to-remove colorectal lesions. In addition to allowing patients to avoid the risks of surgery, recurrence rates following such procedures are fairly low (10.5–20.4%).

This study included patients with large (≥2 cm) colorectal polyps in whom primary removal had failed or was not attempted due to the polyp's size and/or location. The EMR technique used in these patients included submucosal injection, multiple snare sizes, avulsion techniques with specialized forceps, and ablation with argon plasma. For polyps in difficult locations, caps and retroflexion were used.

Of the 262 patients included in this analysis, 67% were male, and the mean age was 74 years (range, 52–92 years). The success rate of the procedure was high, with only 5.7% of patients (15/262) experiencing a recurrence. The majority of recurrences (86%) were in the right colon. Of the 15 cases of polyp recurrence, histology revealed that 13 were tubular adenomas (87%), 2 were high-grade dysplasia (13%), and 1 was a serrated adenoma (7%). Diverticulosis was more common in patients who experienced a polyp recurrence (60%) than in patients who did not experience a recurrence (30%).

The investigators concluded that the EMR technique evaluated in this study was safe and effective for patients with large, sessile, or difficult-to-remove colorectal polyps. The vast majority of these patients did not require surgery (90%), and the overall success rate for the procedure was 94%, with a recurrence rate (5.4%) much lower than that previously reported in the literature. Sonpal and colleagues noted that this EMR approach should be developed further to improve patient care, reduce the need for surgery, and reduce costs.

Safety and Efficacy of EMR Prior to Radiofrequency Ablation for Patients with Dysplastic Barrett Esophagus

The outcomes of EMR followed by radiofrequency ablation (RFA) for the treatment of nodular dysplastic Barrett esophagus have not previously been investigated in a large series of patients. At the 2012 DDW meeting, however, William J. Bulsiewicz and colleagues reported results of an analysis in which they used data from the US RFA Registry to assess the safety and efficacy of this approach. This prospective registry includes patients with Barrett esophagus who were treated with RFA at 113 community-based and 35 academically affiliated institutions. Among patients with high-grade dysplastic Barrett esophagus or intramucosal carcinoma, treatment with EMR/RFA for nodular dysplastic Barrett esophagus was compared to treatment with RFA alone for non-nodular dysplastic Barrett esophagus. This study assessed both safety (rates of stricture, bleeding, and hospitalization) and efficacy (complete eradication of intestinal metaplasia [CEIM], complete eradication of dysplasia [CED], and number of treatment sessions to CEIM).

A total of 1,248 patients were treated with RFA for high-grade dysplastic Barrett esophagus or intramucosal carcinoma. Among the 418 patients (33%) who had undergone 1 or more prior EMR procedures, strictures developed in 3.6%, bleeding occurred in 0.7%, hospitalization was necessary in 1.4%, and 0% had perforations. There were no significant differences in the rates of stricture, bleeding, or hospitalization for patients receiving EMR/RFA compared to those receiving RFA alone.

In terms of efficacy, biopsy data were available for 44% of patients (554/1,248). Among patients treated with EMR/RFA, 65% achieved CEIM, and 81% achieved CED. Among patients with high-grade dysplastic Barrett esophagus

and intramucosal carcinoma, those treated with EMR/RFA did not differ significantly from those who received RFA alone in terms of the rate of CEIM (61–72% vs 61–75%, respectively) or the rate of CED (77–88% vs 84–75%, respectively). Overall, the results of this large, multicenter registry found that treatment with EMR/RFA for nodular dysplastic Barrett esophagus yielded similar rates of CEIM, CED, and complications compared to treatment with RFA alone for non-nodular dysplastic Barrett esophagus.

Impact of Periampullary Diverticula on Success and Complication Rates of ERCP

Periampullary diverticula (PAD) have been detected in 5–25% of patients undergoing endoscopic retrograde cholangiopancreatography (ERCP), but the effect of PAD on ERCP success and complication rates is unclear. At the 2012 DDW meeting, Olga Barkay and associates presented the results of a retrospective analysis that addressed this question using data from a prospectively maintained database at the ERCP Unit of the Indiana University Hospital. Between 1994 and 2009, a total of 31,635 ERCP procedures were performed in 19,197 patients; 1,315 of these patients had PAD (6.85%). After excluding those patients who had undergone a previous sphincterotomy, 780 patients remained in the PAD group (mean age, 63.5 years; 64.7% female). The age-matched control group for this study included 1,566 patients with naïve papilla who did not have PAD (58.2% female). Barkay and colleagues' study compared these 2 groups in terms of the following outcomes: rate of prior ERCP failure, rate of successful cannulation, rate of difficult cannulation, use of precut sphincterotomy, and complication rate.

ERCP was performed for a variety of indications: choledocholithiasis (30% in the PAD group vs 13.2% in the control group), suspected sphincter of Oddi dysfunction (15.8% vs 16%), pancreatitis (22.9% vs 23.5%), obstructive jaundice (11.7% vs 23.9%), biliary dilation (11% vs 13.5%), and other indications (8.2% vs 9.9%). The proportion of patients who had previously failed ERCP in a community hospital was greater in the PAD group (21%) compared to the control group (13.8%; $P<.001$). There was no significant difference in the rate of successful cannulation (95.2% in the PAD group vs 94.9% in the control group; $P=.7$); however, cannulation was deemed to be difficult in a higher proportion of patients in the PAD group compared to the control group (18.2% vs 6.3%; $P<.001$). Other differences between the PAD group and the control group included more frequent use of precut sphincterotomy (10.8% vs 5.8%; $P<.001$), more frequent bleeding (1.28% vs 0.38%; $P=.01$), and more frequent perforation (1% vs 0.13%; $P=.002$). There was no difference in the rate of post-ERCP pancreatitis (2.95% in the PAD group vs 2.94% in the control group; $P=.99$). The authors concluded that ERCP can be successfully performed in patients with PAD, although these patients frequently require use of more aggressive techniques, such as precut sphincterotomy.

Early and More Aggressive Fluid Resuscitation Is Associated with Less Severe Post-ERCP Pancreatitis

Early fluid resuscitation can reduce the severity of acute pancreatitis, but data are lacking regarding the impact of volume resuscitation on the severity of post-ERCP pancreatitis. During the 2012 DDW meeting, Sashidhar Sagi and colleagues presented the results of a retrospective cohort study that compared intravenous volume resuscitation in patients with mild or moderate/severe post-ERCP pancreatitis (PEP). All patients included in this analysis were admitted with pancreatitis (new or worsening abdominal pain with elevation in amylase or lipase level >3 times ULN) within 24 hours after ERCP. PEP was categorized as mild (hospitalization for ≤3 days), moderate (hospitalization for 4–10 days), or severe (hospitalization for >10 days). Exclusion criteria included absence of data on intravenous volume resuscitation, acute pancreatitis within 7 days of ERCP, chronic kidney disease, and congestive heart failure.

Of the 113 cases of PEP that were identified, 70 met the eligibility requirements. Forty patients had mild PEP, 27 patients had moderate PEP, and 3 patients had severe PEP. Patients with mild or moderate/severe PEP had comparable demographic and procedural risk factors for PEP; however, patients with moderate/severe PEP were older than those with mild PEP (median age, 50 years vs 36 years; $P=.05$).

There was no difference between patients with mild PEP versus those with moderate/severe PEP in terms of the median intravenous volume infused before and during ERCP (600 mL for both groups). However, a greater intravenous volume was infused during the first 24 hours after ERCP for patients with mild PEP (2,892 mL) compared to those with moderate/severe PEP (2,147 mL; $P=.03$). The proportion of patients who were discharged and then readmitted was also significantly lower in the group with mild PEP versus those with moderate/severe PEP (15% vs 40%; $P<.01$).

Presentations in IBD

Safety and Efficacy of Subcutaneous Golimumab Induction Therapy in Patients with Moderately to Severely Active Ulcerative Colitis

Numerous agents that inhibit tumor necrosis factor-α (TNF-α) have been tested for the treatment of ulcerative colitis (UC). One anti–TNF-α agent, golimumab (Simponi, Janssen Biotech)—currently approved for treatment of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis—is being evaluated for treatment of UC in the PURSUIT-SC study, the results of which were presented by William Sandborn at the 2012 DDW meeting.

PURSUIT-SC was a randomized, placebo-controlled, double-blind, phase II/III trial that enrolled UC patients with moderately to severely active disease who were naïve to anti–TNF-α therapy. The PURSUIT-SC trial began as a phase II dose-ranging study, after which patients were integrated into the confirmatory phase III portion of the study. During the dose-ranging portion of the study, patients were randomized to 1 of 4 arms: placebo, 100/50 mg golimumab (100 mg at Week 0 and 50 mg at Week 2), 200/100 mg golimumab (200 mg at Week 0 and 100 mg at Week 2), or 400/200 mg golimumab (400 mg at Week 0 and 200 mg at Week 2). During the phase III portion of the study, only the 200/100 mg and 400/200 mg doses of golimumab were used. Golimumab was administered subcutaneously in all groups.

The primary endpoint of the study was clinical response at Week 6, which was defined as a decrease in the Mayo Clinic score of at least 30% and at least 3 points from baseline, with either a decrease in the rectal bleeding subscore of at least 1 point from baseline or a rectal bleeding subscore of 0 or 1. Secondary endpoints included clinical remission (defined as a Mayo Clinic score ≤2 with no individual subscore >1), mucosal healing (defined as a Mayo Clinic endoscopy subscore of 0 or 1), and change from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) score, all assessed at Week 6.

A significantly higher proportion of patients in the golimumab treatment groups attained clinical response at Week 6 (51.8% and 55.0% in the 200/100 mg and 400/200 mg golimumab arms, respectively, vs 29.7% in the placebo arm; $P<.0001$ for both comparisons vs placebo). A highly significant difference also emerged in terms of the proportion of patients who achieved clinical remission at Week 6 (6.3%, 18.7%, and 17.8% in the placebo, 200/100 mg golimumab, and 400/200 mg golimumab groups, respectively; $P<.0001$ for both comparisons vs placebo) and mucosal healing at Week 6 (28.5% in the placebo group vs 43.2% in the 200/100 mg golimumab group and 45.3% in the 400/200 mg golimumab group; $P=.0005$ and $P<.0001$, respectively). The mean change from baseline in IBDQ scores at Week 6 was 14.6 points in the control group versus 27.4 points in the 200/100 mg golimumab group and 27.0 points in the 400/200 mg golimumab group ($P<.0001$ for both comparisons vs placebo).

The PURSUIT-SC study also evaluated the overall phase II/III trial population through Week 6 to assess the safety profile of golimumab; this analysis included a total of 1,065 patients. The total proportion of patients who experienced an adverse event was 38.2% in the placebo group versus 39.1% for the combined golimumab group. The number of patients who experienced a serious adverse event was also relatively similar in both groups (6.1% in the placebo group vs 3.0% in the combined golimumab group). One patient in the 400/200 mg golimumab arm died, and demyelination (a well-described toxicity of anti–TNF-α therapy) was reported in 1 patient in the 400/200 mg golimumab arm.

Vedolizumab Induction Therapy for Ulcerative Colitis

A potential new therapy for UC, vedolizumab, is a novel, gut-selective, monoclonal antibody directed against the α4β7 integrin that induces selective inhibition of lymphocytic trafficking in the gut. At the 2012 DDW meeting, Brian Feagan presented the results of a randomized, placebo-controlled, double-blind, multicenter, phase III trial designed to determine the long-term efficacy and safety of vedolizumab when given as induction therapy for UC. The intent-to-treat population for the induction phase of this study consisted of 374 patients with active UC. Patients were randomized 3:2 to treatment with vedolizumab or placebo; vedolizumab was administered as a 300-mg intravenous dose on Days 1 and 15.

The primary study endpoint for the induction phase of the study was clinical response at Week 6; clinical response was defined as a reduction in the total Mayo Clinic score of at least 3 points and a decrease from baseline of at least 30% plus a decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore no greater than 1. Secondary endpoints for the induction phase of the study included mucosal healing and clinical remission. Clinical remission was defined as a total Mayo Clinic score

no greater than 2 points with no individual subscore greater than 1; mucosal healing was defined as a Mayo Clinic endoscopy subscore no greater than 1.

The rate of clinical response at Week 6 was significantly higher in the vedolizumab arm compared to the placebo arm (47.1% vs 25.5%; *P*<.0001). Vedolizumab also showed significantly higher rates of clinical remission at Week 6 (16.9% for vedolizumab vs 5.4% for placebo; *P*=.0010) and mucosal healing at Week 6 (40.9% for vedolizumab vs 24.8% for placebo; *P*=.0013). Finally, preliminary analyses of the safety data through Week 6 showed similar rates of adverse events, serious adverse events, and serious infections for the vedolizumab group and the placebo group.

Analysis of a Prospective Registry of Pregnancy Outcomes in Women with IBD Exposed to Immunomodulators and Biologic Therapy

At the 2012 DDW meeting, Uma Mahadevan summarized results from a study designed to determine the safety of immunomodulator and biologic therapy during pregnancy. This study enrolled a large prospective cohort of pregnant women with inflammatory bowel disease (IBD; N=1,115); 57% of these patients had Crohn's disease (CD), and 40% had UC. Patients were divided into 4 categories based on their drug exposure between conception and delivery: (1) unexposed patients (n=306) who did not receive immunomodulator or biologic therapy during the study; (2) immunomodulator-treated patients (n=204) who received either azathioprine or 6-mercaptopurine; (3) anti–TNF-α–treated patients (n=291) who received either infliximab (Remicade, Janssen Biotech), adalimumab (Humira, Abbott), certolizumab pegol (Cimzia, UCB), or natalizumab (Tysabri, Elan/Biogen Idec) during the study; or (4) combination-treated patients (n=75) who received both immunomodulators and anti–TNF-α agents during the study.

After adjusting for the effects of the underlying disease, most adverse incidents—including spontaneous abortions or congenital anomalies—did not occur at a significantly increased rate among women enrolled in this study compared to community-based or national rates. However, there were a few exceptions: Women in this study had a higher rate of Cesarean sections, and their babies had a higher rate of neonatal intensive care unit stay. Also, there were higher rates of spontaneous abortions and Cesarean sections in the anti–TNF-α group, and there was a higher rate of preterm births among women in the combination therapy group.

While babies of mothers with CD showed no increase in any complications or adverse effects, a nearly 5-fold higher rate of spontaneous abortion was observed among mothers with UC who were treated with anti–TNF-α agents. Further, UC mothers in the combination therapy group had an increased risk of any complication—including preterm birth, low birth weight, and neonatal intensive care unit stay—after the analysis adjusted for disease activity.

There were no significant differences in the growth characteristics of the babies throughout their first year, including height, weight, and developmental measurements at 4, 9, and 12 months of age (adjusted for maternal age and disease activity). In addition, no association was found between congenital anomalies and drug exposure. Finally, the rate of infections among the infants was not significantly affected by drug exposure. Taken together, these results suggest that the mother's disease may confer a higher risk to the fetus than the risks associated with the use of immunomodulator or biologic therapy.

One Third of Patients Treated with Adalimumab or Infliximab Permanently Dose Escalate Due to Loss of Response

Despite the significant efficacy of infliximab and adalimumab for the treatment of IBD, many patients lose response to these drugs. In a poster presented at the 2012 DDW meeting, Darryl Fedorak and colleagues reported the findings of a retrospective chart review in which they sought to determine the incidence of loss of response among patients treated with either of these 2 agents.

The investigators identified 363 patients who met the inclusion criteria for this study. All enrolled patients had an initial response to induction dosing with either infliximab (5 mg/kg administered at Weeks 0, 2, and 6) or adalimumab (160 mg and 80 mg administered at Weeks 0 and 2, respectively). Patients also had to have advanced to scheduled maintenance therapy (every 8 weeks with infliximab or every 2 weeks with adalimumab), achieved a stable corticosteroid-free clinical benefit that was durable for a minimum of 6 months, and exhibited a loss of response to their anti–TNF-α therapy.

At the time of the analysis, 65% of infliximab-treated patients remained in remission while on infliximab maintenance therapy (5 mg/kg every 8 weeks). Similarly, 72% of adalimumab-treated patients were in remission on maintenance therapy (40 mg every other week). Thirty-five percent of patients who received infliximab required dose escalation (to 5 mg/kg every 4 weeks). Twenty-eight percent of adalimumab-treated patients required dose escalation (to 40 mg weekly). There was no significant difference in the rates of dose escalation between UC and CD patients. Further, a Kaplan-Meier plot found no significant difference in the time to treatment failure between infliximab and adalimumab (log-rank test, *P*=.56). Only 7 infliximab-treated patients underwent dose de-escala-

tion to the original doses; none of the adalimumab-treated patients underwent dose de-escalation.

New Assay Can Detect Infliximab Levels and Anti-Infliximab Antibodies From a Single Serum Sample

The most widespread method for detection of antibodies to infliximab (ATIs) is a double-antigen enzyme-linked immunosorbent assay, which uses infliximab as both the ligand and the detection antibody. However, this assay is limited by its inability to accurately determine ATI levels in the presence of serum infliximab concentrations. In a poster presented at the 2012 DDW meeting, Gabor Veres and colleagues reported on the development of a novel homogeneous mobility shift assay and demonstrated that it could detect both infliximab and ATIs in the same serum sample.

This novel homogeneous mobility shift assay was used to measure serum infliximab concentrations and ATI levels in 230 serum samples from 71 pediatric IBD patients. A subset of these children (n=31) also had 6 serial trough infliximab measurements, each taken prior to an infusion. A 5 mg/kg–induction dose of infliximab was administered at Weeks 0, 2, and 6, followed by maintenance dosing every 8 weeks.

ATIs were detected in 20.4% of the serum samples (range, 0.28–800+ U/mL) and in 29.6% of the 71 children. Of the 47 ATI-positive serum samples, 8 also demonstrated measurable infliximab serum concentrations (range, 0.77–19.27 mg/mL). In the subset of children with serial trough level measurements, 8 had ATI-positive serum samples. Among ATI-positive samples, the median infliximab serum concentration was 0 mg/mL; in contrast, the median infliximab serum concentration among ATI-negative samples was 2.55 mg/mL (P<.0001). None of the ATI-positive samples exhibited infliximab serum concentrations of 3 mg/mL or higher, while 45% of the ATI-negative samples had infliximab levels of 3 mg/mL or higher. Finally, ATI-positive patients also had C-reactive protein (CRP) levels that were approximately 1.5-fold higher than CRP levels in ATI-negative patients. A linear regression model found that a majority (88%) of children in the subset of patients with serum infliximab concentrations of 3 mg/mL or higher showed a decrease in CRP levels.

Association of Serum Infliximab and Antibodies to Infliximab to Long-Term Clinical Outcome in Acute Ulcerative Colitis

In a poster presented at the 2012 DDW meeting, Sanjay Murthy and colleagues used a newly developed homogeneous mobility shift assay to assess the relationships among trough infliximab levels, ATI levels, and long-term clinical outcomes in patients with acute UC. A total of 134 patients with corticosteroid-refractory acute UC were included in this analysis; 103 patients had pancolitis, and 31 patients had disease limited to the splenic fixture. All patients had received 5 mg/kg infliximab induction therapy on Weeks 0, 2, and 6, followed by scheduled maintenance therapy.

After a median follow-up period of 19.9 months (interquartile range [IQR], 7.6–47.4 months), 43.3% of patients were in corticosteroid-free remission, and 39.6% had undergone colectomy. The median time to colectomy was 6.5 months (IQR, 2.3–13.4 months). Among 125 patients with evaluable serum samples, 54.4% (n=68) had detectable trough levels of serum infliximab. Of these 68 patients, 6 patients (8.8%) also had detectable levels of ATIs. Of the 57 patients (45.6%) who had undetectable trough serum infliximab levels, 45 patients (78.9%) were ATI-positive, and 12 patients (21.1%) were ATI-negative.

Importantly, the investigators showed that a trough infliximab level above 2 mg/mL was associated with a higher rate of corticosteroid-free remission compared to a trough infliximab level of 2 mg/mL or lower (69% vs 16%; P<.001). This relationship was sustained throughout the follow-up period. In contrast, a trough infliximab level below 2 mg/mL was significantly associated with an increased risk for colectomy compared to a trough infliximab level above 2 mg/mL (64% vs 13%; P<.001).

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BRIEF SUMMARY

INTENDED USE:

The BreathTek® UBT for *H. pylori* Kit (BreathTek UBT Kit) is intended for use in the qualitative detection of urease associated with *H. pylori* in the human stomach and is indicated 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, in clinical laboratories or point-of-care settings.

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 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. False negative test results may be caused by:
- — Ingestion of antimicrobials, proton pump inhibitors, and bismuth preparations within 2 weeks prior to performing the BreathTek UBT
- — Premature POST-DOSE breath collection time for a patient with a marginally positive BreathTek UBT result
- — Post-treatment assessment with the BreathTek UBT less than 4 weeks after completion of treatment for the eradication of *H. pylori*.

6. False positive test results may be caused by:
- — Urease associated with other gastric spiral organisms observed in humans such as *Helicobacter heilmannii*
- — Achlorhydria.

7. If particulate matter is visible in the reconstituted Pranactin-Citric solution after thorough mixing, the solution should not be used.

8. Hypersensitivity: Patients who are hypersensitive to mannitol, citric acid or Aspartame should avoid taking the drug solution as this drug solution contains these ingredients.

9. 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.

10. Pregnancy: No information is available on use of the Pranactin-Citric solution during pregnancy.

POSTMARKETING EXPERIENCE:

During post-approval use of the BreathTek UBT, the following adverse events have been identified: anaphylactic reaction, hypersensitivity, rash, burning sensation in the stomach, tingling in the skin, vomiting and diarrhea. 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.

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 specimen integrity of breath samples and reference gases stored in breath bags under ambient conditions has not been determined beyond 7 days.

3. A correlation between the number of *H. pylori* organisms in the stomach and the BreathTek UBT result has not been established.

0512L-4244 April 2012

References: 1. McNulty CA, Whiting JW. Patients' attitudes to Helicobacter pylori breath and stool antigen tests compared to blood serology. *J Infect.* 2007;55(1):19-22. **2.** Chey WD, Wong BCY; Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of Helicobacter pylori infection. *Am J Gastroenterol.* 2007;102(8):1808-1825. **3.** Talley NJ, Vakil NB, Moayyedi P. American Gastroenterological Association technical review on the evaluation of dyspepsia. *Gastroenterology.* 2005;129(5):1756-1780. **4.** Malfertheiner P, Mégraud F, O'Morain C, et al; European Helicobacter Pylori Study Group (EHPSG). Current concepts in the management of Helicobacter pylori infection—the Maastricht 2-2000 Consensus Report. *Aliment Pharmacol Ther.* 2002;16(2):167-180. **5.** Vakil N, Fendrick AM. How to test for Helicobacter pylori in 2005. *Cleve Clin J Med.* 2005;72(suppl 2):S8-S13. **6.** Package Insert for BreathTek UBT. Otsuka America Pharmaceutical, Inc; 2012.

Learn more and see Current Package Insert at TheBreathDetective.com or call 888.637.3835

Otsuka
Medical Device Division of
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Urea Breath Test for *H. pylori*
BreathTek®
Detection made convenient

September 2012 0512P-5592

Is H. pylori behind the symptoms?

A convenient way to reveal the evidence.

Patients prefer the UBT method vs fecal antigen test[1]

- In a patient survey (n=140) comparing UBT and FAT vs serology, more patients preferred to be tested for *H. pylori* with the UBT method vs a stool sample[1]
- Simple, quick administration in your office or at a lab

Serological tests are not appropriate to confirm H. pylori diagnosis or eradication[2-4]

- ACG* and AGA† guidelines do not recommend serological testing to detect *H. pylori*[2-4]
- Serology cannot distinguish between active and past infection[5]

*American College of Gastroenterology.
†American Gastroenterological Association.

Learn more at TheBreathDetective.com or call 888.637.3835

Please see Brief Summary on next page.

Test for H. pylori before you prescribe PPI therapy

- Both ACG and AGA guidelines recommend the UBT method as an appropriate choice for initial diagnosis and confirmation of eradication[2,3]

Excellent sensitivity (95.5%) and specificity (96.0%)[6]

- BreathTek UBT provides excellent accuracy to confirm eradication in adult patients[6]

Urea Breath Test for *H. pylori*

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Detection made convenient