

FDA Approves First Oral Once-daily MMX Mesalamine For Patients With Active Mild-to-Moderate Ulcerative Colitis

The US Food and Drug Administration (FDA) recently approved the novel MMX mesalamine formulation (Lialda, Shire) for the induction of remission in patients with active mild-to-moderate ulcerative colitis (UC). MMX mesalamine is the first and only FDA-approved once-daily oral formulation of mesalamine, which is a well-established drug of choice and often a first-line treatment for patients with mild-to-moderate UC. MMX mesalamine will be available in the US in the first quarter of this year.

MMX mesalamine contains the highest mesalamine dose available per tablet (1.2 g), so patients can take as few as 2 tablets once daily. Other currently available mesalamines require 2- to 4-times daily dosing and 6–16 pills a day. A recent study conducted by the Crohn's and Colitis Foundation of America (CCFA) found that 65% of patients with UC are poorly compliant with their medication, citing pill burden and inconvenience associated with the medication. "The introduction of new treatments with more convenient dosing regimens may be an important step in helping patients with ulcerative colitis remain compliant with their medication," said Jonathan Braun, MD, PhD, Chair of CCFA's National Scientific Advisory Committee.

The FDA approval was based on the results of two double-blind, placebo-controlled Phase III clinical studies. The first study assessed the efficacy and safety of MMX mesalamine 2.4 g/day given in divided doses twice daily and 4.8 g/day given once daily against placebo in 262 patients. At 8 weeks, both doses demonstrated superiority over placebo in the induction of remission (34.1% with 2.4 g/day, 29.2% with 4.8 g/day, and 12.9% with placebo). The second study assessed the efficacy and safety of MMX mesalamine 2.4 g/day and 4.8 g/day (both given once daily) against placebo in 255 patients. At 8 weeks, both once-daily doses demonstrated superiority over placebo in the induction of remission (40.5% with 2.4 g/day, 41.2% with 4.8 g/day, and 22.1% with placebo). Safety and effectiveness of MMX mesalamine beyond 8 weeks have not been established.

MMX mesalamine is generally well-tolerated and has a similar safety profile to other currently available mesalamines. The majority of adverse events in the trials were mild or moderate in severity. In clinical trials (N=535), the most common treatment-related adverse events with

MMX mesalamine 2.4 g/day and 4.8 g/day were headache (5.6% and 3.4%, respectively) and flatulence (4% and 2.8%, respectively). MMX mesalamine is contraindicated in patients with hypersensitivity to salicylates (including mesalamine) or to any of its components. Caution should be used in patients with impaired hepatic or renal function.

Study Finds Similar First-day Acid Suppression Between Omeprazole Magnesium and Famotidine

In a study published in *Alimentary Pharmacology & Therapeutics*, researchers directly compared the early therapeutic response of omeprazole magnesium (Prilosec, AstraZeneca), a proton pump inhibitor (PPI), and famotidine (Pepcid AC, Merck), a histamine-2 receptor antagonist (H2RA), in an over-the-counter (OTC) setting. In contrast to the general consensus that H2RAs are superior on the first day of usage, the study found similar acid suppression on the first day of dosing between these drugs. Researchers also reported evidence that with daily use, the body develops a rapid onset of tolerance to even a low-dose H2RA.

In this 14-day study, subjects were randomly assigned to one of six treatment sequences, each including three regimens: omeprazole magnesium 20.6 mg once daily, famotidine 10 mg twice daily, and famotidine 20 mg twice daily. During the treatment period, the amount of acid production was measured over 24 hours several times. Results showed that omeprazole magnesium provided significant acid suppression on the very first day of treatment compared to baseline, which was comparable to the acid suppression of H2RAs. After day 1 of treatment, omeprazole magnesium was consistently superior in acid suppression in comparison to the H2RAs. In addition, while using the lower-dose H2RAs, the degree of acid suppression ability was found to decrease significantly after the first day of use.

According to Philip Miner, MD, Clinical Professor of Medicine at the University of Oklahoma and lead investigator at the Oklahoma Foundation for Digestive Research, "Because these two drugs work in fundamentally different ways to suppress acid production, we didn't expect that the PPI would work as well as the H2RAs within the first 24 hour period after treatment. In addition, while using the lower-dose H2RAs, the degree of acid suppression ability was found to significantly decrease after the first

day of use. While this study measured acid suppression, it did not measure symptom relief or the speed of onset of action. However, both PPIs and H2RAs owe their clinical efficacy to their ability to suppress gastric acid secretion. This means that for people who have frequent heartburn, that is, heartburn 2 or more days per week, taking an over-the-counter PPI is an excellent option.”

Detection of Precancerous Polyps During Colonoscopy Linked to Withdrawal Time

A study published in a recent issue of the *New England Journal of Medicine* reported that withdrawal time of the colonoscope during a colonoscopy is related to detection rates of adenomas. The authors, led by Robert L. Barclay, MD, of Rockford Gastroenterology Associates, Rockford, Ill., compared the rates of detection of neoplastic lesions among gastrointestinal (GI) endoscopists who had mean withdrawal times of less than 6 minutes with the rates of those who had mean withdrawal times of 6 minutes or more. They found that those endoscopists with colonoscopy withdrawal times greater than 6 minutes had detection rates for neoplasia over 28%, whereas those with mean withdrawal times of less than 6 minutes had detection rates under 12% and concluded that variation of withdrawal times may affect the prevention of colorectal cancer as it relates to routine screenings.

In the study, 7,882 colonoscopies performed by 12 experienced endoscopists over a 15-month period were examined. These findings substantiate a recent guideline of the American Society for Gastrointestinal Endoscopy, “Quality Indicators for Colonoscopy,” which was published as a supplement in the April 2006 issue of *Gastrointestinal Endoscopy*. In “Quality Indicators for Colonoscopy,” experts identified increased detection of significant neoplastic lesions in colonoscopic examinations where the withdrawal time is 6 minutes or more and concluded that withdrawal time is an appropriate quality indicator.

“The significance of this study for the field of gastrointestinal endoscopy goes beyond its findings. This research demonstrates the ability of private practitioners to measure quality indicators in their practice and identify areas for improvement. There is a perception that evaluating the quality of procedures is unrealistic within the practice setting. In other words, that it is only feasible for academicians in institutions. This study provides an example of how measuring quality indicators can lead to improvement in practice. This should become part of the culture of every practice,” said David Lieberman, MD, of the Division of Gastroenterology at Oregon Health & Science State University, Portland, Ore.

Stool DNA Testing for Colon Cancer

Mount Sinai School of Medicine, in conjunction with EXACT Sciences Corporation, recently announced the publication of results from a prospective, multicenter study of stool DNA testing. The study was published in the January 2007 issue of *Clinical Gastroenterology and Hepatology*.

The investigators found that the test demonstrated an 88% sensitivity for colorectal cancer with equal detection across all stages of cancer, regardless of the cancer’s location in the colon. “This study confirms that stool-based DNA technologies can achieve high sensitivities for detecting colorectal cancer,” stated Steven Itzkowitz, MD, principal investigator and Professor and Associate Director of Gastroenterology at Mount Sinai School of Medicine. “For those individuals who are unwilling or unable to undergo colonoscopy, stool DNA testing offers a valuable and patient-friendly screening option.”

The published study evaluated 162 patients, 40 individuals with cancer and 122 individuals with normal colonoscopies. An enhanced marker panel, using a refined DNA capture and stabilization process, detected 88% of cancers with a specificity of 82%.

Whole-body Scans May Provide Option for Diagnosing Colorectal Cancer

Preliminary research suggests that whole-body positron emission tomography (PET) and computed tomography (CT) scans could provide a suitable method for diagnosing the stage of colorectal cancer, according to a study in the December issue of the *Journal of the American Medical Association*.

Patrick Veit-Haibach, MD, and colleagues of the University Hospital Essen in Germany, evaluated the diagnostic accuracy of whole-body PET/CT colonography for 47 patients with colorectal cancer and compared those findings with the accuracy of conventional CT staging alone and CT followed by PET (CT + PET). In the study, patients with clinical findings and optical colonoscopy that suggested primary colorectal cancer were enrolled between May 2004 and June 2006. Patients underwent whole-body PET/CT colonography 1 day after colonoscopy. Fifty lesions were detected in the 47 patients.

Based on a lesion-to-lesion analysis, tumor, nodal, and metastasis (TNM) stages were correctly determined by PET/CT colonography in 37 of 50 lesions (74%) and by CT alone in 26 of 50 lesions (52%) at a certain threshold of measurement. With CT + PET, TNM stages were correctly determined in 32 of 50 lesions (64%). Compared with optimized abdominal CT staging alone,

PET/CT colonography was more accurate in defining TNM stage (difference, 22%), which was mainly based on a more accurate definition of the T-stage.

Of the 47 patients, PET/CT colonography changed therapy management in 4 (9%), compared with conventional staging. The change in patient management was based either on a more accurate assessment of the T-stage of colorectal cancer or on accompanying findings on PET/CT colonography.

According to Dr. Veit-Haibach, whole-body PET/CT colonography “is less time-consuming than a conventional multistep approach with CT alone (abdomen and thorax) and PET imaging if required. Thus, it represents a psychological and physical advantage when considering the burden to the patient of different imaging procedures.”

Dua Antireflux Valve Found to Improve Quality of Life For Bile Duct/Pancreatic Cancer Patients

Patients undergoing bile duct stenting with the Dua antireflux valve (the Dua stent) instead of the standard biliary stent needed fewer repeat endoscopies and, thus, have a better quality of life, according to a recent study. D. N. Reddy, MD, of the Asian Institute of Gastroenterology in Hyderabad, India, found in his study of 60 patients that the Dua stent remained open for a longer time compared to the standard stent. This resulted in fewer repeat endoscopies for stent changes.

“That means a better quality of life for these cancer patients,” says the inventor of the Dua stent, Kulwinder S. Dua, MD, Associate Professor of Medicine at the Medical College of Wisconsin. The Dua stent was approved for use by the FDA last year.

Dr. Reddy conducted his study on 60 consecutive patients in whom the bile duct was obstructed from cancer of the pancreas or the bile duct. He placed a standard biliary stent in 30 patients and the Dua stent in the remaining 30 patients. Adding the antireflux valve on the Dua stent did not compromise the stent’s bile drainage capacity, as both stents were equally effective in improving liver tests, and complication rates were similar.

Balsalazide Approved for Treatment of Children and Teens With Mildly-to-Moderately Active Ulcerative Colitis

In December of 2006, the FDA approved balsalazide (Colazal, Salix) for the treatment of mildly-to-moderately active UC in patients 5–17 years of age. Balsalazide

had been previously approved for use in adult patients with mildly-to-moderately active UC. The drug’s safety and effectiveness in children 5–17 years of age with mildly-to-moderately active UC was demonstrated in a multicenter study in 68 patients who were randomized to receive either 6.75 g or 2.25 g of balsalazide per day for 8 weeks. In the study, 45% of the children on the higher dose and 37% on the lower dose showed clinical improvement in rectal bleeding and the appearance of GI mucosa.

The most common adverse events associated with the use of balsalazide were headache and symptoms associated with the GI tract, such as abdominal pain, vomiting, and diarrhea. The overall rate of drug-related adverse events was higher in the low-dose group as compared to the high-dose group. This may have been due to the lower efficacy seen in the low-dose group.

Pediatric use of balsalazide was granted orphan drug status under the FDA’s Orphan Drug program, which provides financial incentives for firms that develop therapies for diseases affecting fewer than 200,000 patients a year.

In Brief

Iron-deficiency anemia may be a clinical presenting sign of pouchitis, according to a retrospective study.

Hemoglobin levels may be considered as surveillance tools for pouchitis in patients with ileal pouch with anal anastomosis.

(J Clin Gastroenterol. 2007 Jan;41(1):41-44.)

Continuous 24 hour intra-arterial infusion is more effective for advanced hepatocellular carcinoma

and can markedly prolong survival time as compared to 6 hour infusion, according to a study.

(World J Gastroenterol. 2007 Jan 14;13(2):280-284.)

Retrospective study shows that acute rejection under interferon alfa-based therapy often occurs in liver transplant recipients

being treated for hepatitis C, but early diagnosis with protocol biopsies and early treatment can lead to a favorable outcome.

(Am J Transplant. 2007 Jan;7(1):177-184.)