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Analysis of FDA’s non-approval of domperidone and current access options to cisapride.

How has this impacted the lives of patients living with gastrointestinal (GI) motility disorders?

Time to re-visit access issues for cisapride and domperidone, gastrointestinal-prokinetic drugs.

On February 18, 2005 the FDA advisory panel recommended that COX-2 inhibitors should be tightly restricted with recommendations for Vioxx™ to return to the market under specific conditions.

The voluntary pulling of Vioxx™ from the market by its manufacturer, and now discussion to bring this drug back provides a timely opportunity for revisiting two very important prokinetic medications: domperidone (Motilium™) and cisapride (Propulsid™). These two drugs have had their access greatly restricted and thus do not enjoy the availability as may occur with Vioxx™ or as now occurs with alosetron (Lotronex™), a drug used to treat diarrhea-predominate irritable bowel syndrome. Further, a more recent step by the FDA, issuing an Import Alert on domperidone, has created greater curtailment of this drug’s historically unfettered access for American patients suffering from gastroparesis.

The FDA’s managing of post-marketing risk; it seems some drugs fare better than others. How risk management programs are applied or negotiated between industry and the FDA remains a mystery to outside observers whose lives are left in a lurch due to the impact of such decisions. Uneven handling will be contrasted below between cisapride and alosetron (Losetron™) to demonstrate the need for more post marketing risk management options and the immediate need to re-tool access for cisapride.

Cisapride (Propulsid™) and domperidone have provided the mainstay of treatment for upper gut motor disturbances such as dyspepsia, gastro-esophageal reflux, post-operative ileus, and intestinal and gastric stasis disorders (example: diabetic gastroparesis); additionally, domperidone has an added benefit in the treatment of nausea and vomiting from various causes. These upper gut motor disorders (i.e. gastrointestinal motility disorders) affect the lives of millions of Americans — from infants through to adults.

While the threatened market loss of COX-2 inhibitors would impact the management of inflammation in patients, the inflammatory drug, armamentarium, is broad and deep, still providing plenty of medical
options for sustaining this group of patients and their need to access therapies that return quality of life.

In contrast to this picture for the COX-2 consumers, our patients lack access to the depth and breadth of drugs that have been developed to treat debilitating, and in some situations, life-threatening digestive distress. The prokinetic drugs currently FDA-approved for treating diabetic gastroparesis are erythromycin and metoclopramide (Reglan™).

What many policy makers and others, like Public Citizen (a non-profit public interest organization who vociferously petition the FDA to have Cisapride pulled from the market) fail to understand is how serious these disorders of digestive motility really are. As an example, gastro-esophageal reflux, for some infants and children, is not a benign condition to be healed with a tincture of time. Nor do the severe forms of small bowel or stomach motility problems represent bothersome indigestion. Some of these very ill patients (usually young women) will spend up to 6 months at a time in the hospital. This makes it rather difficult to bring gastroparetic “patient-support” groups to hearings at the FDA to effect more favorable risk management options as was done for alosetron.

Nor are these digestive disorders of motility rare. The National Institutes of Health estimates, 5 million Americans suffer from gastroparesis causing significant disability.

Why then are patients with severe gastrointestinal motility disorders left with crippled access to their vital, medical treatment options — options that have demonstrated in clinical trials the ability to decrease morbidity, arguably even mortality, and without dispute, have returned quality of life? On what basis can the FDA justify bringing back to the market drugs such as Lotronex™ and possibly Vioxx™ yet failed to provide leadership for similar ease of access for cisapride? Why has domperidone never been approved by the FDA yet it is approved throughout the rest of the world?

The non-approval of domperidone by the FDA has created some strange practices within the medical community. Since the United States exists as an isolated island in a sea of availability to domperidone, American physicians have published papers on how to access this effective medication (1,2); even advising in these publications on how to obtain domperidone from the Internet. Obviously, the experts too feel the crimp for gaining access to safe, effective drugs for their patients.

Considered a first-line medical treatment for gastroparesis and other gastrointestinal (GI) motility disorders, domperidone is approved in over 80 countries including Australia, New Zealand and across Europe. Furthermore, domperidone is available as an over-the-counter medication in Belgium, Ireland, Italy, the Netherlands, United Kingdom, Switzerland, and South Africa (3).

The prescribing practice of domperidone by US gastroenterologists is well-entrenched; for over 20 years, American gastroenterologists have established the clinical practice and experience of use with this medication. Throughout the 1990s in the United States, domperidone was available under a compassionate-use program by Janssen Pharmaceutica as Janssen attempted to gain full approval in the U.S. market.

For reasons unknown, on June 7, 2004, the U.S. Food and Drug Administration issued an Import Alert for domperidone citing safety concerns related to the off-label usage of domperidone for increasing milk supply in breast-feeding mothers (4). Though domperidone is not approved in the United States for any use, warning letters were sent to various compounding pharmacies. As well, FDA field personnel were alerted to seize personal-use domperidone coming into the United States. The unintended consequence of this Import Alert meant that diabetic and other gastroparesis patients would not be able to obtain their American-physician-prescribed domperidone. As a result of the import ban for both personal use and compounding purposes, an additional burden was placed on motility patients who already have precious few treatments.

Anxious gastroparetic patients flooded the FDA with phone calls. This resulted in the FDA putting together an Investigational New Drug (IND) protocol for which U.S. researched-based
gastroenterologists could apply. Through the IND process, physician will be able to obtain generic domperidone from Canadian pharmaceutical supply houses.

This troubling action and position taken by the FDA in their “Talk Paper” regarding domperidone is not backed-up by any relevant, scientific rationale.

The import block of domperidone citing risk of cardiac toxicity in the intravenous (IV) formulation is completely disingenuous and not founded on facts. The IV formulation was pulled from the worldwide market by the manufacturer 20 years ago. Further, metoclopramide, which now stands as the main treatment for gastroparesis, also possesses cardiac toxicity problems which have been documented in the IV formulation (5).

What triggered this import ban is not clear, but a transparent and rational reason has not been offered by the FDA compliance division when asked. Instead, a hidden agenda by the FDA desirous to control compounding pharmacies may be at issue. Our patients have been caught-up in this territorial dispute.

Prior to this action taken by the FDA compliance division, creating the unintended consequences of hampering access to “appropriate use” of domperidone; any gastroenterologist by advent of commonly accepted clinical practice, could prescribe domperidone advising their patients to access it either via on-line pharmacies in Canada, or from compounding pharmacies.

**Limitations of the Domperidone Investigational New Drug (IND) process.**

Since this IND protocol is only available to GI specialists at institutions with Investigational Review Boards, patients who do not have specialists at institutions with IRBs will no longer be able to obtain their medication. For them, they will have to incur the added expense and time to find a doctor who is willing to apply for the IND, or do without. Alternatively, some are put into the position of feeling like a common criminal as they continue to gamble on ordering their medication from the Internet hoping that it is not seized at the border. Another problem may present with specialists at a research facility who have too few patients and therefore will not take the added time and paperwork to apply for an IND, in which case they would have to send their patients elsewhere.

The added risk of imposing a domperidone IND is patients may not want to follow through with the additional paperwork. For these patients, they know and understand how effective this medication is for them. They may continue to access on-line domperidone without their physician’s supervision. Feeling so much better with this medication, they are frightened of losing their one effective drug.

Doing without domperidone is not an option for some since without this medication they will be much more symptomatic, incur more hospitalizations for uncontrolled vomiting; all culminating in making enteral feeding access perhaps a necessity.

**Domperidone non-approval in US, What happened?**

So what happened to domperidone? Domperidone was in the approval stages just as cisapride was in the process of being voluntarily pulled by Janssen Pharmaceutica in 2000.

No public record can be found as to what happened with the FDA approval process regarding domperidone. Top gastrointestinal motility experts who participated in clinical trials of domperidone are dismayed. Word on the street is that domperidone was recommended for approval by the FDA GI drug division scientists, but was not signed off at the office level — presumably due to office level concerns over Q/T problems (cardiac toxicity). It may be that more data was wanted regarding Q/T studies and domperidone. Yet, by 1998 Q/T problems were known to exist with cisapride. Domperidone was in clinical trials throughout the 1990s, and it seems reasonable that Q/T studies could have been requested at that time. It is not known if this dialogue occurred between the manufacturer and the FDA.
Further, in light of impending cisapride withdrawal, domperidone approval should have been a top priority.

With the worldwide acceptance and safety profile of domperidone this non-approval by the FDA appears as intransigence.

This overly conservative regulatory approach with regard to domperidone means the consequences of failure to approve this drug is bore largely by the patients who stood to benefit from it--or for those who already gained the knowledge to know how well the drug works for them -- they have to continue to scramble to maintain access.

The FDA’s regulations, known as Subpart H, or accelerated approval regulations, provides the means to fast-track new drugs for serious or life-threatening illnesses; therefore providing meaningful therapeutic benefit to patients over existing treatments. Domperidone represented the first and only drug to go all the way through the full procedural steps for approval for treating diabetic gastroparesis.

Diabetic gastroparesis certainly fulfills the criteria for a serious, life-threatening disorder; with a 30% mortality rate, it leads to wildly fluctuating blood sugar levels and intractable bouts of nausea and vomiting, persistent enough to possibly preclude some of these patients form transplant options. (6,7).

Cardiac Toxicity (prolonged Q/T intervals) and drugs
One-fourth of patients are prescribed drugs which cause heart arrhythmias as a side-effect (8). Some are more potent than others for creating this consequence; while still others may quickly escalate to a dangerous heart rhythm disturbance with certain combinations of drugs. These lethal prescribing combinations are called: “contraindications.” Cisapride combined with erythromycin is an example of contraindicated use.

For gastrointestinal motility patients, this whole area of GI medicine is so devoid of appropriate medical treatments that in order to control the nausea and vomiting wrought by upper digestive motility disturbances, specialists must turn to other options utilizing older, anti-depressant drugs and/or major tranquilizers. Many of these drugs have significant side effects and some have well-documented problems of cardiac toxicity leading to sudden death — the same problem for which cisapride was pulled; yet these drugs (for example Thorazine™, phenothiazines, tricyclic antidepressants such as amitriptyline, and many others) remain on the market and are prescribed with warnings regarding proper monitoring by electrocardiographs to mitigate this risk. Risk management is the name of the game since very ill patients may die if they don’t have access to effective medications.

Loss of Cisapride
The loss of cisapride left a huge, gaping hole in medication options, resulting in lives lost since patients deteriorated clinically and necessitated a stepping-up to riskier, more invasive treatments. Cisapride represented a “unique molecule” (11) with the ability to enhance pan-gastro-intestinal coordination (motility). Nothing yet has been found to replace cisapride. It was the most effective drug for the treatment of GI motor disturbances.

Facts on Cisapride:
- Developed by Janssen Pharmaceutica, a Johnson & Johnson Co. subsidiary, and approved by the FDA in 1993 for the treatment of severe nocturnal gastro-esophageal reflux (GER).
- Gastro-esophageal reflux is a complex disorder of abnormal motor function occurring in the valve between the stomach and esophagus (lower esophageal sphincter), and delayed gastric emptying (9).
- Cisapride addressed the underlying motor disturbances of GER.
Off-label use of Cisapride:

- This unique and highly effective drug was recognized to have applications in various areas of gastroenterology wherein disturbed gastrointestinal motor activity creates significant morbidity and mortality.
- GER disease in neonates and children is primarily a motor disturbance of the upper gut that can result in gagging, retching, vomiting and intolerance for food, failure to gain weight, respiratory problems of asthma and stridor, sudden infant death syndrome, recurrent pneumonia, and erosive esophagitis with strictures (10,12).
- In healthy neonates and young children, GER usually represents a transit upper gut motor disturbance that will resolve. This problem, with its attendant morbidity, responded well to cisapride medical management (10).
- GERD in neonates and children is a significant problem for those who are neurologically impaired by cerebral palsy or Down’s syndrome, for example, or who are premature (11).
- In older children and adults, GER often represents a chronic condition with other upper digestive symptoms of nausea, gagging, retching, vomiting, bloating, and regurgitation.
- Cisapride became the first-line drug choice for treating severe GERD in children. Further, in contrast to most drugs used in pediatrics, cisapride has been well studied in pediatric clinical trials.
- Clinical trials have also demonstrated that cisapride could significantly cut the duration and shorten the length of hospitalization for post-operative ileus (13).
- Infants and children suffering from chronic intestinal pseudo-obstruction responded very well to cisapride and in some cases, this drug was what was keeping these children alive. This disorder of small bowel dysmotility has a high mortality rate.
- Adults with delayed gastric emptying, as found in gastroparesis, were able to reverse weight loss caused by their stomach motor problem. This helped patients avoid the need for enteral feeding in which a feeding tube is surgically placed into the small intestine. Symptom management was sometimes further enhanced for these patients with the additional use of domperidone. Many gastroparetic patients could then avoid repeated hospitalizations and enteral feeding.

A word about Tegaserod (Zelnorm™)

Some gastroenterologist feel that Tegaserod also possess pan-gastro motility enhancing properties. Tegaserod has been approved for use in constipation predominate irritable bowel syndrome. Clinical trials are underway to determine the value of this drug for treating diabetic gastroparesis. While this is good news, we still as of yet do not have anything to exchange for cisapride. The wealth of published clinical trials for use of cisapride in children and in other applications has established cisapride’s clinical safety, efficacy and value.

Cisapride and Cardiac Toxicity — Q/T Prolongation.

- Since cisapride’s introduction and before market withdrawal, the drug was used world-wide in the treatment of 140 million patients. Of that, 18% (25.2 million) were in the age group of 0 to 1 year and 9% (12.6 million) in the age group of 1 to 20 years (14).
- Worldwide, 341 reports of heart rhythm abnormalities and 80 deaths occurred in association with cisapride use. Ten deaths were documented in the pediatric population. None of these resulting deaths were clearly due to cisapride alone (15).
- Of these heart rhythm problems, most could be related to known risk factors (14-16).
Cisapride possesses Class III anti-arrhythmic properties related to dosage and risk factors, such as the existence of an underlying genetic heart rhythm abnormality, or the taking of cisapride in conjunction with a contraindicated drug (16). The risk for congenital prolonged Q/T syndrome is 1:10,000 to 1:15,000 (15). The risk of sudden death from cisapride has been estimated at 1:250,000 (14).

In clinical studies, children withdrawn from cisapride did show increased rates of hospitalizations for reflux-related pneumonia.

In 1998 the FDA issued a warning to doctors regarding cardiac toxicity related to cisapride.

Professional societies were very alarmed over the potential market loss of cisapride. Both the European and North American Society for Pediatric Gastroenterology and Nutrition came out with publications and position statements regarding the safety and efficacy of cisapride (10, 11). The North American team scrutinized all available published and unpublished literature. A committee convened in August 1998 to address the emerging concerns related to cisapride and cardiac toxicity. The members of the committee consisted of six pediatric gastroenterologists, two pediatric cardiologists, a pediatric pharmacologist, and a pediatric pharmacoepidemiologist.

In one of these published papers, the author foreshadowed the concerns that surgical procedures for the treatment of pediatric GER might increase. These surgical techniques, called funduplications show a definite mortality and failure rate of several percentages points (10).

In 1998, the FDA took regulatory action against contraindicated uses of cisapride. Working with Janssen, additions of boxed warnings on the drug label and through communication letters to prescribing physicians was undertaken.

The FDA conducted research to determine the impact of prescribing practices in light of these warnings (17). It was determined that regulatory action regarding cisapride use had no material effect on prescribing habits. In June 2000, the FDA, in discussion with Janssen resulted in a voluntarily withdrawal of cisapride from the market.

The real risk of cardiac toxicity associated with cisapride has been looked at in several studies. In one study, a United States multicenter, double-blinded, placebo-controlled trial was conducted in pediatric patients. Forty-nine children ranging in age from six months to four years were looked at for ECG changes from baseline and 3 to 8 weeks of treatment. Conclusion: in the study group of children who were without underlying cardiac disease or electrolyte imbalances, cisapride was found to have no significant effect on cardiac electrical function compared to placebo. These results are consistent with the drug’s record of exceedingly infrequent cardiac events (18). Other clinical studies looking for adverse prolongation of Q/T intervals with cisapride have come to similar conclusions (19).

As a result of the market loss of cisapride, a restricted access for cisapride was created with a unique twist. The FDA granted restricted access for non-FDA approved uses of cisapride in the pediatric and adult populations. Both the manufacturer and the FDA recognized that this drug decreased mortality and morbidity for adults and children with severe gastrointestinal motility disorders.

Unfortunately, restricted access does not provide the same ease of access as does a supplemental New Drug Application (sNDA). Consequently, in the U.S. this access for cisapride really means ineffective access for the many patients who could benefit. The program is set-up as a limited access study and run in a similar manner as a clinical trial with comprehensive monitoring of patients and data collection. It is an enormously labor intensive and costly process for the physician. This puts doctors in a conflict with wanting to provide an effective medication for their patients, but who may not have the manpower in order to process all the necessary paperwork.

Further, in the litigious U.S. environment, hospitals with IRBs refuse to expose themselves to potential legal liabilities with cisapride and therefore will not grant approval. Janssen does provide a centralized
IRB, but their program still requires the GI division head to grant permission to enroll patients into the program, something that many refuse to do.

Many, if not most, of the top adult GI motility specialists, in tertiary care centers, in the United States do not have access to cisapride for their patients. The patients seen at these tertiary centers represent the very ill patient population. **This risk management solution, isn’t working. The severely ill patients for whom access is meant to serve are not getting access to cisapride. This is a failure of the system and it has not been examined.**

In Canada, access to cisapride is fast and efficient. One phone call by the prescribing physician to the special access program of Health Canada Protection Branch and the medication is mailed from the generic manufacture, Apotex, to the doctor’s office for pick-up by the patient. Health Canada does not dictate how the physician should monitor his or her patients for risk management. Access to cisapride is very easy in many other countries as well.

In contrast, the supplemental New Drug Application designation given to Lotronex™ allows for restricted marketing. The FDA advisory committee has also recommended similar ease of access for Vioxx™.

**Lotronex™ re-marketing**

A comparison of experience with alosetron’s re-marketing to cisapride’s handling by the FDA raises serious questions on the uneven handling of drugs found to have post-marketing safety concerns, and on the FDA’s risk assessment evaluation. A look at the risks related to gained benefits for alosetron as compared to those for cisapride is in stark contrast to reason and logic.

Alosetron is marketed by GlaxoSmithKline and was approved by the FDA in February 2000 for treatment of a benign, though difficult-to-manage problem of diarrhea in irritable bowel patients; in just nine, short months, the FDA had received Adverse Drug Reports (ADRs) on:

- 49 reports of ischemic colitis
- 21 severe cases of alosetron-related constipation
- 44 hospitalizations
- 10 surgical interventions, and
- 3 deaths.

In November 2000 alosetron was voluntarily pulled from the market by its manufacturer. Severe, adverse reactions continued to be reported with the final tally of 84 cases of ischemic colitis, 113 cases of severe constipation, 143 hospitalizations, and 7 deaths. Despite this, the FDA granted a supplemental New Drug Application permitting the marketing of alosetron under a prescribing formula whereby doctors must sign an attestation of qualification and acceptance of responsibilities. Patients, too, must sign a patient-physician agreement attesting that they have been adequately informed of the risks. (20).

The difficulty arises since **no one can predict who gets ischemic colitis** and there is no way to monitor these risks in order to try and mitigate these serious, adverse drug reactions. This supplemental New Drug Application for alosetron to treat approximately 240,000 women for relief from diarrhea-predominating irritable bowel problems could potentially result in 2,000 cases of severe constipation, 5,714 cases of ischemic colitis, 1,109 surgical interventions, and 329 deaths (20).

The FDA created a guide for alosetron to help manage risks. The FDA stated that it believed that the benefits of alosetron outweigh its risks when used in accordance with instructions in the Medication Guide which reflects the FDA’s revised labeling.

This statement creates consternation in comparison to domperidone’s non-approval and hindered access to cisapride.
Shift in management of pediatric and adult motility patients
With the market removal of cisapride and the non-approval of domperidone and the recent introduction of an IND for domperidone, the management of severe gastrointestinal motility disorders has shifted, creating increased morbidity and indirectly, mortality.

Metoclopramide (ReglanTM) has been used in the past to treat diabetic gastroparesis and various other problems of nausea and vomiting. The 1990s saw cisapride enter the market and domperidone readily available as clinical trials for market approval were being conducted for the treatment of diabetic gastroparesis. Metoclopramide, an older drug with numerous side effects, found itself appropriately placed further down the list as a treatment option for these motility disorders.

In 2000, with the loss of cisapride in the American market, there has been an increase in sales of metoclopramide (21).

What are we doing to the children?
In 1998 the FDA warned about Q/T problems with cisapride.

These problems with cardiac toxicity, though rare, are seen as a tip-of-the-iceberg effect. But failing to place these risks in perspective and balancing risks against the severity of digestive motility diseases is perhaps driving prescribing practices into a less well known and potentially greater iceberg effect, that is, the risk of metoclopramide to cause a sometimes irreversible and disabling, neurological consequence called tardive dyskinesia (TD).

An FDA study conducted by Shaffer et al (22) found the same results -- the utilization of metoclopramide decreased following the introduction of cisapride to the market in 1993 and increased following cisapride’s withdrawal in 2000. The majority (62%) of metoclopramide prescriptions are written for women, with the highest rates prescribed for the two age groups of children under 10 years of age, and for the 60- to 80-year-olds. The groups most at risk to develop tardive dyskinesia as a consequence of medications are the very young and the very old with a greater propensity seen in females.

Tardive dyskinesia or other neurological movement disorders produced as side effects by drugs can easily be mistaken for Parkinson’s disease in older adults. In children, the bizarre movements can be mistaken for seizure disorders, Munchausen by proxy, or other neurological disorders. Small children would not be able to report these side effects and the connection to this problem is often missed by prescribing physicians. Further, neurologically impaired children may present with severe reflux making them particularly susceptible to TD, yet difficult to distinguish.

With discontinuation of the offending medication, often these abnormal movement problems can be reversed, but can sometimes lead to permanent neurological damage. Metoclopramide causes a high percentage of these unwanted side effects. Of 87 Adverse Drug Reports received by the FDA of metoclopramide-associated tardive dyskinesia, 26% of these reports document disability (22). Exceptionally few of these reports are from the under-age-10 group, suggesting a significant under-reporting for this vulnerable age group.

In the FDA’s own study on metoclopramide, the authors conclude:

\[TD \text{ is a rare, serious, and potentially irreversible adverse effect of metoclopramide. TD risk factors are notable in clinical practice and reflected in adverse event reports for metoclopramide. If current prescription trends continue, TD incidence may be expected to increase. Given the paucity of evidence that metoclopramide improves the quality of life, TD risk factors relative to the intended benefit and duration of use should be carefully considered in metoclopramide prescribing (22).}\]

Domperidone is in the same pharmacological family as metoclopramide, but since it has a significantly less affinity for the central nervous system, it demonstrates a superior safety profile as compared to metoclopramide. (23,24). Both of these drugs, as well, possess various degrees of cardiac toxicity.
There are no documented reports in the literature of oral preparations of domperidone causing sudden death due to prolongation of Q/T intervals. Also, domperidone has had a number of long term studies done establishing safety of chronic use (25). Gastroparetic patients often need pro-motility drugs for decades. Long term studies with use of metoclopramide have not been done and long term use is not advocated due to increasing risks of TD. Finally, more clinical trials have been published on the use of domperidone for treating diabetic and other gastroparetic patients than the medications currently FDA approved for treating these patients.

Domperidone has a further role where metoclopramide dare not go. Patients with Parkinson’s disease will often suffer from nausea, vomiting, and weight loss either due to delayed gastric emptying induced by anti-Parkinson’s medications, or due to a secondary motor disturbance in the gut resulting from the Parkinson’s disease. Several published clinical trials have shown that domperidone helps to decrease these symptoms and to return quality of life for Parkinson’s patients (26, 27).

The market loss of cisapride has driven the need for more fundoplication surgeries in children and adults.

- Loss of cisapride has meant that doctors cannot prescribe an effective medical treatment for their GERD patients (particularly for the pediatric population).
- Fundoplication procedures have their role especially in severe cases of reflux where uncontrolled gastric regurgitation has significant morbidity and even mortality from pulmonary aspiration.
- Patients who fail medical management are the candidates for surgery; however, with the loss of cisapride, one can argue that medical management failures are far more common now, especially in children.
- Fundoplications are now the third most common surgery for children (12).
- It must be remembered that children with severe GERD generally suffer with a fore-gut motility problem. The regurgitation and vomiting related to a gastric motor disturbance will not be fixed by fundoplication, which can actually cause more suffering due to the inability to vomit after surgery.
- Neurological impairment is the main indication of anti-reflux surgery for children (12).
- Often, the symptoms which prompted the fundoplication procedure may persist or worsen or create a whole new set of problems increasing morbidity (12).
- Complications from fundoplication surgery may consist of failure of the “wrap” and need for revision, small bowel obstruction, lung perforation, infection, gas bloat syndrome, persistent esophageal strictures, and persistent swallowing difficulties (10,11,12).
- Short-term and long-term complications from fundoplications are probably under-reported, illustrating that patients with less successful outcomes may be less likely to participate in follow-up studies (11).
- Inadvertent vagal nerve damage during surgery may produce delayed gastric emptying of solids and accelerated emptying of liquids resulting in nausea, bloating, esophageal spasm, abdominal pain, diarrhea, hypoglycemic episodes from liquid dumping, and generalized dyspepsia. Vagal nerve damage may occur in 20% of patients (11).
- The surgical technique for performing fundoplications is a difficult procedure to master. Less experienced centers will have higher rates of complications, including mortality.
Recommendations

- A public hearing as to why domperidone was never approved.
- Re-examine a mechanism for better access to cisapride.

No drug is safe. A unanimous call for the overhaul of the post-marketing surveillance process at the FDA is needed. Further, a fair and equitable system needs to be consistently applied when post marketing safety concerns arise.

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Sincerely,

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