

August 12, 2004

U.S. Food and Drug Administration, FDA
Department of Health and Human Services
5600 Fisher Lane
Rockville, MD
20857-0001

RE: Violation of the FDA Act for importation of Domperidone medication/raw ingredients and or compounding of this product.

To Whom It May Concern:

The Gastroparesis and Dysmotilities Association is a North American based non-profit association providing a voice for patients suffering with digestive motility disorders/disease. Our focus is on education, awareness, patient advocacy and promotion of research into these poorly understood, life threatening digestive problems.

It was recently brought to our non-profit association's attention that the FDA has decided to exercise its discretionary enforcement powers and has issued warning letters to compounding pharmacies/pharmaceutical supply houses to halt the importation for the ingredients for making Domperidone. This advisory also informs of a directive to FDA field personnel to be on the look-out for foreign supplies of Domperidone shipped to U.S. customers.

The "FDA Talk Paper" issued June 7, 2004 is careful to focus on the use of Domperidone for increasing milk production and minimally draws attention to the use of Domperidone in treating symptomatic gastroparesis patients or other patients suffering from gastrointestinal motility disorders.

It is the latter case for which our non-profit association is very concerned. It shows a lack of understanding by the FDA regarding the serious nature of these neuro-muscular disorders of the digestive tract and the few treatment options for these patients.

Domperidone was brought forward to the FDA, in the late 1990's, by Janssen Pharmaceutical, after U.S. clinical drug trials which showed safety and efficacy (also, long term U.S. clinical trials of 12 months have been published). The FDA turned down the application. This remains a puzzle to all in the medical community for those who understand the severe nature of these digestive disorders, especially when contrasted against the current FDA approved medications for treating gastroparesis.

Why the FDA has now chosen this heavy handed approach towards Domperidone is a mystery. The precedent has been established, and the medical community has been following the status quo by prescribing Domperidone to their American patients with gastroparesis for over 20 years now. Not only do doctors with knowledge in treating patients with gastroparesis prescribe Domperidone to their American patients, but they also advise their patients in how to obtain the medication.

Further, the body of scientific published evidence on the effectiveness of Domperidone in treating patients with gastroparesis has experts in the field of digestive motility disorders agreeing that Domperidone is a first line drug choice for treating gastroparesis.

Metoclopramide and Erythromycin are currently the only two drugs approved by the FDA for treating Gastroparesis.

What the American Society of Consultant Pharmacists (ASCP) advised to the FDA (docket number: 02N-0115) in May 24, 2002 now also holds true for the actions that the FDA is currently mounting against Domperidone:

When useful medications are withdrawn from the market, patients who could benefit from them are deprived of the benefits.

With the FDA's current action against Domperidone, it is effectively removing this useful and safe medication from American patients suffering from gastroparesis.

The American Society of consultant Pharmacists was referring to the loss of Cisapride from the market. Their reflection on this incident applies, in many ways, to what is now occurring with Domperidone. The ASCP comments from their paper are excerpted here:

The withdrawal of Cisapride heightened ASCP's interest in the medication risk management issue. Cisapride was a medication used to increase motility of the upper gastrointestinal tract, and of value in managing a common complication of diabetes called diabetic gastroparesis. Without cisapride, therapeutic options are now more limited. Metoclopramide can be used, but in older adults, metoclopramide frequently causes movement disorders including extrapyramidal symptoms and tardive dyskinesia. These symptoms are similar in appearance to Parkinson's disease and are sometimes irreversible even when the medication is discontinued. One recent study found that prescribers frequently confuse the **drug**-induced side effects of metoclopramide with the onset of true Parkinson's disease. In fact, older adults who take metoclopramide are three times more likely to be placed on a medication for Parkinson's disease. ² As a result, these patients are exposed to the risks of unneeded **drug** therapy.

Erythromycin is another treatment approach ³. It does increase upper gastrointestinal motility and is used for this purpose. But erythromycin is an antibiotic. In this era of increasing concern about antibiotic resistance, the fact that clinicians are using this approach is a clear indication of the need for additional therapeutic options. Cisapride is a prime example of a medication that was lost to clinicians because of the weaknesses in the current system for safe use of medications. It could be brought back onto the market with appropriate safeguards to provide an additional therapeutic option where few are now available

The above line of thinking holds true for Domperidone.

The fact that the FDA has stated: "There have been several reports and case studies of cardiac arrhythmias, cardiac arrest and sudden death in patients receiving an intravenous form of Domperidone that has been withdrawn from the market is several countries." reflects out-dated information. The intravenous form of Domperidone has not been used for over 20 years now. Further, the information that Domperidone may put patients at risk for cardiac rhythm abnormalities is not any startling news, and primarily comes from animals studies. As well, this risk that the FDA is citing is not listed as an "Official Warning" in the Physician's Desk Reference (PDR), the British National Formulary

(BNF), the Italian Summary of Product Characteristics (SPC), the European Public Assessment Reports (EPARs) or the Committee for Proprietary Medicinal Products (CPMP). 1

The clinical use of Domperidone for over 20 years continues to demonstrate that Domperidone is effective, safe, and well tolerated.

The list of non-cardiac drugs which can adversely affect heart rhythms is a lengthy list and include well recognized, widely used agents, from the pharmacological classes of: antihistamine, serotonin agents (example: ondansetron and granisetron), psychiatric medications, antibiotics, anti-malarial, anticonvulsant, and anti-cancer medications. The drugs with the highest risk for potential unwanted heart dysrhythms are: clarithromycin, erythromycin, haloperidol, and amitriptyline. Many of these unwanted side-effects are often dose related, related to co-morbidities, drug idiosyncratic reactions and unidentified underlying genetic heart rhythm abnormalities.

Domperidone is in such wide use and acceptance by U.S. gastroenterologists that it is even cited in the professional literature and advice on obtaining it is provided. In a recent publication by Michael P. Jones, MD: Nutrition in Clinical Practice 19:145-153 (Copyright 2004 American Society for Parenteral and Enteral Nutrition); sited below:

“ Domperidone is not available in the United States despite the fact that its effectiveness and safety has been established in clinical trials. It can be obtained from some compounding pharmacies in the United States. Section 503A of the Federal Food, Drug, and Cosmetic Act as amended by the FDA Modernization Act of 1997 sets forth guidelines regulating pharmacy compounding. 32 Substances that are not approved for commercial marketing by the FDA but that comply with the standards of an applicable United States Pharmacopoeia or National Formulary monograph and the United States Pharmacopoeia chapter on pharmacy compounding may be compounded. Although never released for commercial use in this country, Domperidone is available as a raw compound for which standard were detailed in a US Pharmacopoeia monograph published in November 2000. Therefore, it can be compounded for patient use. To obtain compounded Domperidone, a licensed physician provides a prescription for the compounded product for an identified individual patient to a licensed pharmacist in a state-licensed pharmacy or a federal facility. This is a legally acceptable practice as long as the physician and pharmacist comply with existing guidelines.

Domperidone is also available from pharmacies in other countries where it is often available without a prescription. Many of these pharmacies offer Inter-net or toll-free telephone access. In general, these pharmacies offer branded product at considerably less expense than most compounding pharmacies in the United States, which tend to be quite expensive. Although not covered by health insurance providers, Domperidone can be purchased from many online pharmacies for prices comparable to standard non-generic co-payments with most prescription plans.”

Dr. Michael Jones is not alone in these comments. In fact, most of the worlds leading research physicians from the United States follow the same practices in treating their patients with gastroparesis. It must be noted that these experts recommend Domperidone because they fully understand the serious nature, health related risks, increase in hospitalizations and potentially life threatening problems from uncontrolled gastroparesis. Even the National Institutes of Health on their patient information web site related to gastroparesis; cite Domperidone as a recognized treatment option.

If section 503A pertaining to the compounding of drugs like Domperidone was struck down by the Supreme court in April 2002, it then begs the question: why is FDA now, two years later, taking up vigorous action against the compounding of Domperidone?

For patients with gastroparesis, what does Domperidone mean to those who respond to this medication? It means effective control of their formerly intractable nausea and vomiting, less time in the emergency department for fluid re-hydration, weight stabilization because symptoms are subdued and they can eat, avoidance of feeding tubes, increased quality of life and ability to return to work. This would be in patients who failed to respond to erythromycin and metoclopramide.

This letter will be copied to the compounding pharmacies that the FDA sent letters of warnings to, as well as the congressional digestive disease caucus, and the president of the American Motility Society.

Finally, please advise our association as to what American patients suffering from gastroparesis are suppose to do in order to obtain their current and on-going prescriptions for Domperidone.

Sincerely,

Jeanne Keith-Ferris, RN, BScN
President / Founder, GPDA