DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drug Evaluation
and Research
Food and Drug Administration
Silver Spring, MD 20993

March 3, 2010

Thank you for taking the time to write to the Food and Drug Administration (FDA) regarding your concerns over the current market prices of approved oral colchicine (Colcrys). I am writing to address your concern and to share FDA's perspective regarding the use of unapproved oral colchicine.

While the Agency does not regulate the pricing of prescription drugs, I appreciate your concern about increased prices of Colcrys. At FDA we are well aware that price affects access. Given that important reality, I would like to take this opportunity to discuss the drug approval process and the specific benefits offered by the required approval of oral colchicine.

The mission of FDA's Center for Drug Evaluation and Research (CDER) is to ensure that safe and effective drugs are available to the American public. FDA's drug approval process ensures that drugs are safe, effective, of a suitable quality and purity, and are properly labeled. Drugs that have not been approved by FDA may not be safe and effective, may have been manufactured under sub-standard conditions, may contain too much or too little (if any) active ingredients, and may not have necessary labeling information and warnings.

Although FDA has not, to date, taken any regulatory action to remove unapproved oral colchicine products from the market, we have been in long-term communication with all manufacturers of unapproved drugs Since FDA announced its Unapproved Drugs Initiative in June 2006, marketers of unapproved drugs have been on notice that addressing risks from unapproved drugs is a high priority for FDA, and that the Agency plans to systematically and responsibly ensure that all products on the U.S. prescription drug market become compliant with current FDA approval requirements for safety and efficacy. Although FDA is aware of 21 firms that manufacture and distribute unapproved oral colchicine, so far, only one, Mutual Pharmaceuticals/URL ("Mutual"), has chosen to take the clinically responsible step of seeking approval for unapproved oral colchicine.

Of important note, the colchicine products you are referring to in your communication to FDA are not "generic" drugs. By definition, generic drugs are those evaluated and approved by FDA to demonstrate bioequivalence to a brand name reference product. Healthcare professionals and consumers can be assured that FDA-approved generic drug products have met the same quality, strength, purity and stability as brand-name drugs. Additionally, the generic manufacturing, packaging, and testing sites must meet the same quality standards as those of brand-name drugs. These colchicine products have not been evaluated and approved by FDA. They are unapproved drugs, not generic medications, and neither their safety nor their efficacy can be assured.

Mutual recently obtained approval of its oral colchicine product, Colcrys. During the drug approval process, FDA identified two previously uncharacterized safety concerns associated with the use of colchicine (marketed as Colcrys).

First, FDA analyzed safety data for colchicine-related deaths described in the published literature, adverse events reported to FDA's Adverse Event Reporting System (AERS), and company-sponsored pharmacokinetic and drug interaction studies. All of the reported safety data were related to unapproved oral colchicine. The analysis found 169 deaths associated with the use of unapproved oral colchicine.

Of the 169 deaths, 117 were not reported as overdoses; the majority of reported deaths had colchicine doses within the therapeutic range of less than or equal to 2 mg per day. The reported death cases did not contain information regarding patients' renal or hepatic function. Sixty of the 117 reported deaths (51%) involved patients who were concomitantly using clarithromycin. These reports suggest alterations in the pharmacokinetics of colchicine played a central role in the development of toxicity.

Based on review and analysis, FDA concluded there is a risk for severe drug interactions in certain patients treated with colchicine and concomitant P-gp or strong CYP3A4 inhibitors. FDA recommends that P-gp or strong CYP3A4 inhibitors not be used in patients with renal or hepatic impairment who are currently taking colchicine. Furthermore, FDA recommends that healthcare professionals consider a dose reduction or interruption of colchicine in patients with normal renal and hepatic function if treatment with a P-gp or a strong CYP3A4 inhibitor is required. The FDA-approved prescribing information for Colcrys contains recommended dosage adjustments.

Second, as part of the approval process, the sponsor of Colcrys submitted data from a clinical trial to evaluate the safety and efficacy of a low-dose regimen of oral colchicine for treatment of acute gout flares compared to the traditional high-dose regimen. The trial was a multicenter, randomized, double-blind, placebo-controlled trial of patients meeting American College of Rheumatology criteria for gout who were assigned to one of three treatment groups within 12 hours of a gout flare, as follows:

- Group 1: high-dose colchicine (1.2 mg, then 0.6 mg hourly for 6 hours [4.8 mg total])
- Group 2: low-dose colchicine (1.2 mg, then 0.6 mg in 1 hour [1.8 mg total] followed by 5 placebo doses hourly)
- Group 3: placebo (2 capsules, then 1 capsule hourly for 6 hours).

The trial found that a statistically significantly greater proportion of patients in the low-dose (38%) and high-dose (33%) colchicine groups achieved a 50% reduction in pain in the target joint compared to placebo (16%). Additionally, the rate of gastrointestinal adverse events (diarrhea, nausea, vomiting, abdominal pain) was considerably lower in low-dose patients (26%) compared to high-dose patients (77%). Further, there were no severe adverse events reported in low-dose patients compared to 10 reported in high-dose patients. These findings suggest that prior use of high-dose colchicine may have exposed patients to increased toxicity with no greater efficacy than the low-dose regimen.

FDA is highlighting these important safety considerations in the approved prescribing information to help ensure safe use of Colcrys. Without this review by FDA, outdated assumptions of what is safe and effective for treatment with oral colchicine would have remained unchecked, and patients would have continued to suffer from adverse reactions such as severe gastro-intestinal complications -- and even death -- needlessly.

The fatalities associated with unapproved oral colchicine products are among many other serious adverse events associated with unapproved drugs. These adverse events, in addition to being tragic and in many cases preventable, place a serious burden on the healthcare system. The Agency is particularly concerned because labeling of many unapproved drugs does not adequately convey the risks of the drugs and how to best use drugs safely, such as what kind of other medicines should be avoided at the same time to lower the chances of side effects. When a drug is not used properly because the labeling is inadequate, there is a cost to patients and the healthcare system because of the care required as a result of adverse events.

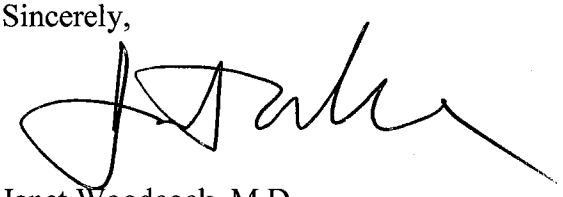
The approval of Colcrys demonstrates that while a patient or prescriber may believe that a drug is safe or effective because of individual experience, such subjective experiences can be misleading and insufficient to establish safety and effectiveness. Instead, FDA relies on carefully designed clinical trials that weigh the risks and benefits of taking a drug compared with the risks and benefits of taking a placebo or another accepted therapy. Carefully designed clinical trials have repeatedly demonstrated that the safety and effectiveness of drugs cannot be adequately established from anecdotal evidence or consumer or prescriber preferences.

Only Mutual has submitted an application to FDA for the approval of single-ingredient oral colchicine. We have discussed with the American College of Rheumatology (ACR) the importance of unapproved oral colchicine products obtaining FDA approval. ACR informed us that it would reach out to the unapproved manufacturers to encourage them to become engaged in the FDA approval process. FDA has an Unapproved Drugs Coordinator in the Office of New Drugs who is available to assist manufacturers in obtaining information regarding the application process.

I recognize that there is a real concern that prices of oral colchicine have increased substantially following the approval of Colcrys. Again, FDA has no statutory authority to control the prices charged for marketed drugs in the U.S. These prices are established by manufacturers, distributors, and retailers. I would, however, like to note that Mutual has started the Colcrys Patient Assistance Program, an initiative that will enable some patients with various limited financial means to save on Colcrys prescriptions. Unlike other patient assistance programs that may target primarily patients at or near the poverty level, Mutual's tiered program is designed to help patients in a variety of socio-economic situations. For instance, according to a December 22, 2009 letter written by Mutual president and chief executive officer Richard H. Roberts, M.D., Ph.D. to the American College of Rheumatology, a patient in a family of four whose yearly income is $132,000 would be eligible to receive a month's supply of Colcrys for $30. [see http://www.urlpharma.com/NewsView.aspx?code=140O5M23J30&archived=False.]

The Agency will continue to ensure that all prescription drugs are safe, effective, high quality, and properly labeled by encouraging companies to comply with FDA approval requirements. I ask your support in this important initiative.

Sincerely,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research