



Summary of January 21 Teleconference with FDA Regarding Colchicine

On January 21, a teleconference was held with the Food and Drug Administration and the American College of Rheumatology regarding concern over the potential increase in the cost of unapproved colchicine.

Stanley Cohen, MD, ACR president, and Aiken Hackett, director of government affairs, represented the College, and Janet Woodcock, MD, director, Center for Drug Evaluation and Research, Bob Rappaport, MD, director, Division of Anesthesia, Analgesia, and Rheumatology Products, CDER, Jeffrey Siegel, MD, clinical team leader, Division of Anesthesia, Analgesia, and Rheumatology Products, CDER, Sarah Okada, MD, medical team leader, Division of Anesthesia, Analgesia, and Rheumatology Products, CDER, Michael Levy, director, Division of New Drugs and Labeling Compliance, Office of Compliance, CDER represented the FDA.

The FDA reviewed the history of their plan to bring unapproved drugs under FDA control, which began in earnest in 2006. Dr. Woodcock cited the experiences with Synthroid[®]. This drug had issues with formulation /stability that was only recognized when the drug was evaluated through the regulatory process of requiring FDA approval (e.g. drugs historically marketed without FDA approval). Dr. Woodcock stated that this ongoing effort to bring these drugs under the regulatory process is a major focus of the FDA.

Colchicine was one of the “unapproved” drugs that was on the market and targeted by the FDA. URL Pharma was the only manufacturer to step forward and complete the testing required to meet FDA approval. During the application process, it was determined for the first time that colchicine toxicity was potentially exacerbated by drugs that inhibit CYP3A4, an enzyme involved in the metabolism of colchicine, and p-glycoprotein, a protein involved in its oral absorption. Drugs that inhibit CYP3A4 and p-glycoprotein include clarithromycin, erythromycin, cyclosporine, verapamil, diltiazem, ketoconazole and itraconazole

In addition, a small study of 126 patents evaluating Colcris[®] in acute gout showed clinical efficacy and tolerability with a lower dose of colchicine than had been used in the past. Based on this study, URL Pharma was granted three-year exclusivity for marketing the acute gout indication. In addition, seven-year exclusivity was provided for marketing the indication for familial Mediterranean fever based on a literature review. Use of colchicine for chronic gout prophylaxis was not addressed by the FDA and, therefore, URL Pharma does not have exclusivity for this indication.

We acknowledge the desire of the FDA to ensure efficacy and safety of available drugs. However, in this situation, implementation of this new approach has had unintended consequence – namely, the price of colchicine has increased from ~10 cents/pill to \$5 /pill,

creating new financial hardships for our patients. Even with patient assistance programs, nearly all patients will face an increase in price for colchicine.

Notably, URL Pharma has brought litigation against other drug manufacturers of unapproved colchicine with the intent to close down the production of this drug by other companies. The ACR suggested that the FDA prolong the usual “grace” period of one year before forcing other manufacturers to cease production of unapproved colchicine. In the FDA’s document- “Marketing Unapproved Drugs-Compliance Policy Guide” (section 440.100; page 6) it states if drug removal, “creates a burden on affected parties,” the grace period could vary. The FDA did not clearly respond to that query.

The bottom line was that the FDA regretted the price increase in colchicine. The FDA had hoped that a price increase would not result from this new policy and hoped additional manufacturers would have stepped forward to create competition in the marketplace –lowering the price for patients. The FDA informed the ACR that the concerns raised by the rheumatology community over colchicine are similar to concerns voiced previously by endocrinologists over Synthroid®.

Importantly, no exclusivity exists for the chronic gout indication, leaving open the possibility that other manufacturers of colchicine could apply and potentially receive approval for this indication. It was inferred that that the evaluation process would possibly be limited to drug formulation and the manufacturing process. Rheumatologists rarely use colchicine for acute gout flares but utilize colchicine frequently for chronic gout prophylaxis.

Based on this teleconference, the ACR plans the following actions:

- Initiate discussion with URL Pharma to ensure our patients have access to colchicine and request them to enhance their patient assistance programs
- Obtain a list from the FDA of other manufacturers of unapproved colchicine and encourage these companies to apply for FDA market approval of colchicine for “chronic gout prophylaxis”

Although the ACR would have expected a better result for our patients taking colchicine than the current situation, our organization will continue to be proactive with the FDA and URL Pharma to bring about a satisfactory resolution to this problem.