



TRANSMITTED BY FACSIMILE

AR Holding Company, Inc.
c/o Mutual Pharmaceutical Company, Inc.
Attn: Sherry Schultz, Associate Director, Regulatory Operations
1100 Orthodox Street
Philadelphia, PA 19124

RE: NDA 022352
COLCRYS[®] (colchicine, USP) tablets for Oral use
MA #51 and #66

Dear Ms. Schultz:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a Pharmacy Sell Sheet (COL-266) (sell sheet) and professional video (COL-271) entitled, "Myth vs. Reality" (video) for COLCRYS[®] (colchicine, USP) tablets for Oral use (Colcrys) submitted by Mutual Pharmaceutical Company, Inc. (Mutual) under cover of Form FDA-2253. These pieces are false or misleading because they omit and minimize risk information associated with the use of Colcrys. Furthermore, the video is false or misleading because it makes unsubstantiated safety superiority claims and overstates the efficacy of Colcrys. Thus, the sell sheet and video misbrand Colcrys in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 352(a) & 321(n). Cf. 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i) & (ii); (e)(7)(viii).

Background

Below is an indication and summary of the most serious and most common risks associated with the use of Colcrys.¹

The INDICATIONS AND USAGE section of the FDA-approved product labeling (PI) for Colcrys states (in pertinent part), "COLCRYS[®] (colchicine, USP) tablets are indicated for prophylaxis and the treatment of acute gout flares."

Colcrys is also associated with serious risks, as reflected in its PI. Specifically, Colcrys is contraindicated in patients with renal or hepatic impairment who are receiving P-gp or strong CYP3A4 inhibitors. The PI for Colcrys contains WARNINGS AND PRECAUTIONS regarding fatal overdoses, blood dyscrasias, monitoring for toxicity, life-threatening and fatal drug interactions in patients receiving P-gp or strong CYP3A4 inhibitors, and neuromuscular toxicity. In addition, according to the ADVERSE REACTIONS section of the PI, the most

¹ This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional pieces cited in this letter.

common reported adverse reaction in clinical trials for the prophylaxis of gout flares was diarrhea. The most common adverse reactions reported in the clinical trial for the treatment of gout flares were diarrhea and pharyngolaryngeal pain.

Omission and Minimization of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials.

Although the sell sheet and video include some information regarding the risk of rhabdomyolysis associated with Colcrys (i.e., “Rhabdomyolysis has been occasionally observed, especially when colchicine is prescribed in combination with other drugs known to cause this effect”), they omit important material facts regarding this risk. Specifically, the WARNINGS AND PRECAUTIONS section of the PI states the following (in pertinent part; emphasis added):

Colchicine-induced neuromuscular toxicity and rhabdomyolysis have been reported with chronic treatment **in therapeutic doses. Patients with renal dysfunction and elderly patients, even those with normal renal and hepatic function, are at increased risk.**

The omission of this important risk information misleadingly suggests that Colcrys is safer than has been demonstrated by substantial evidence or substantial clinical experience.

The sell sheet includes the headline claim, “**TOUGH, BUT GENTLE**” (bolded emphasis in original; underlined emphasis added) in conjunction with a graphic of a man wearing motorcycle gear delicately holding a china teacup. This presentation minimizes the risks associated with Colcrys by implying that Colcrys is not risky or harmful (i.e., “gentle”), when this is not supported by substantial evidence or substantial clinical experience. Such claims and presentations are particularly concerning in light of the serious risks that are mentioned in the PI for Colcrys including fatal overdoses, blood dyscrasias, life-threatening and fatal drug interactions, and neuromuscular toxicity.

The sell sheet also includes the claim, “**COLCRYS TOLERABILITY IS COMPARABLE TO PLACEBO**” (emphasis in original). Similarly, the video includes the claim that Colcrys has a “tolerability similar to placebo.” Such claims minimize risk by implying that the safety profiles for Colcrys and placebo are not different or that the difference is minimal, when this is not the case. According to the ADVERSE REACTIONS section of the PI, the percentage of patients who experienced diarrhea was 23% in the recommended low-dose group versus 14% in the placebo group.

Promotional materials are misleading if they fail to present information about risks associated with a drug with a prominence and readability reasonably comparable to the presentation of information related to the effectiveness of the drug. The video minimizes the risks of Colcrys by failing to convey serious and significant risk information associated with the use of Colcrys during the main part of the video. Specifically, the first 15 minutes and 14 seconds of the video features a discussion by Matthew W. Davis, MD, RPh (Chief Medical Officer, URL

Pharma) that is primarily devoted to the discussion of unapproved colchicine products as well as the benefits of Colcris. This discussion is presented in conjunction with large, bolded claims on the right-hand side of the screen with the continuous display of the Colcris logo and tagline (i.e., "Start and Stay With") on the bottom, right-hand side of the screen. In contrast, the majority of risk information is presented after this prominent presentation in a running telescript format with accompanying voiceover, with no signal to alert the viewer that important risk information follows the presentation of benefit information. The only risk information included during the main part of the video are statements regarding drug interactions with Colcris and the need for dose modification for patients receiving interacting drugs, in addition to the lower rate of diarrhea observed in the low dose arm of the Colcris trial. The main part of the video omits discussion of serious and significant risks, including Contraindications, Warnings and Precautions such as fatal overdoses, blood dyscrasias, monitoring for toxicity, and neuromuscular toxicity, and the most commonly reported Adverse Reactions. The overall effect of this presentation undermines the communication of important risk information, minimizing the risks associated with Colcris and misleadingly suggesting that the drug is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Minimization of Risk Information/Unsubstantiated Safety Superiority Claims

In addition, the video includes claims such as the following (emphasis in original):

- Audiovisual presentation: "NSAIDs, which have a black box, are not indicated nor have they ever been approved for the prophylaxis of gout flares. As with all medication, please remember that your gout patients suffer from many comorbid conditions and caution is needed in the concomitant medications you prescribe for your patients."
- Screen text: "**REALITY** NSAIDs have never been FDA-approved for gout flare prophylaxis. Many patients with gout have comorbid conditions that preclude the use of NSAIDs long term. COLCRYS is approved for prophylaxis of gout flares as part of the management of gout."

The totality of this presentation is misleading because it minimizes the risks associated with the use of Colcris by suggesting that there are not significant safety concerns for Colcris in patients who have comorbid conditions and are taking concomitant medications, when this has not been demonstrated by substantial evidence or substantial clinical experience. Furthermore, this presentation misleadingly implies that Colcris is clinically superior (i.e., safer) in patients with comorbid conditions and has fewer drug interactions when taken with concomitant medications compared to NSAIDs. FDA is not aware of adequate and well-controlled head-to-head studies to support this implication. Such claims are particularly concerning in light of the fact that the PI for Colcris includes Warnings and Precautions regarding fatal overdoses, blood dyscrasias, life-threatening and fatal drug interactions, and neuromuscular toxicity.

Overstatement of Efficacy

Promotional materials are misleading if they represent or suggest that a drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience.

The video includes the following claims (emphasis added):

- “In a randomized clinical trial, Colcrys showed significant separation from placebo when looking at pain in **16 hours** and reached its primary outcome measure in 24 hours.”
- “COLCRYS significantly reduces the pain associated with gout flares **within 16 hours.**”²

These claims misleadingly overstate the efficacy of Colcrys by implying that Colcrys effectively reduces pain associated with gout flares within 16 hours, when this has not been demonstrated by substantial evidence or substantial clinical experience. According to the CLINICAL STUDIES section of the PI for Colcrys, the efficacy in the treatment of gout flares was assessed at **24 hours** following the time of first dose in the clinical trial. This study was **not** appropriately powered to evaluate outcomes at the 16-hour time point, nor were appropriate pre-specified adjustments for multiple comparisons between treatment groups applied during the analysis of the study data.

Conclusion and Requested Action

For the reasons discussed above, the sell sheet and video misbrand Colcrys in violation of the FD&C Act, 21 U.S.C. 352(a) & 321(n). *Cf.* 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i) & (ii); (e)(7)(viii).

OPDP requests that Mutual immediately cease the dissemination of violative promotional materials for Colcrys such as those described above. Please submit a written response to this letter on or before January 5, 2012, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Colcrys that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, Division of Professional Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at 301-847-8444. Please note that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has been reorganized and elevated to the Office of Prescription Drug Promotion (OPDP). OPDP consists of the Immediate Office, the Division of Professional Promotion (DPP) and the Division of Direct-to-Consumer Promotion (DDTCP). To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. In addition, OPDP recently migrated to a different tracking system. Therefore, OPDP letters will now refer to MA numbers instead of MACMIS numbers. Please refer to MA #51 and #66 in addition to the NDA number in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official.

² Data on file, URL Pharma, Inc. (AGREE Trial clinical study report. Figure 11:2; page 83 of 663). This study is described in the CLINICAL STUDIES section of the PI for Colcrys.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Colcrys comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Roberta Szydlo, R.Ph.
Regulatory Review Officer
Division of Professional Promotion
Office of Prescription Drug Promotion

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERTA T SZYDLO
12/22/2011