I. Background

Colchicine is an alkaloid of the Colchicum autumnale plant, also known as autumn crocus or meadow saffron. Colchicine was initially described in the 1st century A.D. by Dioscorides in the Materia Medica. Medical use of colchicine for gout pain dates back to the 6th century. It was used for several centuries, but the use of colchicine in the treatment of gout substantially declined by the 15th century because of its toxicity. Colchicine was reintroduced as a treatment for acute gout beginning in 1763. Colchicine was first isolated from colchicum in 1820 and made available in oral dosage form during the 19th century. Colchicine in oral dosage form is currently marketed in the United States as approved and unapproved products, both as a single ingredient and in combination with probenecid. Colchicine for injection has been available in the United States since the 1950s and has been administered intravenously for the treatment of acute gout flares. In the Federal Register of February 8, 2008 (73 FR 7565), FDA announced its intention to take enforcement action against unapproved drug products containing colchicine for injection. Single-ingredient oral colchicine products, the subject of this notice, have also been marketed in the United States without approved applications to treat acute gout flares, and are more commonly marketed in conjunction with uric acid lowering agents for the daily prophylaxis of flares of gout. Daily oral colchicine has also been the standard of care since the 1970s for the prophylaxis of attacks of FMF.

II. Comments

Interested persons may submit to the Division of Dockets Management (see ADDRESSES) either electronic or written comments regarding this document. It is only necessary to send one set of comments. It is no longer necessary to send two copies of mailed comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

Dated: September 27, 2010.

Leslie Kux,
Acting Assistant Commissioner for Policy.

FOR FURTHER INFORMATION CONTACT:
Karen Rothchild, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 5237, Silver Spring, MD 20993–0002, 301–796–3689, e-mail: Karen.Rothschild@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

A “person” includes individuals, partnerships, corporations, or associations (section 201 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(a)).

Because the incidence of FMF in the United States is rare, Mutual sought and was granted orphan drug status for its product covered by NDA 22–352 under section 526 of the act (21 U.S.C. 360bb). The term “orphan drug” refers to a product that treats a rare disease affecting fewer than 200,000 Americans. Enacted in 1983, the intent of the Orphan Drug Act is to stimulate the research, development, and approval of products that treat...
be reported to postmarketing adverse event databases. Postmarketing adverse event databases, including FDA’s AERS database, reveal that half of non-overdose colchicine fatalities are related to the concommitant use of colchicine and clarithromycin. This information suggests that despite the literature, awareness regarding colchicine interactions may not be widespread in the healthcare community. Another variable in this equation is that interactions are potentially more severe and lethal in patients with an underlying susceptibility. Based on the published literature, a 4-fold decrease in colchicine clearance is noted in severely renal impaired subjects undergoing hemodialysis compared to healthy volunteers. A 2.5- to 10-fold lower clearance has been reported in cirrhotic patients when compared to healthy subjects. No pharmacokinetic studies have been performed in the elderly or in pediatric patients. However, because the elderly are more likely to have significant renal or hepatic impairment, as a whole, they are more at risk. In light of these safety concerns, there are specific dose modification and reduction recommendations in the recently approved colchicine labeling pertaining to drug interactions and to patients with renal impairment. Furthermore, a new clinical trial in acute gout that was conducted in support of the NDA found that a lower dose of oral colchicine than had been considered the standard of care was just as effective for the treatment of an acute gout flare, but resulted in fewer adverse events. The approved labeling for oral colchicine reflects this newly discovered information.

In general, the labeling for unapproved single-ingredient oral colchicine products listed with FDA under section 510(j) of the act (21 U.S.C. 360(j)) does not reflect the most current data regarding the safety and effectiveness of single-ingredient oral colchicine. As noted previously in this document, the newly approved labeling reflects the new dosing for acute gout flares. Additionally, based on pharmacokinetic studies conducted in support of the approved NDAs, new specific-dose modification and reduction recommendations are provided in the approved colchicine labeling for its use with drugs that use certain enzymes, such as CYP3A4 or P-gp, for their metabolism or absorption. Because no applications have been submitted to and reviewed by FDA for the unapproved single-ingredient oral colchicine products, the safety and effectiveness of these unapproved products cannot be assured.

The expected risks associated with use of oral products that contain single-ingredient colchicine are potentially greater for unapproved products because the quality, safety, and efficacy of unapproved formulations have not been demonstrated to FDA. For example, the ingredients and bioavailability of unapproved products have not been submitted for FDA review, nor has FDA had the opportunity to assess the adequacy of their chemistry, manufacturing, and controls specifications. Further, as noted previously, a clinical trial revealed that a substantially lower dose of colchicine is as effective as the higher dose traditionally considered to be the standard of care, with significantly reduced adverse reactions. Because FDA has not approved the labeling for unapproved single-ingredient colchicine products, their labeling likely does not contain appropriate dosing and drug interaction information.

III. Legal Status
A. Current Status of Single-Ingredient Oral Colchicine

As stated previously, only one firm, Mutual Pharmaceutical, Inc. (Mutual), has obtained approved applications for single-ingredient oral colchicine tablets. Mutual submitted three NDAs for its single-ingredient colchicine tablets: NDA 22-352 for the indication of FMF, which was approved on July 29, 2009; NDA 22-351 for the treatment of acute gout, which was approved on July 30, 2009; and NDA 22-353 for the prevention of gout flares in the chronic treatment of gout, which was approved on October 16, 2009. Mutual is marketing these products under the trade name COLCRYS. As stated previously, because the incidence of FMF in the United States is rare, Mutual sought and was granted orphan drug status for its product covered by NDA 22-352 under section 526 of the act.

Unapproved single-ingredient oral colchicine tablets are also available on the market. The agency reviewed the labeling of unapproved colchicine products listed with FDA under section 510(j) of the act. In general, labeling for the unapproved products does not reflect the most current data regarding single-ingredient oral colchicine. As noted previously, the newly approved labeling reflects the new dosing for acute gout flares. Based on pharmacokinetic studies, new specific-dose modification and reduction recommendations are provided in the approved colchicine label for its use...
with drugs that use certain enzymes, such as CYP3A4 or P-gp, for their metabolism or absorption. Because no applications have been filed and reviewed by the agency for the unapproved products, the safety and effectiveness of these products cannot be ensured.

B. Single-Ingredient Oral Colchicine Products Are New Drugs Requiring Approved Applications

Based on both the safety considerations previously described and the absence of published literature documenting that single-ingredient oral colchicine is safe and effective, unapproved single-ingredient oral colchicine is not generally recognized as safe and effective for any indication including treatment of acute gout flares or for the daily prophylaxis of gout. Agency review of individual applications to ensure appropriate manufacturing and labeling is required to ensure the safe and effective use of the drug. Therefore, single-ingredient oral colchicine is regarded as a new drug as defined in section 201(p) of the act (21 U.S.C. 321(p)) and is subject to the requirements of section 505 of the act. As set forth in this notice, approval of an NDA or ANDA under section 505 of the act is required as a condition for manufacturing or marketing all single-ingredient oral colchicine products. Any person who submits an application for a single-ingredient oral colchicine product but has not received approval must comply with this notice.

C. Notice of Enforcement Action

Although not required to do so by the Administrative Procedure Act, the act, or any rules issued under its authority, or for any other legal reason, FDA is providing this notice to persons who are manufacturing unapproved single-ingredient oral colchicine products that after the dates identified in this notice, the agency intends to take enforcement action against such products and those who manufacture them or cause them to be manufactured or shipped in interstate commerce.

Manufacturing or shipping unapproved single-ingredient oral colchicine products can result in enforcement action, including seizure, injunction, or other judicial or administrative proceedings. Consistent with policies described in the agency’s guidance entitled “Marketed Unapproved Drugs—Compliance Policy Guide” (the Marketed Unapproved Drugs CPG), the agency does not expect to issue a warning letter or any other further warning to firms marketing unapproved single-ingredient oral colchicine products prior to taking enforcement action. The agency also reminds firms that, as stated in the Marketed Unapproved Drugs CPG, any unapproved drug marketed without a required approved drug application is subject to agency enforcement action at any time. The issuance of this notice does not in any way obligate the agency to issue similar notices or any notice in the future regarding marketed unapproved drugs.

As described in the Marketed Unapproved Drugs CPG, the agency may, at its discretion, identify a period of time during which the agency does not intend to initiate an enforcement action against a currently marketed unapproved drug solely on the ground that it lacks an approved application under section 505 of the act. With respect to unapproved single-ingredient oral colchicine products, the agency intends to exercise its enforcement discretion for only a limited period of time because single-ingredient oral colchicine products are drugs with potential safety risks, and, in light of the fact that the agency has approved applications for single-ingredient oral colchicine products for the treatment of acute gout flares, prophylaxis of gout flares, and prophylaxis of attacks of FMF, the continued marketing of unapproved single-ingredient oral colchicine products is a direct challenge to the drug approval process. Therefore, the agency intends to implement this notice as follows.

This notice is effective October 1, 2010. FDA intends to take action to enforce section 505(a) of the act against any unapproved single-ingredient oral colchicine products that are not listed with FDA in full compliance with section 510 of the act before September 30, 2010, and that are manufactured, shipped, or otherwise introduced or delivered for introduction into interstate commerce by any person on or after October 1, 2010. FDA also intends to take action to enforce section 505(a) of the act against any unapproved single-ingredient oral colchicine products that have a National Drug Code (NDC) number listed with FDA in full compliance with section 510 of the act but were not being commercially used or sold in the United States on September 30, 2010, and that are manufactured, shipped, or otherwise introduced or delivered for introduction into interstate commerce by any person on or after October 1, 2010.

Nothing in this notice, including FDA’s intent to exercise its enforcement discretion, alters any person’s liability or obligations in any other enforcement action or litigation, or precludes the agency from initiating or proceeding with enforcement action in connection with any other alleged violation of the act, whether or not related to an unapproved drug product covered by this notice. Similarly, a person who is

The agency’s general approach for dealing with these products in an orderly manner is spelled out in the Marketed Unapproved Drugs CPG.

For the purpose of this notice, the term “commercially used or sold” means that the product has been used in a business or activity involving retail or wholesale marketing and/or sale.

However, for unapproved single-ingredient oral colchicine products that are commercially used or sold in the United States, have an NDC number listed with FDA, and are in full compliance with section 510 of the act before September 30, 2010 ("currently marketed and listed"), the agency intends to exercise its enforcement discretion as follows. FDA intends to initiate enforcement action against any currently marketed and listed unapproved single-ingredient oral colchicine products that are manufactured on or after November 15, 2010, or that are shipped on or after December 30, 2010. Further, FDA intends to take enforcement action against any person who manufactures or ships such products after these dates. Any person who has submitted or submits an application for a single-ingredient oral colchicine product but has not received approval must comply with this notice.

The agency, however, does not intend to exercise its enforcement discretion as outlined previously if either of the following applies: (1) A manufacturer or distributor of an unapproved single-ingredient oral colchicine product is violating any other provisions of the act (including but not limited to violations related to FDA’s current good manufacturing practices, adverse drug event reporting, labeling or misbranding requirements) or (2) it appears that a firm, in response to this notice, increases its or interstate shipment of unapproved single-ingredient oral colchicine products above its usual volume.

6 If FDA finds it necessary to take enforcement action against multiple violations of the act at the same time (see, e.g., United States v. Sage Pharmaceuticals, 410 F. 3d 479, 480 (6th Cir. 2004) (permitting the agency to combine all violations of the act in one proceeding, rather than taking action against multiple violations of the act in “piecemeal fashion”).
or becomes enjoined from marketing unapproved drugs may not resume marketing of unapproved single-ingredient oral colchicine products based on FDA’s exercise of enforcement discretion as set forth in this notice.

Drug manufacturers and distributors should be aware that the agency is exercising its enforcement discretion as described previously only in regard to unapproved single-ingredient oral colchicine products that are marketed under an NDC number listed with the agency in full compliance with section 510 of the act before September 30, 2010. As previously stated, unapproved single-ingredient oral colchicine products that are currently marketed but not listed with the agency on the date of this notice must, as of the effective date of this notice, have approved applications before shipment in interstate commerce.

D. Discontinued Products

Some firms may have previously discontinued the manufacturing or distribution of products covered by this notice without removing them from the listing of their products under section 510(j) of the act. Other firms may continue manufacturing or marketing listed products in response to this notice. Firms that wish to notify the agency of product discontinuation should send a letter, signed by the firm’s chief executive officer, fully identifying the discontinued product(s), including the product NDC number(s), and stating that the product(s) has (have) been discontinued. The letter should be sent electronically to edrls@fda.hhs.gov. Firms should also update the listing of their products under section 510(j) of the act to reflect discontinuation of unapproved single-ingredient colchicine products. FDA plans to rely on its available information when we evaluate products. FDA plans to exercise its enforcement discretion as set forth in this notice.

Information on Services for Individuals with Disabilities: For information on facilities or services for individuals with disabilities or to request special assistance at the meeting, contact the CIPAC Secretariat at 703–235–3999 or by e-mail at cipac@dhs.gov.

Dated: September 27, 2010.

Leslie Kux,
Acting Assistant Commissioner for Policy.

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