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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Display Date 2-6-08  
Publication Date 2-8-08  
Certifier D. Hawkins

[Docket No. FDA-2008-N-0014]

Drug Products Containing Colchicine for Injection; Enforcement Action

Dates

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

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**SUMMARY:** The Food and Drug Administration (FDA) is announcing its intention to take enforcement action, as described in this notice, against unapproved drug products containing colchicine for injection (hereinafter “colchicine for injection products”), and persons who manufacture or cause the manufacture of such products or their shipment in interstate commerce. All colchicine for injection products are administered intravenously. Colchicine is associated with a variety of serious adverse events, some of them potentially fatal. Furthermore, a narrow margin of safety exists between a therapeutic dose of colchicine and a toxic dose of the drug. Colchicine for injection products are new drugs that require approved applications because they are not generally recognized as safe and effective. Manufacturers who wish to market a colchicine for injection product must obtain FDA approval of a new drug application (NDA).

**DATES:** Effective [*insert date of publication in the Federal Register*]. For information about enforcement dates, please see the **SUPPLEMENTARY INFORMATION** section.

**ADDRESSES:** All communications in response to this notice should be identified with Docket No. FDA-2008-N-0014 and directed to the appropriate office listed as follows:

*Regarding applications under section 505(b) of the act (21 U.S.C. 355(b)):*

Parinda Jani, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Silver Spring, MD 20993-0002, 301-796-1232, Parinda.Jani@fda.hhs.gov.

*All other communications:* See the **FOR FURTHER INFORMATION CONTACT** section.

**FOR FURTHER INFORMATION CONTACT:** Jennifer Devine, Center for Drug Evaluation and Research (HFD-310), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-8965, e-mail: *Jennifer.Devine@fda.hhs.gov*.

**SUPPLEMENTARY INFORMATION:**

**I. Enforcement Dates**

FDA intends to take enforcement action to enforce section 505(a) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 255(a)) against any unapproved colchicine for injection product that does not have a National Drug Code (NDC) number listed with FDA in full compliance with section 510 of the act (21 U.S.C. 360) before [*insert Federal Register display date*], that is manufactured, shipped, or otherwise introduced or delivered for introduction into interstate commerce by any person<sup>1</sup> on or after [*insert date of publication in the Federal Register*], or against any colchicine for injection product that has an NDC number listed with FDA and is not commercially used or sold in the United States before [*insert Federal Register display date*], but is manufactured, shipped, or otherwise introduced or delivered for introduction

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<sup>1</sup>A "person" includes individuals, partnerships, corporations, or associations (21 U.S.C. 321(e)).

into interstate commerce by any person on or after [*insert date of publication in the Federal Register*].

However, for unapproved colchicine for injection products that are commercially used or sold in the United States and have an NDC number listed with FDA in full compliance with section 510 of the act before [*insert Federal Register display date*] (“currently marketed and listed”), the agency intends to exercise its enforcement discretion after as identified elsewhere in this document. FDA intends to initiate enforcement action against any currently marketed and listed colchicine for injection product that is manufactured on or after [*insert date 30 days after date of publication in the Federal Register*], or that is shipped, introduced, or delivered for introduction (“shipped”) on or after [*insert date 180 days after date of publication in the Federal Register*]. Further, FDA intends to take enforcement action against any person who manufactures or ships such products after the dates set forth previously. Any person who submits a new drug application (NDA) for a colchicine for injection product but has not received approval must comply with this notice. Unapproved colchicine for injection products that are not currently marketed, or that are currently marketed but are not listed with the agency before [*insert Federal Register display date*] must, as of the date of this notice, have approved applications prior to their introduction or delivery for introduction into interstate commerce.

## II. Background

Colchicine is an alkaloid of the *colchicum autumnale* plant, also known as autumn crocus or meadow saffron. Colchicum was initially described in the 1st century A.D. by Dioscorides in the *Materia Medica*. Medical use of colchicum for gout pain dates back to the 6th century. It was used for several

centuries, but the use of colchicum in the treatment of gout substantially declined by the 15th century because of its toxicity. Colchicum 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 available in both as a single ingredient and in combination with probenecid, but these products are not covered by this notice. Colchicine for injection has been available in the United States since the 1950s and has been administered intravenously for the treatment of acute attacks of gout. Because of toxicities associated with the use of intravenous (IV) colchicine and the emergence of safer alternative therapies, IV colchicine is rarely used in current practice for acute gout treatment.

### **III. Current Status of Colchicine for Injection Products**

There are currently no approved applications for colchicine for injection products. FDA is aware of only one manufacturer of a currently marketed unapproved colchicine for injection product. This manufacturer has notified the agency that it has ceased manufacturing colchicine for injection.

### **IV. Safety Issues in Use of Colchicine for Injection Products**

Serious safety concerns, including fatalities, associated with colchicine for injection products are well documented in the literature and in adverse drug events reported to the agency. Many of these adverse events are caused by colchicine toxicity, which typically occurs in three phases. The initial phase, occurring within 24 hours of administration of a toxic dose of colchicine, is characterized by abdominal pain, anorexia, nausea, vomiting, diarrhea, leukocytosis, hypovolemia, and electrolyte imbalance. The second phase, 2 to 7 days after colchicine administration, involves bone marrow aplasia, coagulopathies, cardiac arrhythmia, renal failure, rhabdomyolysis, seizures,

peripheral neuropathy with ascending paralysis, and respiratory distress. If the patient survives, the third phase is a recovery phase involving leukocytosis and alopecia. Overall, FDA is aware of 50 reports of adverse events associated with IV colchicine use, including 23 deaths, through June 2007.<sup>2</sup> Three of these deaths occurred in March and April of 2007 and were associated with the use of compounded IV colchicine. Among the commonly reported events (n=50) that had medical significance were neutropenia, acute renal failure, thrombocytopenia, congestive heart failure, and pancytopenia.

Compared to oral administration of colchicine, there is an increased likelihood of colchicine toxicity when the drug is administered intravenously. For oral dosing in the treatment of acute gout, the dose is usually titrated by administering the drug over time until symptoms resolve or the patient begins to experience side effects, which are typically gastrointestinal. This emergence of side effects during oral dosing provides a margin of safety that often prevents serious and fatal overdoses. In the case of IV administration, side effects are generally not experienced until the patient has already received toxic levels of colchicine. Therefore, extreme care must be exercised when colchicine is administered by this route.

Colchicine is also known to have a narrow therapeutic index, with a narrow margin of safety between doses that are therapeutic in the treatment of gout and doses that are toxic. Many of the adverse events associated with colchicine are dose-related. Overdosing of colchicine, as discussed previously, can result in bone marrow suppression, organ failure, and death. The rate of clearance of colchicine tends to decline in persons with diminished renal or hepatic function. This means that the blood level of colchicine in persons with

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<sup>2</sup>Data in the current system adverse event reporting system (AERS) dates back to when the AES was first implemented in 1969.

diminished renal or hepatic function tends to be higher for a longer period of time for a given dose compared to persons with normal renal or hepatic function. The frequency and severity of adverse effects, including colchicine toxicity, may also be greater in these populations.

FDA is generally aware of the use of IV colchicine as a treatment for back pain and that compounding pharmacies often produce colchicine for injection products that are administered intravenously for back pain treatment. FDA has not approved colchicine in any dosage form for the treatment of back pain. FDA's policy regarding the practice of pharmacy compounding is articulated in the Agency's Compliance Policy Guide Sec. 460.200 on Pharmacy Compounding (Pharmacy Compounding CPG). This notice does not affect the applicability or interpretation of the Pharmacy Compounding CPG.

FDA wants to underscore that there are serious risks associated with IV colchicine products, because there is a limited margin of safety due to both the narrow therapeutic index and serious toxicity of colchicine. Any dosing errors with the administration of IV colchicine could have potentially serious and fatal consequences.

## **V. Legal Status**

### *A. Colchicine Products for Injection Are New Drugs Requiring Approved Applications*

Based on the safety considerations described previously, colchicine for injection products are not generally recognized as safe and effective under section 201(p) of the act (21 U.S.C. 321(p)) for the treatment or prevention of gout or any other condition. Therefore, an injectable drug product containing colchicine, alone or in combination with other drugs, is regarded as a new drug as defined in section 201(p) of the act and is subject to the requirements

of section 505 of the act. As set forth in this notice, approval of an NDA or an abbreviated new drug application under section 505 of the act is required as a condition for manufacturing or marketing all colchicine for injection products. After the dates identified in this notice, FDA intends to take enforcement action as described in this notice against any person who is marketing or shipping unapproved colchicine for injection products. Any person who submits an NDA for a colchicine for injection product but has not received approval must comply with this notice. Furthermore, this notice does not affect the applicability or interpretation of the Pharmacy Compounding CPG.

This notice does not affect the legal status of products containing colchicine in oral dosage forms, which FDA intends to address at a later date.

#### *B. 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 marketing unapproved colchicine for injection products that the agency intends to take enforcement action against such products and those who market them or cause them to be marketed or shipped in interstate commerce. Consistent with the priorities identified in the agency's CPG Sec. 440.100 entitled "Marketed Unapproved Drugs--Compliance Policy Guide" (Marketed Unapproved Drugs CPG), the agency is taking action at this time against unapproved colchicine for injection products because, as described in section III of this notice, colchicine for injection is a drug with significant safety risks.

Manufacturing or shipping unapproved colchicine for injection products can result in enforcement action, including seizure, injunction, or other

judicial or administrative proceeding. Consistent with policies described in the Marketed Unapproved Drugs CPG, the agency does not expect to issue a warning letter or any other further warning to firms marketing unapproved colchicine for injection 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.<sup>3</sup>

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 grounds that it lacks an approved application under section 505 of the act. With respect to unapproved colchicine for injection products, the agency intends to exercise its enforcement discretion for only a limited period of time for the following reasons: (1) Colchicine for injection is a drug with significant safety risks, (2) colchicine is available in an oral dosage form for those patients for whom use of the drug is medically necessary, and (3) colchicine in combination with probenecid as an oral tablet has FDA approval and is indicated for the treatment of gout. Therefore, the agency intends to implement this notice as identified elsewhere in this document.

FDA intends to take enforcement action to enforce section 505(a) of the act against any unapproved colchicine for injection product that is not listed

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<sup>3</sup>The agency's general approach in dealing with these products in an orderly manner is spelled out in the Marketed Unapproved Drugs CPG. That CPG, however, provides notice that any product that is being marketed illegally, and the persons responsible for causing the illegal marketing of the product, are subject to FDA enforcement action at any time.

in full compliance with section 510 of the act before [*insert Federal Register display date*], that is manufactured, shipped, or otherwise introduced or delivered for introduction into interstate commerce by any person on or after [*insert date of publication in the Federal Register*], or is not currently marketed but is subsequently manufactured, shipped, or otherwise introduced or delivered for introduction into interstate commerce by any person on or after [*insert date of publication in the Federal Register*].

However, for currently marketed and listed unapproved colchicine for injection products, the agency intends to exercise its enforcement discretion after [*insert date of publication in the Federal Register*], as identified elsewhere in this document. FDA intends to initiate enforcement action against any currently marketed and listed colchicine for injection product that is manufactured on or after [*insert date 30 days after date of publication in the Federal Register*], or that is shipped on or after [*insert date 180 days after date of publication in the Federal Register*]<sup>4</sup>. Further, FDA intends to take enforcement action against any person who manufactures or ships such products after the dates set forth previously. Any person who submits an NDA for a colchicine for injection 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 the following apply: (1) A manufacturer or distributor of an unapproved injectable colchicine product covered by this

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<sup>4</sup>If FDA finds it necessary to take enforcement action against a product covered by this notice, the agency may take action relating to all of the defendant's other violations of the act at the same time. For example, if a firm continues to manufacture or market a product covered by this notice after the applicable enforcement date has passed, to preserve limited agency resources, FDA may take enforcement action relating to all of the firm's unapproved drugs that require applications at the same time (see e.g. *United States v. Sage Pharmaceuticals*, 210 F3d 475, 479-480 (5th Cir. 2000) (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")).

notice is violating other provisions of the act, including but not limited to, violations related to FDA's current good manufacturing practices, adverse drug event reporting, misbranding, or other violations, or (2) it appears that a firm, in response to this notice, increases its manufacture or interstate shipment of injectable colchicine drug products above its usual volume during these periods.

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 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 or becomes enjoined from marketing unapproved drugs may not resume marketing of unapproved injectable colchicine products based on FDA's exercise of enforcement discretion as set forth in this notice.

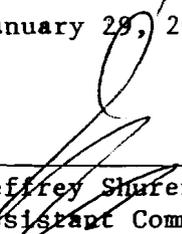
Drug manufacturers and distributors should be aware that the agency is exercising its enforcement discretion as described previously only in regard to colchicine for injection products that are marketed under an NDC number listed with the agency before [*insert Federal Register display date*]. As previously stated, unapproved colchicine for injection products that are currently marketed and not listed with the agency on the date of this notice must, as of the effective date of this notice, have approved applications prior to their shipment in interstate commerce. Moreover, any person or firm that submits an NDA but has yet to receive approval for such products is still responsible for full compliance with this notice.

*C. 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 discontinue 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 NDC number(s), and stating that the product(s) has (have) been discontinued and will not be marketed again without FDA approval. The letter should be sent to Jennifer Devine, (see **ADDRESSES**). Firms should also update the listing of their products under section 510(j) of the act to reflect discontinuation of unapproved colchicine for injection products. FDA plans to rely on its existing records, the results of a subsequent inspection, or other available information when it initiates enforcement action.

This notice is issued under the act (sections 502 (21 U.S.C. 352)) and 505 and under authority delegated to the Deputy Commissioner for Policy under section 1410.10 of the FDA Staff Manual Guide.

Dated: 1/29/08  
January 29, 2008.

  
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Jeffrey Shuren,  
Assistant Commissioner for Policy.

[FR Doc. 08-????? Filed ??-??-08; 8:45 am]

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