4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2012-N-1134

Sodium Nitrite Injection and Sodium Thiosulfate Injection Drug Products Labeled for the Treatment of Cyanide Poisoning; Enforcement Action Dates

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its intention to take enforcement action against unapproved injectable drug products containing sodium nitrite labeled for the treatment of cyanide poisoning and unapproved injectable drug products containing sodium thiosulfate labeled for the treatment of cyanide poisoning, and persons who manufacture or cause the manufacture or distribution of such products in interstate commerce. Cyanide antidotes carry serious risks and some unapproved drug products may lack Boxed Warnings and other warnings required in the labeling of approved cyanide antidotes. These unapproved drug products compete with approved products, and thus pose a direct challenge to the drug approval system. Injectable drug products containing sodium nitrite or sodium thiosulfate that are labeled for the treatment of cyanide poisoning are new drugs that require approved new drug applications (NDAs) or abbreviated new drug applications (ANDAs) in order to be legally marketed.

DATES: This notice is effective [INSERT DATE OF PUBLICATION IN THE FEDERAL REGISTER]. For information about enforcement dates, see SUPPLEMENTARY INFORMATION, section IV.

ADDRESSES: All communications in response to this notice should be identified with Docket No. FDA-2012-N-1134 and directed to the appropriate office listed in this document.

Applications under section 505(b) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(b)): Division of Anesthesia, Analgesia, and Addiction Products, Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Silver Spring, MD 20993–0002.

Applications under section 505(j) of the FD&C Act (21 U.S.C. 355(j)): Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, 7519 Standish Pl., Rockville, MD 20855.

All other communications: Lori Cantin, Office of Unapproved Drugs and Labeling Compliance, Division of Prescription Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 5239, Silver Spring, MD 20993-0002.

FOR FURTHER INFORMATION CONTACT:

Lori Cantin,

Center for Drug Evaluation and Research,

Food and Drug Administration,

10903 New Hampshire Ave.,

Bldg. 51, rm. 5239,

Silver Spring, MD 20993-0002,

301-796-1212,

email: lori.cantin@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

Cyanide is highly toxic in humans and can be fatal if not immediately treated with an effective antidote. On January 14, 2011, FDA approved NDA 201444 for Nithiodote, a co-packaged Sodium Nitrite Injection and Sodium Thiosulfate Injection drug product, labeled for treatment of acute cyanide poisoning that is judged to be life-threatening. On February 14, 2012, FDA approved NDA 203922 for Sodium Nitrite Injection for sequential use with sodium thiosulfate for treatment of acute cyanide poisoning that is judged to be life-threatening, and NDA 203923 for Sodium Thiosulfate Injection for sequential use with sodium nitrite for treatment of acute cyanide poisoning that is judged to be life-threatening. Sodium thiosulfate and sodium nitrite pose the risk of hypotension (low blood pressure), and sodium nitrite also poses the risk of methemoglobinemia, a disorder characterized by the presence of a higher than normal level of methemoglobin in the blood. Methemoglobin is an oxidized form of hemoglobin that has a decreased affinity for oxygen, resulting in a reduced ability to release oxygen to body tissue. Methemoglobinemia can lead to neurological and cardiac symptoms due to lack of adequate oxygen in body tissues. The approved Sodium Nitrite Injection and Nithiodote carry Boxed Warnings for these serious adverse reactions.

FDA is aware of several unapproved drug products containing sodium nitrite or sodium thiosulfate labeled to treat cyanide poisoning. These unapproved drug products containing sodium nitrite or sodium thiosulfate are sold individually, as well as in cyanide antidote kits. Unapproved cyanide antidote kits may also contain other unapproved drugs (e.g., amyl nitrite) or medical products (e.g., syringes) that are intended for potential use with sodium nitrite and sodium thiosulfate. This notice is issued under sections 502 (21 U.S.C. 352) and 505 of the

FD&C Act and applies to unapproved injectable drug products containing sodium nitrite or sodium thiosulfate labeled to treat cyanide poisoning that are currently being manufactured or distributed.

II. Safety Concerns With Unapproved New Drugs

Because marketed unapproved new drug products have not been through FDA's approval process, there are safety risks associated with them. Some unapproved drug product labeling omits safety warnings, such as the Boxed Warnings required on Sodium Nitrite Injection and Nithiodote, which are important for safe use of the drug products. Without these warnings, the unapproved drug products may be used in inappropriate circumstances or without appropriate monitoring, posing an increased risk to public health. Patients being treated for cyanide poisoning require close monitoring and may require repeat doses of antidote, supplemental oxygen, and ventilatory support. Cyanide antidotes containing sodium nitrite or amyl nitrite may induce methemoglobinemia, which may require additional treatment.

The expected risks associated with use of sodium nitrite or sodium thiosulfate drug products are also potentially greater for unapproved drug products because the quality, safety, and efficacy of unapproved formulations have not been demonstrated to FDA. For example, information on the ingredients and data on the bioavailability of unapproved drug products have not been submitted for FDA review, nor has FDA had the opportunity to assess the adequacy of their chemistry, manufacturing, and control specifications. Also, unapproved drug products have unapproved labeling that may not contain appropriate dosing information. For example, the sodium thiosulfate component of Nithiodote is dosed for children based on body weight or body surface area, whereas FDA is aware of unapproved sodium thiosulfate products labeled for use in

children at a lower dose based only on body surface area. Such discrepancies in dosing may lead to underdosing of sodium thiosulfate in children.

III. Legal Status of Products Identified in This Notice

FDA has reviewed the publicly available scientific literature for unapproved injectable sodium nitrite and sodium thiosulfate products labeled for treatment of cyanide poisoning. In no case did FDA find literature sufficient to support a determination that any of these drug products are generally recognized as safe and effective. Therefore, these products are "new drugs" within the meaning of section 201(p) of the FD&C Act (21 U.S.C. 321(p)), and they require approved NDAs or ANDAs in order to be legally marketed.

Also, the unapproved drug products covered by this notice are labeled for prescription use. Prescription drugs are defined under section 503(b)(1)(A) of the FD&C Act (21 U.S.C. 353(b)(1)(A)) as drugs that, because of their toxicity or other potentiality for harmful effect, are not safe to use except under the supervision of a practitioner licensed by law to administer such drugs. Because any drug product covered by this notice meets the definition of "prescription drug" in 503(b)(1)(A), adequate directions cannot be written for it so that a layman can use the product safely for its intended uses (21 CFR 201.5). Consequently, it is misbranded under section 502(f)(1) of the FD&C Act in that it fails to bear adequate directions for use. An approved prescription drug is exempt from the requirement in section 502(f)(1) that it bear adequate direction for use if, among other things, it bears the NDA-approved labeling (21 CFR 201.100(c)(2) and 21 CFR 201.115). Because the unapproved prescription drug products subject to this notice do not have approved applications with approved labeling, they fail to qualify for the exemptions to the requirement that they bear "adequate directions for use," and they are misbranded under section 502(f)(1).

IV. Notice of Intent to Take Enforcement Action

Although not required to do so by the Administrative Procedure Act, the FD&C Act (or any rules issued under its authority), or for any other legal reason, FDA is providing this notice to persons[1] who are marketing unapproved and misbranded drug products containing sodium nitrite and sodium thiosulfate labeled to treat cyanide poisoning, either sold individually or as part of a kit. 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. In the event that unapproved sodium nitrite and sodium thiosulfate are packaged in a kit with other unapproved drugs (e.g., amyl nitrite) or medical products (e.g., syringes) and labeled for treatment of cyanide poisoning, FDA intends to take action against the entire kit based on the unapproved sodium thiosulfate and sodium nitrite components.

Manufacturing or shipping the drug products covered by this notice can result in enforcement action, including seizure, injunction, or other judicial or administrative proceeding. Consistent with policies described in the Agency's guidance entitled "Marketed Unapproved Drugs--Compliance Policy Guide" (the Marketed Unapproved Drugs CPG) (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070290.pdf), the Agency does not expect to issue a warning letter or any other further warning to firms marketing drug products covered by this notice before 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 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,

[1] The term person includes individuals, partnerships, corporations, and associations (21 U.S.C. 321(e)).

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 FD&C Act. With respect to drug products covered by this notice, the Agency intends to exercise its enforcement discretion for only a limited period of time because there are safety risks with respect to the products covered by this notice, and there are FDA-approved drug products to meet patient needs. Therefore, the Agency intends to implement this notice as follows.

For the effective date of this notice, see the DATES section of this document. Any drug product covered by this notice that a company (including a manufacturer or distributor) began marketing after September 19, 2011, is subject to immediate enforcement action. For products covered by this notice that a company (including a manufacturer or distributor) began marketing in the United States on or before September 19, 2011, FDA intends to take enforcement action against any such product that is not listed with the Agency in full compliance with section 510 of the FD&C Act (21 U.S.C. 360) before [INSERT FEDERAL REGISTER DISPLAY DATE], and is manufactured, shipped, or otherwise introduced or delivered for introduction into interstate commerce by any person on or after [INSERT FEDERAL REGISTER DISPLAY DATE]. FDA also intends to take enforcement action against any drug product covered by this notice that is listed with FDA in full compliance with section 510 of the FD&C Act but is not being commercially used or sold[2] in the United States before [INSERT FEDERAL REGISTER DISPLAY DATE] and 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].

[2] For purposes of this notice, the phrase "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 drug products covered by this notice that a company (including a manufacturer or distributor) began marketing in the United States on or before September 19, 2011, are listed with FDA in full compliance with section 510 of the FD&C Act before [INSERT FEDERAL REGISTER DISPLAY DATE] ("currently marketed and listed"), and are 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] the Agency intends to exercise its enforcement discretion as follows: FDA intends to initiate enforcement action against any such currently marketed and listed product that is manufactured on or after [INSERT DATE 90 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]. 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 drug product covered by this notice 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 drug products covered by this notice is violating other provisions of the FD&C Act, including, but not limited to, violations related to FDA's current good manufacturing practice, adverse event reporting, labeling, or misbranding requirements other than those identified in this notice, or (2) it appears that a firm, in response to this notice, increases its manufacture or interstate shipment of drug products covered by this notice above its usual volume during these periods.[3]

[3] 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 FD&C 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

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 FD&C Act, whether or not related to a drug product covered by this notice. Similarly, a person who is or becomes enjoined from marketing unapproved or misbranded drugs may not resume marketing of such products based on FDA's exercise of enforcement discretion as described 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 drug products covered by this notice that are marketed under a National Drug Code number listed with the Agency in full compliance with section 510 of the FD&C Act before [INSERT FEDERAL REGISTER DISPLAY DATE]. As previously stated, drug products covered by this notice 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 their shipment in interstate commerce. Moreover, any person or firm that has submitted or submits an application but has yet to receive approval for such products is still responsible for full compliance with this notice.

V. 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 FD&C Act. Other firms may discontinue manufacturing or distributing 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

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unapproved drugs that require applications at the same time (see, e.g., United States v. Sage Pharmaceuticals, 210 F.3d 475, 479-480 (5th Cir. 2000) (permitting the Agency to combine all violations of the FD&C Act in one proceeding, rather than taking action against multiple violations of the FD&C Act in "piecemeal fashion")).

the discontinued product(s), including NDC number(s), and stating that the manufacturing and/or distribution of the products has (have) been discontinued. The letter should be sent electronically to Lori Cantin (see ADDRESSES). Firms should also electronically update the listing of their products under section 510(j) of the FD&C Act to reflect discontinuation of products covered by this notice. Questions on electronic drug listing updates should be sent to: eDRLS@fda.hhs.gov. FDA plans to rely on its existing records, including its drug listing records, the results of any subsequent inspections, or other available information, when it targets violations for enforcement action.

Dated: November 20, 2012.

Leslie Kux,

Assistant Commissioner for Policy.

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